THE
PLANT ALKALOIDS

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PREFACE

In certain respects the plant alkaloids rank among the most interesting of naturally occurring substances. For the most part they are of very complex structure, so that the determination of their constitution and the discovery of methods of producing them synthetically offer attractive problems to the chemist; and though a great deal has been accomplished, much still remains to be done in this direction. Their mode of origin and their function in plants are still unknown, and these two questions, with the more important one of correlating the structure of the alkaloids with their physiological action, form still almost untouched fields for combined work on the part of physiologists and chemists. Many of the alkaloids are of great importance in medicine, and the manufacture of these alkaloids and of products containing them constitutes important branches of the "fine chemical" industry.

In compiling this volume the author has kept in view these various aspects of the subject, and the articles on all the more important alkaloids describe not only the properties and the chemistry of these products, but also their occurrence, methods of estimation, and physiological action. In most cases the original memoirs have been consulted and references to these are given in foot-notes, but for descriptions of the physiological action of the better-known alkaloids Professor Cushny's "Textbook of Pharmacology and Therapeutics" has been largely utilised. The chemical

nomenclature and the system of abbreviations used are, with a few unimportant exceptions, those employed in the "Abstracts" published by the Chemical Society of London, with which most English-speaking chemists are familiar.

For much laborious work in checking formulæ and references and in reading proofs the author is indebted to Mrs. Henry, B.A., B.Sc. (Lond.), and to Miss A. Holmes, B.A. (Lond.).

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INTRODUCTION

THE word alkaloid was at first used to describe all organic bases, including the natural alkali-like substances which occur in plants. At the time this name was introduced comparatively few of these latter substances were known, and these were all alike in possessing basic properties and in exhibiting physiological activity. These two characteristics, in conjunction with their complex structure, have made it possible until recently to regard the natural alkaloids as forming a well-differentiated group of chemical compounds, but recent work has tended to render indistinct the border lines between this and other groups. On the one hand such simple basic substances as ammonia and methylamine, and on the other substances that contain nitrogen and are yet acidic rather than basic, have been found in plants. And, again, complex substances closely related to typical alkaloids and which must be regarded as belonging to the class of alkaloids, though they have no marked physiological action, are known. Königs proposed to avoid this difficulty by confining the name alkaloid to naturally occurring pyridine derivatives, but this rules out such important substances as the purine and glyoxaline derivatives, and for that reason can hardly be accepted as a satisfactory use of the name. The term alkaloid is, however, generally understood as meaning a relatively complex basic substance, occurring naturally, and possessing some physiological action, and it will be understood in that sense in this volume, though the definition cannot be rigidly applied.

Certain of the alkaloids are common to plants and animals, and there is no logical ground for the separate treatment of "vegetable alkaloids" and "animal alkaloids." Most of the animal alkaloids are different in type from the majority of the vegetable alkaloids, and they are even more difficult to isolate in a pure state and to investigate. Further, the literature relating to animal

alkaloids has grown rapidly in recent years, and their investigation has developed in many ways on special lines, so that for practical purposes they can be dealt with most conveniently as a separate class, and in this volume only alkaloids found in plants will be considered.

A number of comparatively simple amino-substances, such as asparagine (aminosuccinamic acid), have been recorded in recent years as occurring in plant seedlings. Most of these substances can scarcely be classed as alkaloids, and they are fully dealt with, as a rule, in the larger text-books on organic chemistry, and for these reasons they are not described in detail in this volume.

Classification of Alkaloids

The chemistry of this group of compounds dates from 1817, when Sertürner announced his discovery of a crystalline, salt-forming, physiologically active substance (morphine) in opium. This was followed by Robiquet's discovery of narcotine in the same year, and in the next year by Pelletier and Caventou's isolation of strychnine. Since then a large number of such substances have been isolated from plants and characterised. A good deal is now known regarding the molecular structure of many of the more important alkaloids, and syntheses have been effected of a considerable number of them. It is possible, therefore, to classify many of the alkaloids according to their nuclear structure. Any system of classification is, however, liable to become obsolete soon after its introduction, as the result of the great activity now being shown in the investigation of alkaloids. Further, methods of investigation are now so delicate, and the chemistry of cyclic compounds is becoming so much better understood, that far-reaching deductions regarding the structure of compounds can be drawn from relatively few and simple reactions and observations, so that for purposes of hard-and-fast classification the chemistry of alkaloids is in a very unstable condition.

The vegetable alkaloids can, however, be arranged at present

in the following groups, according to the nature of the bases from which they are derived.

	Nature of Nucleus	*Examples*
Group 1.	Pyrrole	Hygrine, Stachydrine
Group 2.	Pyridine	Coniine
Group 3.	Diheterocyclic, with a common nitrogen atom	Atropine, Sparteine
Group 4.	Quinoline	Strychnine
Group 5.	*iso*Quinoline	Papaverine
Group 6.	Glyoxaline	Pilocarpine
Group 7.	Purine	Caffeine
Group 8.	Cyclic or acyclic derivatives of aliphatic amines	Choline, Arginine
Group 9.	Alkaloids of unknown constitution	

Certain of the alkaloids belong to more than one of these groups; thus, nicotine contains both a pyridine and a pyrrolidine nucleus, whilst quinine has two heterocyclic nuclei, one belonging to Group 3 and the other to Group 4.

Apart from the difficulties just referred to, it is inconvenient to arrange the alkaloids for discussion according to their chemical constitution, since this separates alkaloids which occur in the same plant and which for practical purposes it is desirable should be dealt with together. In this volume, therefore, while the scheme of arrangement referred to above will be adopted, it will be modified by a sub-classification according to source, and all the alkaloids from the same plant will be dealt with together. In Group 9 the alkaloids will be taken for the most part in the alphabetical order of the botanical names of the plants yielding them. There are obvious disadvantages about using a botanical basis for arranging alkaloids, since chemists rarely devote sufficient attention to ensuring that the plants they work with really bear the botanical names assigned to them, and there is the further difficulty that the same scientific name may have been given to different plants by

different botanists; but, on the whole, this system seems to be that best adapted to bring together alkaloids which are of similar constitution or which, from the mode of their occurrence, are natura associates.

Physical Properties of Alkaloids

The great majority of the alkaloids are colourless, crystalline substances containing carbon, hydrogen, oxygen, and nitrogen, but a few are liquid, and these are generally free from oxygen and are more or less readily volatile.

Comparatively few of the alkaloids are coloured, but berberine and certain of the corydalis alkaloids are notable exceptions, since in these cases the more unsaturated members are in some cases yellow, but become colourless on reduction; berberine and dehydrocorydaline being yellow, but furnishing on reduction colourless tetrahydrides. A few of the alkaloids are themselves colourless, but yield coloured salts; thus the colourless sanguinarine gives red salts.

Most of the alkaloids show characteristic absorption spectra, and this property has been successfully used by Professor Dobbie and his collaborators in settling various knotty points in the constitution of some of the more complex alkaloids. A very large proportion of the alkaloids are optically active, and in a few cases, *e.g.* the aconitines and narcotine, the salts show an optical activity opposite to that of the free alkaloid. The optically active alkaloids have frequently been used in deracemising optically inactive acids produced synthetically, since they often form sparingly soluble salts, which are readily separated into their optical antipodes by fractional crystallisation.

Chemical Properties of Alkaloids

In order to obtain a satisfactory idea of the chemical properties of the alkaloids as a class, it would be necessary to discuss in some detail a typical member of each of the first eight groups referred to in the scheme of classification already given, and as this is done

in the special sections relating to these groups it need not be repeated here. It is necessary, however, to refer in a general way to the chemical characteristics of the alkaloids in so far as these affect their isolation, purification, detection, and estimation. For a full general discussion of these subjects, which are of special importance in analytical work connected with alkaloids, the introductory article on alkaloids in Allen's "Organic Analysis," 4th edition, vol. vi. p. 167, should be consulted.

Preparation. In isolating the plant alkaloids advantage is taken of the fact that they generally occur in the form of salts, which are soluble in alcohol or in water. In the comparatively rare cases in which alkaloids occur in the free state they may also, as a rule, be extracted by alcohol, or by chloroform, or ether, or in some cases by light petroleum. Where they occur in the form of salts, insoluble in alcohol, they may be obtained by mixing the ground plant with lime or magnesia and then extracting with alcohol, chloroform, ether, or petroleum. In such cases, extraction with alcohol slightly acidulated may also be resorted to. Extraction in presence of even mild alkalis, such as lime or magnesia, or by means of dilute mineral acids in alcoholic or aqueous solution should not be resorted to unless no other means is available, as many alkaloids suffer decomposition under such treatment. For the concentration of extraction liquors containing alkaloids, evaporation of the neutral liquid *in vacuo* should always be resorted to in order to avoid risk of decomposing the alkaloid. From the concentrated liquors fat, resin, and other matters are generally removed by adding water, or, if necessary, very dilute acid to keep the alkaloid in solution. This aqueous or acid solution may then be shaken with an indifferent, immiscible solvent to remove colouring matter, &c., but care must be taken that the alkaloid is not also removed by the solvents used, since some of the weakly basic alkaloids can be removed even from acid solution by indifferent solvents. The purified concentrated liquid is then made alkaline, a weak alkali such as dilute ammonia, sodium carbonate or sodium hydrogen carbonate solution being used in preference to solutions of alkali hydroxides for this purpose. Most

of the alkaloids are precipitated by this treatment, and may then be separated by shaking out with an immiscible solvent such as chloroform or ether. A few alkaloids, which contain phenolic hydroxyl groups (*e.g.* morphine), are dissolved by alkali hydroxide solutions, but, as a rule, these are precipitated by ammonia or alkali carbonate solutions. Certain alkaloids are miscible with water in all proportions, and are not removed from water by indifferent immiscible solvents. In such cases precipitation with one of the alkaloidal precipitants mentioned below may be resorted to and the alkaloid recovered from the washed precipitate. Examples of these and other methods of preparation will be found in the special sections of this volume, but reference may be made more especially to the methods described under aconitine (p. 340), solanaceous alkaloids (p. 50), strychnine (p. 183), and the opium alkaloids (p. 207). For the isolation of volatile alkaloids the sections on nicotine (p. 39) and coniine (p. 26) should be consulted.

The "total alkaloid" having been isolated from a plant, it is necessary to ascertain that it consists of a single substance, or, if it is a mixture, to separate it into its constituents. For this purpose fractional crystallisation of the free alkaloid, or mixture of alkaloids, from suitable solvents must be resorted to, the usual method being to dissolve the material in a suitable solvent, and then add drop by drop a second medium in which the alkaloid is insoluble or only sparingly soluble, until the liquid becomes cloudy. On standing, crystals may be deposited; if not, the clear liquid is poured off and the treatment repeated. To avoid change in the composition of the mixed solvent this process should be conducted in stoppered bottles or corked flasks. The purification of an alkaloid is often greatly facilitated by converting it into a salt. For this purpose the haloid salts are generally better suited than the sulphates or nitrates. Other useful salts for this purpose are the oxalates, picrolonates, picrates, and especially the aurichlorides. The latter may generally be recrystallised from alcohol or water containing a little hydrochloric acid. The method of fractionation

referred to above is also applicable to alkaloidal salts, the *dry* substance being dissolved in *dry* alcohol and *dry* ether added, drop by drop, till a faint cloudiness appears.

For the identification of an alkaloid the usual means adopted for organic compounds, viz. determination of the melting-point or some other physical constant for the free alkaloid and for one or more of its derivatives, should be resorted to. Colour reactions, which are so often used for this purpose, are unsatisfactory, and when they have to be used should be applied side by side to the substance under examination and to a pure specimen of the same alkaloid.

Estimation of Alkaloids in Plants. The estimation of alkaloids in plants involves their complete extraction on the lines just described and their separation in a form in which they can be weighed or titrated. Typical methods of estimation are described under opium (p. 200), cinchona (p. 131), coca (p. 92), and solanaceous drugs (p. 52).

It should be remembered that in titrating alkaloids and their salts, some of them are indifferent to indicators so that their salts react like a corresponding quantity of free acid, others are monacidic to one indicator and diacidic to another, whilst still others give unsatisfactory end reactions with some indicators.

Alkaloidal Precipitants

One of the most characteristic properties of alkaloids is that of forming complex double salts with certain metallic haloids. These double salts are generally nearly insoluble in water, so that mere traces of alkaloids can be detected by their formation. The following are a few of the most useful precipitants of this kind.

Auric Chloride. A solution of auric chloride gives yellow or orange-coloured precipitates (the aurichlorides) with many alkaloids. The latter should be dissolved in a very slight excess of dilute hydrochloric acid. As a rule, the precipitates can be recrystallised from alcohol, or water, containing a little hydrochloric acid. They have the general composition, $B.HCl.AuCl_3$, but compounds of

the type, $B.AuCl_3$, are also sometimes produced, and under certain conditions aurichlor-derivatives of the alkaloids, containing the group $AuCl_2$ in place of a hydrogen atom of the alkaloid, are formed. Examples of such compounds are referred to under japaconitine (p. 349) and caffeine (p. 314). The aurichlorides of the solanaceous alkaloids are especially useful in separating and characterising the members of this group.

Platinic Chloride. Similar compounds, the platinichlorides, $(B.HCl)_2.PtCl_4$ or $B.H_2PtCl_6$, in the case of diacidic alkaloids, are formed with platinic chloride, but as a rule these are more soluble than the aurichlorides, especially in dilute hydrochloric acid.

Mercuric Chloride. With solutions of this salt many of the alkaloids give characteristic, crystalline mercurichlorides of the general composition, $B.HCl.HgCl_2$.

Among other precipitants of this class may be mentioned ferric chloride, lead tetrachloride, telluric chloride, and thallic chloride.

Solutions of certain double metallic haloids form the best known group of alkaloidal precipitants and include the reagents most commonly used for detecting their presence. Among these are the following.

Potassium Mercuric Iodide (*Mayer's Reagent*). This is best prepared by adding 6·8 grm. of mercuric chloride, dissolved in water, to 25 grm. of potassium iodide, dissolved in water, and diluting to 1000 c.c. This solution gives white, curdy precipitates with minute traces of alkaloids in solutions slightly acidified with hydrochloric or sulphuric acid. The precipitates vary in composition with the conditions of precipitation. The alkaloids may be recovered from these precipitates by suspending them in water and passing a current of sulphuretted hydrogen, when the alkaloidal hydriodide is formed and may be recovered by concentrating the filtrate.

Similar precipitates are afforded by solutions of potassium bismuth iodide (Dragendorff's reagent), potassium cadmium

iodide (Marmé's reagent), iodine in potassium iodide (Wagner's reagent), and other like solutions.

In addition to the foregoing precipitants, which give insoluble complex double salts with the alkaloids, a number of acids form insoluble alkaloidal salts and therefore act as precipitants.

Gallotannic Acid. A solution of gallotannic acid gives precipitates of the corresponding tannates with most alkaloids in neutral solution. These precipitates are generally soluble in ammonia and sometimes in dilute acids.

Picric Acid (Hager's Reagent). The picrates of most of the alkaloids are sparingly soluble in water or dilute acids and are precipitated when a cold, saturated, aqueous solution of picric acid is added to a solution of an alkaloidal salt. They can usually be recrystallised from alcohol and are often characteristic.

Phosphomolybdic Acid (Sonnenschein's Reagent). A solution of this substance gives amorphous yellow precipitates with many alkaloids, and may be used for separating them from associated non-alkaloidal organic matter, since the alkaloids may be regenerated by treating the precipitates with sodium carbonate and extracting rapidly with alcohol.

Phosphotungstic acid and metatungstic acid have been also used as alkaloidal precipitants.

Biological Significance of Alkaloids

Alkaloids have so far been found in comparatively few natural orders of plants: the Ranunculaceæ, Rubiaceæ, Papaveraceæ, Fumariaceæ, Solanaceæ, Leguminoseæ, and Apocynaceæ are typically rich in these constituents; the Rosaceæ, Graminaceæ, and Labiatæ are typically poor in alkaloids; whilst the Compositæ occupy an intermediate position.

The alkaloids found in a natural order and especially in any one genus are usually somewhat closely related; thus the various aconitines form a closely related group, found only in members of the genus Aconitum. In some cases a single alkaloid is almost

characteristic of an order, *e.g.* protopine occurs in many plants of the natural order Papaveraceæ and of the closely related order, Fumariaceæ. The purine alkaloids, on the contrary, furnish an instance of closely related alkaloids occurring in plants belonging to different orders.

The phanerogams or flowering plants are richer in alkaloids than the cryptogams or so-called flowerless plants, and of the former class the sub-class dicotyledons is richer in alkaloids than the monocotyledons.

In comparatively few cases have investigations been made of all parts of a plant for alkaloids, but where this has been done, as in the cases of hemlock, poppy, and some of the solanaceous plants, it has been found that alkaloids usually occur in all parts of the plant. It is generally impossible to say with certainty that one particular part of a plant is always richer than another in alkaloids, since the richness of each part varies with the season and with the condition of the plant. Thus in the case of belladonna the amounts of "total alkaloid" recorded vary from 0·15 to 0·60 per cent. in the roots and from 0·05 to 0·64 per cent. in the leaves. The quantity of alkaloid can be greatly increased by special cultivation and especially by selection for richness in alkaloid; thus the average quinine content in Java cinchona bark is steadily rising as a result of these two processes. Chevalier has also shown recently that the alkaloidal content of solanaceous plants can be increased by manuring.

A great deal of discussion has taken place regarding the mode of formation and the function of alkaloids in plants. The discussion on both questions has been mostly speculative, and there are comparatively few experimental data available on either. Many of the simpler substances which are now included among the alkaloids are undoubtedly products of the decomposition of proteins, and this is now generally admitted to be one of the methods by which the vegetable alkaloids are produced in nature. Kerbosch, for example, has recently brought forward evidence of the formation of narcotine from protein in the germination of poppy seeds.

It has also been pointed out that pyridine derivatives are produced by the action of ammonia on pyrones and that organic acids and aldehydes, which are either pyrone derivatives or can be converted into such substances, are of common occurrence in plants; and that by the action of ammonia these substances might be converted into pyridine compounds in nature.

A more acceptable hypothesis is that of Pictet, who suggested that the mother substances of alkaloids are the nitrogenous decomposition products of more complex substances, such as proteins, chlorophyll, &c., arising in the ordinary processes of metabolism. These decomposition products he supposes are rendered harmless by the plant in various ways, but more especially by methylation, by the action of formaldehyde. On this view alkaloids containing the pyrrole or indole group are probably protein decomposition products, whilst those containing a pyridine nucleus are probably produced by the further change of an alkylated pyrrole into pyridine. The possibility of such a change Pictet had previously demonstrated by showing that *l*-methylpyrrole, *l*-methylindole, and methylphthalimidine can be converted respectively into pyridine, quinoline, and *iso*quinoline by the action of heat. In support of this theory Pictet and Court have since shown that tobacco, pepper, carrot leaves, coca, and parsley all yield volatile pyrrole bases, probably derived from proteins. Winterstein and Trier[1] have critically examined Pictet's hypothesis and have themselves suggested that such decomposition products of the proteins as lysine and arginine are raw materials for alkaloidal syntheses in plants, and their views receive some support from Ciamician and Ravenna's experiments, which show that whilst inoculation of plants with pyridine or pyrrolidine derivatives produces scarcely any increase in alkaloidal content, similar application of dextrose or asparagine causes a considerable increase.

As regards the function of alkaloids in plants three views have been held: (1) That they are nutritive materials used by the plant in metabolism; (2) that they act as protective materials against

[1] *Die Alkaloide*, Berlin, 1910.

attack of the plants by animals; (3) that they are end products of metabolism, rendered harmless to the plant and stored for the most part in special cells where they are not readily re-absorbed into the active plant tissues.

The third view is that now generally held, though recent work on the subject also affords some support to the view that certain of the alkaloids are plastic materials used in plant metabolism.

Physiological Action of Alkaloids

The commercial importance of alkaloids depends wholly on their physiological action, and certain of them, such as quinine and morphine, are, and have long been, among the most commonly used drugs in medicine. In recent years a good deal of attention has been given to the possibility of correlating the chemical constitution of alkaloids with their physiological action, but this subject is so full of difficulties on both the chemical and physiological sides that comparatively little progress has been made. As an example of the difficulties encountered even in a comparatively simple case, the investigations of Jowett and Pyman on the mydriatic effects of a whole series of tropëines may be quoted (p. 88), as a result of which they concluded that no generalisation as to the relation between the mydriatic action and chemical constitution of the tropëines can be made, which will explain the results they obtained.

In spite of these difficulties a large number of important and useful observations on this subject have been made, and references to these are made in the special sections of this volume.

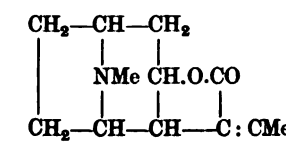
I. PYRROLE GROUP

ALKALOID OF *DIOSCOREA HIRSUTA*

Dioscorine, $C_{13}H_{19}O_2N$, was obtained from the stems of the Javanese plant *Dioscorea hirsuta*, Blume, by Boorsma,[1] and was afterwards investigated by Schutte[2] and by Gorter.[3] It forms greenish-yellow plates, m.p. 43·5°, distils unchanged *in vacuo*, is soluble in water, alcohol, or chloroform and sparingly so in ether or benzene. The hydrochloride, $B.HCl.2H_2O$, forms colourless needles, m.p. 204°, $[\alpha]_D + 4°\ 40'$, from alcohol; the platinichloride, $(B.HCl)_2.PtCl_4.3H_2O$, orange-yellow tablets, m.p. 199°–200° (*dry*); the aurichloride, $B.HAuCl_4.\frac{1}{2}H_2O$, yellow needles, m.p. 171° (*dry*).

With sulphuric acid and potassium iodate dioscorine gives a blue-violet coloration and a reddish-violet with sodium nitroprusside in presence of alkalis.

According to Gorter, dioscorine contains a $:NCH_3$, but no $-OH$ group. When heated with potash it yields a salt from which acids regenerate the alkaloid, so that the latter is probably a lactone. Heated with silver oxide dioscorine methiodide gives demethyldioscoridine, $C_{13}H_{21}N$, and the methiodide of this when heated with silver oxide gives trimethylamine and a hydrocarbon, $C_{11}H_{14}$, which appears to be a butenyl*cyclo*heptatriene. On these grounds Gorter[4] assigns the following formula to dioscorine:



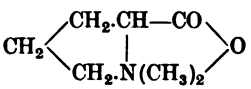
The alkaloid is bitter and poisonous; it produces paralysis of the central nervous system and in general behaves like picrotoxin. This

[1] *Meded. uit 's Lands Plantentuin*, 1894, p. 13.
[2] *Chem. Centr.* 1897, ii. 130.
[3] *Ann. Jard. Bot. Buit.* 1909, ii.; *Suppl.* 3, 385.
[4] *Rec. Trav. Chim.* 1911, **30**, 161.

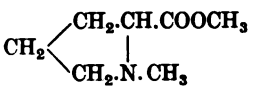
action appears to be correlated with the $-CO.\dot{C}:\dot{C}-$ group, since on the disappearance of this, as in the corresponding acid, the toxicity disappears.

ALKALOID OF *STACHYS TUBERIFERA*

Stachydrine, $C_7H_{13}O_2N.H_2O$, was obtained from the roots of *Stachys tuberifera* (*S. Sieboldii*, Miq.) by von Planta and Schulze,[1] and was examined later by Jahns,[2] who also prepared it from orange leaves. It forms deliquescent crystals, m.p. 210° (*dry*), soluble in alcohol or water, insoluble in ether or chloroform; the hydrochloride, B.HCl, crystallises in prisms, m.p. 235°, and the aurichloride, $B.HAuCl_4$, in leaflets, m.p. 225°, which melt when warmed in water. The methyl ester is unstable and is hydrolysed into stachydrine and methyl alcohol by cold water. When heated with strong potash solution, stachydrine yields dimethylamine. According to Schulze and Trier, it yields methyl hygrinate when distilled alone, and the same authors have synthesised it by treating ethyl hygrinate methiodide with silver oxide. On these grounds they have assigned the following formula to stachydrine:[3]



Stachydrine



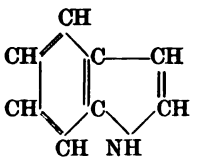
Methyl hygrinate

Indole, C_8H_7N. This substance, m.p. 52°, which is one of the products of putrefaction of protein, was found by A. Hesse in jasmine flower oil and subsequently in orange flower oil (neroli oil).[4]

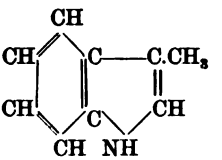
β-Methylindole. This occurs along with its lower homologue indole in the putrefaction of protein, and was found by Dunstan in the wood of *Celtis reticulosa*, Miq., which is so far the only record of its occurrence in a plant. It forms colourless leaflets, m.p. 95°.[5]

[1] *Berichte*, 1890, **23**, 1699; 1893, **26**, 939. [2] *Ibid.* 1896, **29**, 2065.
[3] *Zeits. physiol. Chem.* 1909, **59**, 233; *Berichte*, 1909, **42**, 4654. Compare Engeland, *Arch. Pharm.* 1909, **247**, 463.
[4] *Berichte*, 1899, **32**, 2611. [5] *Proc. Roy. Soc.* 1890, **46**, 211.

These two substances have the following formulæ :



Indole



Skatole (β-methylindole)

ALKALOID OF *ERYTHRINA HYPAPHORUS*

The seeds of this plant, which is grown as a shade tree in Java, were examined by Greshoff [1] and found to contain a crystalline alkaloid, hypaphorine, which has been further examined by van Romburgh and Barger.[2]

Hypaphorine, $C_{14}H_{18}O_2N_2$, crystallises with $1H_2O$, m.p. 255°, $[\alpha]_D$ + 91° to + 93°, and yields a sparingly soluble nitrate, m.p. 215°–220°. When heated with aqueous potassium hydroxide it yields trimethylamine and indole.

When trytophan (β-indole-α-aminopropionic acid) is methylated with methyl alcohol in presence of sodium hydroxide, and the resulting product heated at 100° for a few minutes with dilute sodium hydroxide solution, hypaphorine is formed. The latter is regarded therefore as α-trimethyl-β-indolepropiobetaine.

For other alkaloids containing a pyrrole or reduced pyrrole nucleus, *see under* carrot leaves (p. 398), coca (p. 108), tobacco (p. 39).

[1] *Meded. uit 's Lands Plant.* 1890, **7**, 29.

[2] *Proc. K. Akad. Weten. Amst.* 1911, **13**, 1177 ; *Trans. Chem. Soc.* 1911, **99**, 2068.

II. PYRIDINE GROUP

ALKALOID OF *TRIGONELLA FŒNUM-GRÆCUM*

Trigonelline, $C_7H_7O_2N$. This alkaloid was isolated by Jahns[1] from the seeds of *Trigonella Fœnum-græcum*, a leguminous annual extensively cultivated in India and Egypt for the sake of its seeds, which when ground are used to a small extent in the preparation of curries, but more especially for the manufacture of cattle foods. Trigonelline has also been detected by Schulze and Frankfort [2] in the seeds of *Pisum sativum*, whilst *Strophanthus hispidus* and *Strophanthus Kombe* contain it in small quantity.[3] According to Gorter [4] it is also present in coffee, whence it was isolated under the name " coffearine " by Palladino.[5]

Jahns obtained the alkaloid by exhausting ground fœnugrec seeds with 70 per cent. alcohol. The residue left after removal of the greater part of the solvent by distillation was freed from colouring matter by lead acetate, and from soluble proteins by concentration to a syrup and addition of strong alcohol. An aqueous solution of potassium-bismuth iodide was then added and the mixture set aside for some weeks. The precipitate was treated with solution of caustic soda and the filtrate from this exactly neutralised by sulphuric acid. Sufficient mercuric chloride was then added to form sodium-mercuric iodide, which under these conditions precipitates the small amount of *choline* present. Trigonelline mercuric iodide crystallises from the filtrate on addition of an acid, and from this the pure alkaloid may be regenerated by any of the ordinary methods.

Trigonelline crystallises from alcohol in hygroscopic prisms

[1] *Berichte*, 1885, **18**, 2518. [2] *Ibid.* 1894, **27**, 769.
[3] Thoms, *ibid.* 1898, **31**, 271, 404. [4] *Annalen*, 1910, **372**, 237.
[5] *Chem. Soc. Abstr.* 1894, i. 214 ; 1895, i. 629. Compare Graf, *ibid.* 1904, i. 915.

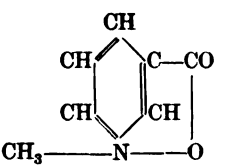
containing one molecule of water, m.p. 130° or 218° (*dry, decomp.*). It is very soluble in water, less so in cold alcohol, and slightly so in ether or chloroform.

The salts crystallise well, the hydrochloride, B.HCl, in anhydrous leaflets, and the platinichloride in yellow prisms. The alkaloid forms several aurichlorides: the normal salt, $B.HCl.AuCl_3$, is precipitated when excess of gold chloride is added to trigonelline hydrochloride. It can be recrystallised from dilute hydrochloric acid and then forms flattened prisms, m.p. 198°. Crystallised from very dilute hydrochloric acid fine needles, $B_4.3HAuCl_4$, are obtained.

When trigonelline is heated in closed tubes with baryta water at 120° it gives rise to methylamine, indicating the existence in its molecule of a methyl group attached to a nitrogen atom. Hydrochloric acid at 260° furnishes methyl chloride and nicotinic acid.[1] This reaction, which may be represented by the equation

$$\underset{\textit{Trigonelline}}{C_7H_7O_2N} + HCl = \underset{\textit{β-Pyridinecarboxylic acid}}{C_6H_5O_2N} + CH_3Cl$$

indicates that the alkaloid is a methyl betäine of nicotinic acid.



Trigonelline

Hantzsch prepared trigonelline synthetically in 1886[2] by hydrolysing nicotinic acid methiodide with silver hydroxide, and Jahns subsequently identified trigonelline with Hantzsch's synthetic betäine.[3]

ALKALOIDS OF *ARECA NUT* (*Areca Catechu*)

The areca or betel-nut palm (*Areca Catechu*) is indigenous to the Sunda Islands, but is now widely cultivated in tropical countries of the Far East, where the seeds are employed mixed with lime and betel

[1] β-pyridinecarboxylic acid, Jahns, *Berichte*, 1887, **20**, 2840.
[2] *Berichte*, 1886, **19**, 31. [3] *Loc. cit.*

pepper leaves (*Piper Betle* L.) as a masticatory by the natives. In China and India the ground areca nut is used as a vermifuge, and it is also employed in this way in Europe in veterinary medicine.

The seeds were first examined by Bombelon [1] and later by Jahns,[2] who isolated from this source the following group of alkaloids, together with choline :

Arecaïdine, $C_7H_{11}O_2N.H_2O$	Arecoline, $C_8H_{13}O_2N$
Arecaïne, $C_7H_{11}O_2N.H_2O$	Guvacine, $C_6H_9O_2N$

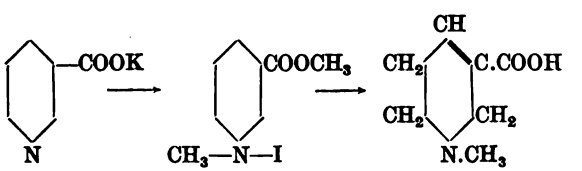
by digesting the ground seeds three times with water containing 2 grm. of sulphuric acid per kilogramme of seeds, and precipitating the extract so obtained with potassium-bismuth iodide solution ; from the precipitate the alkaloids were regenerated by boiling with water containing barium carbonate, when they dissolved in the water. The aqueous solution on concentration and addition of barium hydroxide gave up to ether, arecoline. The residual solution was neutralised with sulphuric acid and treated successively with silver sulphate, barium hydroxide, and carbon dioxide, and the final filtrate evaporated to dryness and extracted with dry alcohol or chloroform, which left arecaïne undissolved, arecaïdine and guvacine passing into solution. Arecaïne is purified by repeated crystallisation from 60 per cent. alcohol and finally by treating the crude product with methyl alcohol and hydrogen chloride, which converts arecaïdine into arecoline, but leaves arecaïne unaffected. Guvacine replaces arecaïne in part sometimes in the seeds, and is separated from arecaïne and arecaïdine by taking advantage of its smaller solubility in water or dilute alcohol. Guvacine, like arecaïne, is unaffected by treatment with methyl alcohol and hydrogen chloride, and may in this way be purified from the last traces of arecaïdine. Arecoline is present to the extent of 0·07 to 0·1 and arecaïne to about 0·1 per cent. Arecaïdine and guvacine occur in smaller quantities.

[1] *Pharm. Zeit.* 1886, p. 146.

[2] *Berichte*, 1888, **21**, 3404 ; 1890, **23**, 2972 ; 1891, **24**, 2615 ; *Arch. Pharm.* 1892, **229**, 669.

Arecaïdine, $C_7H_{11}O_2N.H_2O$. This alkaloid forms colourless four- or six-sided tablets, m.p. 222–223° (*dry*), is readily soluble in water, but practically insoluble in all organic solvents, including dry alcohol. The platinichloride, $B_2H_2PtCl_6$, forms octahedra, m.p. 208°–209° (225°–226°, Wohl and Johnson), and the aurichloride, $B.HAuCl_4$, prisms, m.p. 197°–198°, from dilute hydrochloric acid. The base and its salts are not poisonous, whilst the methyl ester (arecoline) is highly toxic. When methylated, arecoline is produced.

Constitution. Since arecaïne furnishes a methyl ester (arecoline) it must contain a carboxyl group, and its formula may therefore be written $C_6H_{10}(COOH)N$, which is that of a tetrahydromethylpyridinecarboxylic acid. This consideration led Jahns to attempt the synthesis of arecaïdine by methylating the potassium salt of nicotinic acid and reducing the methyl ester methiodide so formed, with tin and hydrochloric acid, with the result that a base identical with arecaïdine was obtained along with some dihydroarecaïdine. From the fact that arecaïdine, whether isolated from areca nuts or synthesised as already described, is optically inactive and cannot be resolved into two optical isomerides, Meyer concludes that it is N-methyl-Δ^3-tetrahydronicotinic acid,[1] and this has been confirmed by Wohl and Johnson's complete synthesis of the alkaloid from acroleïn as a starting-point.[2]



Potassium nicotinate — *Methyl nicotinate methiodide* — *Arecaïdine* (Jahns and Meyer)

Arecaïne, $C_7H_{11}O_2N.H_2O$. This base is colourless and crystalline, and melts at 213° after drying at 100°. It furnishes crystalline salts which are sparingly soluble in alcohol; the auri-

[1] *Monatshefte*, 1902, **23**, 22.
[2] *Berichte*, 1907, **40**, 4712; *see under* Arecoline, p. 20.

chloride, $B.HAuCl_4$, yellow prismatic crystals, m.p. 186°–187°, and the platinichloride, $[B.HCl]_2.PtCl_4$, m.p. 213°–214°, orange octahedra, are both characteristic.

It is formed from guvacine (*see below*) when that alkaloid is treated with sodium methoxide and potassium methyl sulphate, and is probably N-methylguvacine. It is physiologically inactive.

Arecoline, $C_8H_{13}O_2N$, is a colourless strongly alkaline liquid, b.p. 220°, miscible with water and most organic solvents in all proportions. It is extracted from water by ether only in presence of salts in solution. It furnishes crystalline, but usually deliquescent salts; the hydrobromide, B.HBr, forms slender prisms, m.p. 167°–168° from alcohol; the aurichloride, $B.HAuCl_4$, is an oil, but the platinichloride, $[B.HCl]_2.PtCl_4$, m.p. 176°, crystallises from water in orange-red rhombs. The methiodide forms glancing prisms, m.p. 173°–174°.

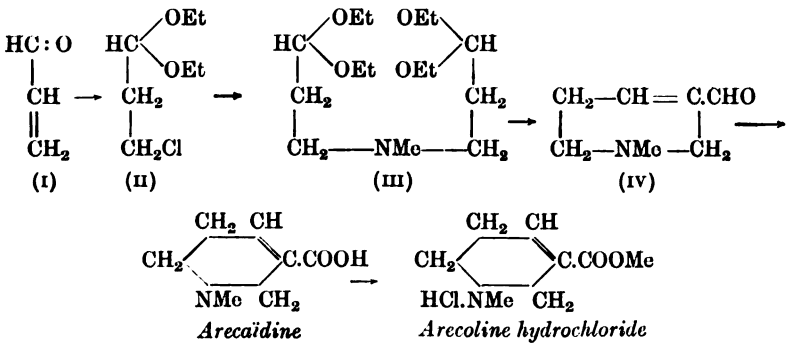
Arecoline and its salts are highly toxic. According to Meier it belongs to the nicotine-pilocarpine group and acts on the central and peripheral parts of the nervous system, producing paralysis, which may be preceded by convulsions. With nicotine the central action is the more marked, and with pilocarpine the peripheral. With arecoline the two are about equal.[1] Arecoline hydrobromide is recognised in several Continental pharmacopœias, being used as a sialogogue and diaphoretic. It has also been used like physostigmine to produce myosis.

When heated with hydrochloric or hydriodic acid, or by the action of alkalis, arecoline yields arecaïdine and methyl chloride, iodide or hydroxide, depending on the hydrolytic agent used. Further, on esterification with methyl alcohol arecaïdine yields arecoline, so that the latter must be the methyl ester of arecaïdine (*see above*). The ethyl ester has been prepared and is known as **homoarecoline;** it closely resembles arecoline, and, like it, is poisonous.

The partial synthesis of arecaïdine from potassium nicotinate as a starting-point has been described already. A complete syn-

[1] *Bio-Chem. Zeit.* 1907, **2**, 415.

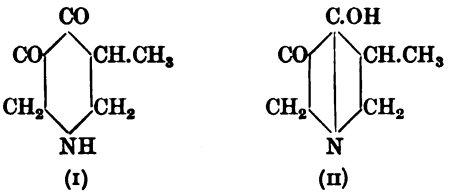
thesis of arecaïdine, and consequently of arecoline, has been effected by Wohl and Johnson.[1] Acrolëin (I) was converted into β-chloropropaldehyde acetal (II) by the action of alcohol and hydrogen chloride, and this was condensed with methylamine, giving β-methyliminodipropaldehyde tetraethylacetal (III). This on treatment with cold strong hydrochloric acid gave N-methyl-Δ^3-tetrahydropyridine-3-aldehyde (IV), which yielded an oxime from which thionyl chloride abstracted the elements of water, yielding 3-cyano-N-methyl-Δ^3-tetrahydropyridine hydrochloride, and this on hydrolysis gave arecaïdine, from which arecoline may be prepared by methylation in the usual way.



Guvacine, $C_6H_9O_2N$. This alkaloid was isolated by Jahns[2] from commercial arecaïne. It forms small lustrous needles, m.p. 271°–272°, and is moderately soluble in water or dilute alcohol. The hydrochloride, B.HCl, crystallises in prisms and is sparingly soluble in dilute hydrochloric acid; the platinichloride forms yellow tablets, m.p. 210° (*decomp.*), and the aurichloride, flattened prisms, m.p. 194°–195°. It is physiologically inactive.

Constitution. The alkaloid reacts like a secondary amine, furnishing a nitroso derivative and an acetyl compound, whilst on distillation with zinc dust it gives β-picoline. From a consideration of these reactions Jahns has assigned to it the following formula (I) with the suggestion that it may also act in the sense of the tautomeric structure (II), which is necessary in view of the phenolic character

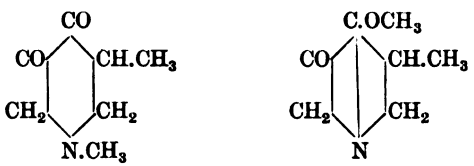
[1] *Loc. cit.* [2] *Berichte*, 1891, **24**, 2615.



(I) (II)

Guvacine (Jahns)

of some of its reactions. On methylation with potassium methyl sulphate guvacine yields two monomethyl derivatives, one of which is identical with arecaïne (*see above*). The second methyl derivative, unlike arecaïne, yields methyl iodide when heated with hydriodic acid, and is therefore believed to be a 4-methyl ether derived from the tautomeric form of guvacine (*see formula* II *above*). Arecaïne and its isomeride may therefore be represented thus :



Arecaïne *Methyl ether of Guvacine* (enol-form)

ALKALOID OF *CHRYSANTHEMUM CINERARIÆFOLIUM*

Chrysanthemine, $C_{14}H_{28}O_3N_2$. This alkaloid was isolated in 1890 by Marino-Zuco [1] from the flowers of *Chrysanthemum cinerariæfolium* (Dalmatian insect flowers) used for the destruction of insect pests. It was prepared by decolorising an aqueous decoction of the flowers with lead acetate and precipitating the liquor so obtained with bismuth-potassium iodide solution. The alkaloidal hydriodide was regenerated from this precipitate by the action of hydrogen sulphide and the free base obtained by the addition of silver hydroxide and evaporation of the solution of the free alkaloid *in vacuo*.

Chrysanthemine crystallises in radiating masses of colourless needles, dissolves readily in water or alcohol, but is insoluble in ether or chloroform, is optically inactive and strongly alkaline.

[1] *Chem. Soc. Abstr.* 1891, **60**, 333 ; 1892, **62**, 84.

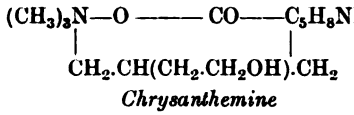
The salts crystallise well, are readily soluble in water and are those of a diacidic base; the aurichloride, $B(HAuCl_4)_2$, forms golden-yellow prisms, sparingly soluble in water, and the platinichloride, $B.H_2PtCl_6$, orange-yellow prisms. The alkaloid is only slightly active physiologically.

Chrysanthemine combines with two molecules of methyl iodide. When heated with concentrated potassium hydroxide solution, trimethylamine is formed together with γ-hydroxybutyric acid and piperidinecarboxylic acid as shown by the following equation:

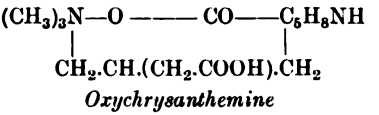
$$\underset{\textit{Chrysanthemine}}{C_{14}H_{28}O_3N_2} + 4KOH + H_2O = K_2CO_3 + 4H_2 + \underset{\textit{Trimethylamine}}{N(CH_3)_3} +$$

$$\underset{\textit{Potassium γ-hydroxybutyrate}}{C_4H_7O_3K} + \underset{\textit{Potassium piperidinecarboxylate}}{C_5H_9NH.COOK}$$

When oxidised with bromine and an alkali, the base is converted into **oxychrysanthemine**, $C_{14}H_{26}O_4N_2$, which, when heated with alkali, loses carbon dioxide and hydrogen, and is at the same time completely decomposed into trimethylamine and piperidinecarboxylic and succinic acids. These reactions led Marino-Zuco to assign to the base and its oxidation product the following formulæ:



Chrysanthemine



Oxychrysanthemine

ALKALOIDS OF *CONIUM MACULATUM* (HEMLOCK)

The common hemlock, *Conium maculatum*, contains a series of six alkaloids. Power and Tutin have found that a similar mixture of alkaloids probably occurs in fool's parsley.[1] A volatile alkaloid resembling coniine also occurs in certain aroids.[2] The toxic properties of hemlock juice have been known from very early times; thus it was the chief ingredient in the poison administered to criminals by the Greeks, and several references to the poisonous nature of hemlock extracts occur in classical literature. The value

[1] *Æthusa Cynapium. Journ. Amer. Chem. Soc.* 1905, **27**, 1461.

[2] Hébert and Heim, *Bull. Soc. chim.* 1898 [iii], **17**, 664.

of hemlock as a medicine was recognised by the Anglo-Saxons, but its modern employment is due to the recommendations of Storck in 1760 and Harley in 1867, although it has to some extent fallen into disrepute owing to the uncertainty of action shown by galenical preparations made from it.[1] The leaves and the unripe fruits are the parts of the plant used in medicine. Altogether six different but closely related alkaloids have been isolated from hemlock and named as follows:

Coniine, $C_8H_{17}N$.	*γ-Conicëine*, $C_8H_{15}N$.
N-*Methyl*-d-*coniine*, $C_8H_{16}N.CH_3$.	*Conhydrine*, $C_8H_{17}ON$.
N-*Methyl*-l-*coniine*, $C_8H_{16}N.CH_3$.	*ψ-Conhydrine*, $C_8H_{17}ON$.

Estimation of the Total Alkaloids of Hemlock. The following method is prescribed in the United States Pharmacopœia (8th Revision) for the estimation of "coniine" (really the total alkaloids) in hemlock fruits.

Ten grammes of the fruits in No. 60 powder are mixed with 100 c.c. of a mixture of ether 98 parts, alcohol 8 parts, and ammonia water (sp. gr. 0·958 at 25°) 3 parts, and allowed to stand with occasional shaking during four hours. Fifty c.c. of the clear liquid (= 5 grm. of the fruits) are decanted into a beaker, sufficient *N*-sulphuric acid added to give an acid reaction, and the ether evaporated; 15 c.c. of alcohol are then added, and the mixture set aside during two hours to allow ammonium sulphate to deposit. The liquid is filtered off, the filter and residue being washed with a little alcohol and the washings added to the filtrate, to which sodium carbonate solution is added until it remains faintly acid. The filtrate is then evaporated on the water-bath to 3 c.c., its own volume of water added, and 2 drops of *N*-sulphuric acid. This is then washed twice, using 15 c.c. of ether each time, transferred to a separator, sodium carbonate solution added until the liquid is slightly alkaline, and the alkaloids extracted by shaking successively with 15, 15, and 10 c.c. of ether. The combined ether solutions are run into a tared beaker, 5 per cent. hydrochloric acid added

[1] *Pharmacographia*, London, 1879, 299.

drop by drop until the reaction is acid, and the ether evaporated on the water-bath. The residue is evaporated twice with 3 c.c. of alcohol to remove excess of acid and finally dried at a temperature not exceeding 60° and weighed. This weight multiplied by 0·777 × 20 gives the percentage of total alkaloids in the fruits. The United States Pharmacopœia requires that it should not be less than 0·5 per cent.

Fluid Extract of Hemlock Fruits. For this preparation the United States Pharmacopœia prescribes the following process. Ten c.c. of the extract are placed in an evaporating dish containing a little clean sand, and evaporated to dryness. The residue is then placed in a flask with 100 c.c. of a mixture of ether 100 c.c., alcohol 7 c.c., and ammonia water (sp. gr. 0·958 at 25°) 3 c.c., the solvent being first used in portions to wash out the dish. After standing one hour with occasional agitation 50 c.c. of the clear liquid in the flask are decanted, and the process continued as described above for hemlock fruits. The fluid extract should contain 0·45 grm. of total alkaloids in 100 c.c.

An alternative method of estimating the alkaloidal constituents of hemlock is that devised by Cripps [1] and improved by Farr and Wright.[2] Five grammes of the finely powdered fruits are mixed with sand and exhausted by percolation with a mixture of 95 per cent. alcohol 25 c.c., chloroform 15 c.c., and chloroform saturated with hydrogen chloride 10 c.c. The extract is shaken twice with 25 c.c. of distilled water, the latter clarified by shaking once with a few cubic centimetres of chloroform, made alkaline by addition of caustic soda solution, and the liberated bases extracted by agitation with chloroform, the latter being then run into excess of a saturated solution of hydrogen chloride in chloroform. The solvent is distilled off, and the residue of hydrochlorides dried at 90° in a current of air and weighed. Farr and Wright [3] have shown that this process gives good results with galenical preparations of the drug.

The alkaloidal values (expressed as total hydrochlorides) of

[1] *Pharm. Journ.* 1887–8 [iii], **18**, 13, 511.
[2] *Ibid.* 1891 [iii], **21**, 857, 936.
[3] *Loc. cit.*

the various parts of the plant have been investigated by Farr and Wright,[1] who find that the stem contains 0·01 to 0·06, leaves 0·03 to 0·18, flowers 0·086 to 0·236, and green fruit 0·725 to 0·975 per cent. The fruit, which is the part mostly used in medicine, appears to contain most alkaloid when from three-fourths to full grown. An examination of many commercial samples of the drug as imported into the United Kingdom in 1904 [2] showed that these contained percentages of alkaloid varying from 0·096 to 0·832, whereas English fruits collected by the authors yielded 1·05 to 3·57 per cent.

Coniine, $C_8H_{17}N$. This alkaloid was first isolated by Giesecke in 1827. For many years its formula was thought to be $C_8H_{15}N$, and its true composition was first demonstrated by Hofmann.[3]

Coniine is most readily obtained from crushed hemlock fruits by allowing these to stand with dilute sodium carbonate solution and steam-distilling the mixture. The distillate contains the mixed volatile alkaloids with ammonia. It is neutralised with hydrochloric acid, evaporated to dryness, and the dry residue extracted with alcohol, which dissolves the alkaloidal hydrochlorides and some ammonium chloride. The latter is removed by adding dry ether to the alcoholic solution. The residue left on evaporation of the alcohol-ether solution is dissolved in cold water, ether added, and the bases liberated by the addition of potash, and the whole shaken. The ethereal solution is dried with potassium carbonate and the ether distilled off at a low temperature, when the mixed alkaloids remain as an oily liquid. These may be separated to a certain extent by fractional distillation in a current of hydrogen, conhydrine being left as a residue if the temperature does not exceed 190°; the coniine and γ-conicëine passing over together in the first fractions. For the separation of coniine from conicëine Wolffenstein [4] recommends the conversion of the mixed bases into hydrochlorides. These are dried and extracted with acetone,

[1] *Pharm. Journ.* 1895–6 [iv], **1**, 89.
[2] *Loc. cit.* 1904 [iv], **18**, 185.
[3] *Berichte*, 1881, **14**, 705.
[4] *Ibid.* 1894, **27**, 2615.

which dissolves conicëine hydrochloride, leaving the coniine salt, from which the base may then be regenerated.

For final purification the coniine should be converted into the *d*-hydrogen tartrate by dissolving 135·5 grm. of the product in a solution of 160 grm. of *d*-tartaric acid in 450 grm. of water, kept cool. It is sometimes necessary to start crystallisation by adding a crystal of the desired salt. von Braun distils the crude mixed alkaloids until the temperature rises to 190°, benzoylates the distillate, extracts the tertiary bases by shaking an ethereal solution with dilute acid, pours the concentrated ethereal solution into light petroleum to precipitate most of the benzoyl-4-aminobutyl propyl ketone formed by the action of benzoyl chloride on conicëine, distils the solvent from the filtrate and collects from the residue the fraction boiling at 200°–210° under 16 mm. pressure, which is nearly pure benzoylconiine. From this a mixture of *d*- and *l*-coniines is obtained by hydrolysis.[1]

Coniine when pure is a colourless, strongly alkaline liquid, having a peculiar penetrating odour and a burning taste ; it boils at 166°–167°, has D^0 0·8626 and D^{19} 0·8438, refractive index n_D 1·4505, and is dextrorotatory, $[\alpha]_D^{19} = +15{\cdot}7°$. When cooled to − 2° it solidifies to a soft crystalline mass.

Coniine is slightly soluble (1 in 90) in cold water, but is less soluble in hot water, so that a clear cold solution becomes turbid when warmed. On the other hand, the base dissolves about 25 per cent. of water at atmospheric temperature. It mixes with alcohol in all proportions, is readily soluble in ether, but much less so in chloroform. Coniine slowly oxidises in the air. The ordinary salts crystallise well and are soluble in water or alcohol. The hydrochloride, B.HCl, crystallises from water in large rhombs, m.p. 220°, and the *d*-acid tartrate, $B.C_4H_6O_6.2H_2O$, in large rhombic crystals, m.p. 54°. The platinichloride, $(B.HCl)_2.PtCl_4.H_2O$, separates from concentrated solution as an oil, which solidifies to a mass of orange-yellow crystals, m.p. 175° (*dry*). The aurichloride, $B.HAuCl_4$, crystallises on standing, m.p. 77°.

[1] *Berichte*, 1905, **38**, 3108.

The picrate forms small yellow needles, m.p. 75°. Coniine dissolves in carbon disulphide, forming a complex thiocarbamate.[1] It gives no coloration with sulphuric acid. The precipitate afforded by potassium cadmium iodide solution is crystalline, whilst that given by nicotine with this reagent is amorphous. Sodium nitroprusside gives a deep red colour which disappears on warming, but reappears on cooling, and is changed to blue or violet by aldehydes.[2]

Constitution. When coniine hydrochloride is distilled with zinc dust a new base, conyrine, is produced, which has all the properties of a propylpyridine, and which Ladenburg [3] proved to be *α*-propylpyridine. At a later date Ladenburg showed that the distillate from coniine hydrochloride and zinc dust contained in addition to conyrine a stereoisomeride of *d*-coniine, which differs from the latter mainly in having a higher dextrorotation, and which he called *iso*coniine.[4] According to Wolffenstein [5] *iso*coniine is a mixture of *d*-coniine with *i*-coniine, but according to Ladenburg this is impossible, since *iso*coniine has a higher rotation than *d*-coniine, and he finds that on reducing methylpicolylalkine, $C_5H_4N.CH_2.CHOH.CH_3$, with phosphorus and hydriodic acid, treating the product with zinc dust and water, and reducing the propylpyridine so formed with sodium and alcohol, the propylpiperidine so produced has $[\alpha]_D^{18\cdot5}$ +17·85° and is identical with *iso*coniine.[6] Hofmann [7] reduced conyrine by means of phosphorus and hydriodic acid to coniine, which, however, was optically inactive.

These and other reactions indicated that coniine is *α*-propylpiperidine. Ladenburg confirmed this by synthesising coniine by reducing *α*-allylpyridine with sodium in alcohol.[8] The product was optically inactive, but was resolved into *d*- and *l*-coniines, the former identical with the natural alkaloid, by fractional crystalli-

[1] Melzer, *Arch. Pharm.* 1898, **236**, 701.
[2] Gabutti, *Chem. Soc. Abstr.* 1906, ii, 711.
[3] *Berichte*, 1884, **17**, 772, 1121, 1676; 1885, **18**, 1587.
[4] *Ibid.* 1893, **26**, 854; 1894, **27**, 853, 859; 1896, **29**, 2706.
[5] *Ibid.* 1894, **27**, 2615; 1896, **29**, 1956.
[6] *Ibid.* 1907, **40**, 3734. [7] *Ibid.* 1884, **17**, 831.
[8] *Ibid.* 1886, **19**, 439, 2582; 1889, **22**, 1403.

sation of the *l*-hydrogen tartrates. More recently Ladenburg has stated that synthetic *d*-coniine so obtained has a higher rotation than the natural alkaloid, probably due to the presence of *iso*-coniine (*see above*), but that the rotation can be reduced to that of the natural alkaloid by long-continued heating at 290°.[1]

***N*-Methyl-*d*-coniine,** $C_8H_{16}N.CH_3$. This alkaloid is stated to occur in hemlock in minute quantities.[2] According to Wolffenstein it remains with γ-conicëine, when the latter is separated from coniine by the fractional crystallisation of the acid tartrates. von Braun separates the tertiary bases (methylconiines) from crude coniine by benzoylating the latter, dissolving the product in ether, and extracting the tertiary bases with dilute acid.[3] It has been obtained synthetically by heating coniine with potassium methyl sulphate.[4] It is a colourless oily coniine-like liquid, b.p. 173°–174°, $D^{24\cdot3}$ 0·8318 and $[\alpha]_D^{24\cdot3} + 81\cdot33°$. The ordinary salts are crystalline; the hydrochloride, B.HCl, forms masses of needles, m.p. 188°; the platinichloride, $B_2.H_2PtCl_6$, has m.p. 158°.

***N*-Methyl-*l*-coniine** was obtained by Ahrens[5] from residues left in the preparation of coniine by crystallisation of the hydrobromides, that of *d*-coniine being much less soluble in water, or by converting coniine into the nitroso-compound. It is a colourless, coniine-like liquid, b.p. 175·6°/767 mm., D_{20}^{20} 0·8349, $[\alpha]_D^{20} - 81\cdot92°$. The hydrochloride, B.HCl, forms needles, m.p. 191°–192°, the hydrobromide, B.HBr, crystallises in leaflets, m.p. 189°–190°, the platinichloride in orange crystals, m.p. 153°–154°, and the aurichloride in brilliant leaflets, m.p. 77°–78°.

The relationship of von Braun's methylconiine[6] to the foregoing has not yet been settled. A series of alkylconiines has been prepared and described by Scholtz.[7]

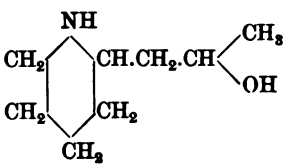
Conhydrine, $C_8H_{17}ON$. This oxygenated alkaloid was first found in hemlock by Wertheim.[8] In the extraction of coniine from

[1] *Berichte*, 1906, **39**, 2486.
[2] Planta and Kekulé, *Annalen*, 1854, **89**, 150.
[3] *Berichte*, 1905, **38**, 3108. [4] Passon, *Berichte*, 1891, **24**, 1678.
[5] *Berichte*, 1902, **35**, 1330. [6] *Loc. cit.*
[7] *Berichte*, 1904, **37**, 3627; 1905, **38**, 595. [8] *Annalen*, 1856, **100**, 1329.

hemlock (p. 26) conhydrine is also removed and may be separated by dissolving the two alkaloids in a little ether and freezing out the conhydrine, or by distilling the crude coniine, when conhydrine remains behind in the retort if the temperature is kept below 190°. It may be recrystallised from ether.

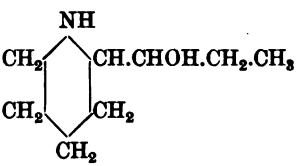
Conhydrine is a solid, crystalline, strongly basic substance, m.p. 121°, b.p. 226°, $[\alpha]_D + 10°$, which closely resembles coniine in its chief properties. It forms crystalline salts; the aurichloride forms small rhombs or prisms, m.p. 133°.

Constitution. Conhydrine yields a benzoyl derivative, m.p. 132°. When heated with hydrochloric acid, conhydrine yields a mixture of α-, β, and γ-conicëines with some *iso*allylpiperidine. β-conicëine on reduction by sodium in alcohol yields *l*-coniine, so that in this way conhydrine may be converted into *l*-coniine. On oxidation with chromic acid it is converted into *l*-piperidine-2-carboxylic acid, which indicates that the hydroxyl group of the alkaloid is in the side-chain, whence Willstätter [1] suggested formula (I) for conhydrine. The substance corresponding to this formula has, however, been synthesised recently by Löffler and Tschunke [2] and shown not to be identical with conhydrine, and on this ground these authors have revived the alternative formula (II), first suggested by Engler and Baur.[3]



(I)

Conhydrine (Willstätter)



(II)

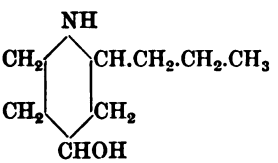
Conhydrine (Engler and Baur)

ψ-Conhydrine, $C_8H_{17}ON$, was found in hemlock by Merck and was examined by Ladenburg and Adam.[4] It closely resembles its isomeride conhydrine, with which it occurs as a residue after the removal of the liquid alkaloids by distillation (*see* p. 26) and from which it can be separated by crystallising the mixed hydrochlorides,

[1] *Berichte*, 1901, **34**, 3166.
[2] *Ibid.* 1909, **42**, 929.
[3] *Ibid.* 1894, **27**, 1777.
[4] *Ibid.* 1891, **24**, 1671.

that of conhydrine separating first from alcohol. The base has been re-examined recently by Löffler,[1] and many of the data previously recorded regarding it shown to be inaccurate. It crystallises from dry ether in slender needles, m.p. 105°–106°, b.p. 236°–236·5°, $[\alpha]_D$ + 10·98° to + 11·06°, or from wet ether in plates, m.p. 80° (*approx.*), and is a strongly alkaline base. The hydrochloride, m.p. 212°–213°, crystallises from alcohol; the aurichloride, $B.HAuCl_4$, m.p. 133°–134°, is not identical with conhydrine aurichloride as was formerly supposed: the platinichloride, m.p. 185°–186°, forms slender golden-yellow needles.

ψ-Conhydrine is a hydroxyconiine since on treatment with hydriodic acid it yields iodoconiine, which on reduction yields *d*-coniine. With phosphoric oxide it yields ψ-conicëine, $C_8H_{15}N$ (*see* p. 33). ψ-Conhydrine is not stereoisomeric with conhydrine, but according to Löffler probably contains the hydroxyl group in the γ-position thus:



ψ-Conhydrine (Löffler)

but this is difficult to reconcile with Willstätter's statement[2] that ψ-conhydrine, like conhydrine, yields piperidine-2-carboxylic acid on oxidation.

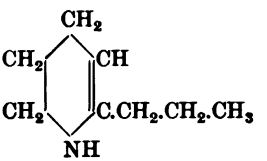
γ-Conicëine, $C_8H_{15}N$. This base was isolated by Wolffenstein from commercial coniine by the method already described.[3] In using von Braun's method of separation the γ-conicëine on benzoylation passes into benzoyl-4-aminobutyl propyl ketone, $COPh.NH.CH_2.CH_2.CH_2.CH_2.CO.C_3H_7$, which remains with the benzoylconiine after extraction of the tertiary bases, and can be partly separated from it by concentrating the ethereal solution and pouring into light petroleum, in which it is insoluble. The rest

[1] *Berichte*, 1909, **42**, 116.
[2] *Ibid.* 1901, **34**, 3166.
[3] *Ibid.* 1895, **28**, 302.

remains in the flask, from which the benzoylconiine is distilled. It yields conicëine on hydrolysis by hydrochloric acid.

γ-Conicëine is a coniine-like oil, b.p. 171°–172°/746 mm., $D^{22\cdot5}$ 0·8825, almost insoluble in water, strongly alkaline and optically inactive. Its salts are crystalline; the hydrochloride, m.p. 143°, is hygroscopic; the hydrobromide, m.p. 139°, is readily soluble in acetone; the aurichloride, m.p. 69°, and the picrate, m.p. 72°, are precipitated as oils, but soon become crystalline. The platinichloride has m.p. 192°. The cadmium iodide salt, $B.HI.CdI_2$, m.p. 146°–147°, crystallises from water in long needles.

γ-Conicëine is a secondary base, and on reduction yields *i*-coniine. It was prepared by Hofmann by the action of alkalis on bromoconiine, and according to Löffler is formed by the action of fuming hydrochloric acid on conhydrine (p. 29). These reactions are explained by the following constitution suggested by Lellmann and Wolffenstein:



γ-Conicëine

γ-Conicëine has been synthesised by Gabriel by hydrolysing δ-phthaliminobutyl propyl ketone.[1]

The Conicëines. Six of these products have been obtained in various ways from coniine, conhydrine, and ψ-conhydrine; their names and chief characters are as follows:[2]

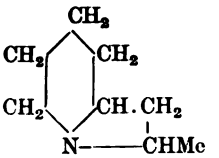
α-, *β-*, and *γ-Conicëines*, produced simultaneously by the action of fuming hydrochloric acid at 220° on conhydrine. With phosphoric oxide β-conicëine is the chief product and no α-conicëine is formed.[3] Löffler assigns the following formula to α-conicëine:[4]

[1] *Berichte*, 1909, **42**, 4059.

[2] Hofmann, *Berichte*, 1885, **18**, 16, 27, 112; Lellmann, *Annalen*, 1890, **259**, 197.

[3] Löffler, *Berichte*, 1905, **38**, 3326.

[4] *Berichte*, 1904, **37**.1879.

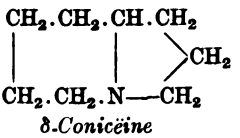


a-Conicëine

According to Löffler and Friedrich [1] β-conicëine is *l*-α-allylpiperidine. On reduction with sodium in alcohol it yields *l*-coniine.

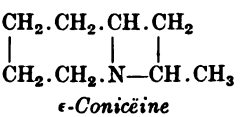
The constitution of γ-conicëine has been discussed already (*see* p. 32).

δ-*Conicëine* is formed by the action of sulphuric acid on bromoconiine. The following constitution was assigned by Lellmann [2] to δ-conicëine, and this has been confirmed by synthesis of the inactive form of this base by Löffler's collaborators [3] by reducing 2-piperolidine, obtained by distilling piperidylpropionic acid:



δ-*Conicëine*

ε-*Conicëine* is formed by the action of alkalis on iodo- or bromoconiine. Lellmann's ε-conicëine has been shown by Löffler [4] to be a mixture of two stereoisomeric bases having the formula



ε-*Conicëine*

ε-Conicëine contains two asymmetric carbon atoms, and the two stereoisomerides consist of the (— —) and (+ —) forms and may be separated by crystallisation of the *d*-tartrates. This dicyclic system has been named conidine by Löffler, and the two isomerides are called 2-methylconidine and *iso*-2-methylconidine.

ψ-*Conicëine* is obtained by dehydrating ψ-conhydrine with phosphoric oxide.[5]

[1] *Berichte*, 1909, **42**, 107. [2] *Loc. cit.* [3] *Berichte*, 1909, **42**, 94, 3420.
[4] *Ibid.* 1909, **42**, 948. [5] Löffler, *ibid.* 1909, **42**, 116.

The principal properties of these isomerides are shown in the following table :

Name	Boiling-point	Melting-point of aurichloride	Specific rotation, $[\alpha]_D$	Relative density	Amino-character
α-Conicëine	158°	196°	+ 18·4°	0·8930 at 15°	Tertiary
β-Conicëine	168° (m.p. 41°)	122·5°	− 52·99°	0·8519 at 50°	Secondary
γ-Conicëine	171°–172°	69°	inactive	0·8825 at 22·5°	Secondary
l-δ-Conicëine	158°	207°	lævorotatory	0·896 at 23°	Tertiary
i-δ-Conicëine	161°	192°	inactive	0·904 at 15°	Tertiary
ε-Conicëine composed of	150°–151°	178°	+ 42·34°	0·8836 at 15°	Tertiary
2-methylconidine and	151°–154°	167°–168°	+ 67·4°	0·8856 at 15°	Tertiary
iso-2-methylconidine	143°–145°	198°–199°	− 87·34°	0·8624 at 15°	Tertiary
ψ-Conicëine	171°–172°	(oily)	+ 122·6°	0·8776 at 15°	Secondary

PHYSIOLOGICAL ACTION OF HEMLOCK ALKALOIDS

All the alkaloids contained in hemlock are poisonous. They produce paralysis of the motor nerve terminations and stimulation followed by depression of the central nervous system, though some authorities maintain that they exert little or no central action. They cause nausea and vomiting at an early stage of their action. In frogs they have a curare-like action on motor nerve terminations, but in mammals this is exhibited to a much less extent. Large doses cause slowing of the heart's action. Respiration is generally accelerated and deepened at first, but eventually becomes slow and laboured and finally ceases, while the heart is still strong and consciousness has just disappeared. According to Albahary and Löffler *d*- and *l*-coniines are identical in physiological activity. By the introduction of a double linking, as in γ-conicëine, the toxicity is greatly increased, whilst by the insertion of a hydroxyl group, as in the conhydrines, it is reduced.

ALKALOID OF *PIPER* SPP.

Piperine, $C_{17}H_{19}O_3N$. This alkaloid occurs in several plants belonging to the natural order Piperaceæ. It was isolated in 1819 by Oersted from the fruits of *Piper nigrum*, which constitute the black and white peppers of commerce. In 1879 Flückiger and Hanbury [1] showed that it was also contained in the two varieties of long pepper derived from *Piper longum* and *Piper officinarum*, whilst in 1881 Stenhouse obtained it from Ashantee black pepper, which consists of the fruits of *Piper Clusii*. Piperine is also said to occur in the berries of *Schinus Molle*.

The amount of piperine contained in commercial pepper is of importance as affording an indication of the freedom of the spice from adulterants.

It may be estimated by mixing a weighed quantity of the pepper with slaked lime, adding enough water to form a stiff paste, which is then dried at 100° and exhausted in a Soxhlet extractor with hot ether contained in a tared flask. The ether is distilled off, the residue dried at 100° and weighed as piperine.

The following table shows the amount of alkaloid contained in some typical commercial varieties of pepper :

Origin of pepper	Variety	Moisture per cent.	Piperine calc. on dry material, per cent.			
			Stevenson	Blyth	Heisch	Cazeneuve and Calliol
Sumatra	black	10·1–14	7·14	4·7	—	8·1
Singapore	black	—	—	—	7·14	7·15
,,	white	—	—	5·6	6·14	9·15
Penang	black	9·53	—	5·57	6·04	5·24
Siam	white	—	—	—	5·13	—
,,	long	14	1·16	1·8	1·71	—
Trang	black	11·6–14	6·62	4·6	4·05	—

The alkaloid may be prepared by a process similar to that described above for its estimation, but more economically by exhausting the finely powdered fruits with 95 per cent. alcohol, the

[1] *Pharmacographia*, p. 584.

solvent being removed by distillation, and the extract so obtained shaken with solution of soda for the removal of resin. The insoluble residue is dissolved by boiling with 95 per cent. alcohol, and from this solution piperine crystallises out on cooling and can be purified by a second crystallisation from alcohol.

The pure alkaloid crystallises from alcohol in long monoclinic needles, m.p. 128°–129·5°, $[\alpha]_D$ 0°. It is slightly soluble in water, more so in alcohol, ether, or chloroform. The alcoholic solution has a pepper-like taste. Its solutions are not alkaline, and it forms salts only with strong acids; the platinichloride, $B_4.H_2PtCl_6$, forms orange-red needles. Strong sulphuric acid gives a dark red solution with piperine, and nitric acid, on warming, a resin which dissolves in aqueous potash with a deep red colour. Iodine in potassium iodide added to an alcoholic solution of the base in presence of a little hydrochloric acid gives a characteristic periodide, $B_2.HI.I_2$, crystallising in lustrous, steel-blue needles, m.p. 145°, slightly soluble in alcohol, easily so in chloroform. Piperine is rarely employed in medicine; it exerts an action similar to that of quinine, but is much less active and rather uncertain in effect. Pepper is used in medicine only as a carminative.

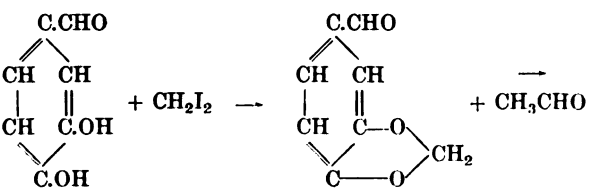
Constitution. The action of hydrolytic agents on piperine was first investigated by Anderson,[1] who observed that when boiled with alkalis it was decomposed with the formation of a base and an acid. Some years later Babo and Keller[2] effected the same decomposition by means of alcoholic potash and named the products piperidine and piperic acid respectively.

$$\underset{\textit{Piperine}}{C_{17}H_{19}O_3N} + H_2O = \underset{\textit{Piperidine}}{C_5H_{11}N} + \underset{\textit{Piperic acid}}{C_{12}H_{10}O_4}.$$

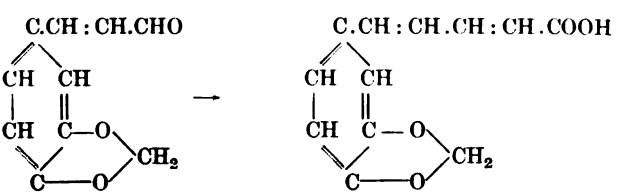
The basic decomposition product had already been obtained by Wertheim and Rochleider,[3] but its constitution was not ascertained with certainty until its synthesis was effected by Ladenburg from pentamethylenediamine, and by the reduction of pyridine, showing it to be hexahydropyridine.

[1] *Annalen*, 1850, **75**, 82; **84**, 345. [2] *Journ. Prakt. Chem.* 1857, **72**, 55.
[3] *Annalen*, 1845, **54**, 255.

Piperic acid, $C_{12}H_{10}O_4$, is obtained by the hydrolysis of piperine with alcoholic potash in the form of its potassium salt, which crystallises in shining prisms. The free acid is insoluble in water and crystallises from alcohol in long needles, m.p. 217°. Its salts are usually insoluble in water. The acid is unsaturated and readily takes up four atoms of bromine or hydrogen. Potassium permanganate oxidises it with the formation of piperonal, whilst on fusion with potash it furnishes protocatechuic, acetic, and oxalic acids. These and other reactions led Fittig [1] to assign to the acid the formula given below, which represents it as a substituted methylenic ether of protocatechuic acid. The validity of this formula was finally proved by Ladenburg and Scholz,[2] who succeeded in synthesising the acid by the following series of reactions. Protocatechuicaldehyde was treated with methylene iodide in presence of alcoholic potash, giving piperonal; the latter by condensation with acetaldehyde in presence of caustic soda was converted into piperylacrolein, which in its turn with acetic anhydride (Perkin's reaction) gave the corresponding unsaturated acid identical with piperic acid.



Protocatechuicaldehyde *Piperonal*



Piperylacrolein *Piperic acid*

Finally, as had already been shown by Rugheimer,[3] piperidine, when treated with piperoyl chloride in benzene solution, furnished piperine.

[1] *Annalen*, 1885, **227**, 31.
[2] *Berichte*, 1894, **27**, 2958.
[3] *Ibid.* 1882, **15**, 1390.

According to Madan, piperine heated at 180° during sixty minutes passes into a colloidal form possessing a high refractivity $\mu_{H\gamma} = 1{\cdot}810$, and coefficient of dispersion $\mu_{H\gamma} - \mu_{H\alpha} = 0{\cdot}142$.[1]

ALKALOID OF *PIPER OVATUM*

Piperovatine, $C_{16}H_{21}O_2N$, was isolated by Dunstan and Garnett [2] from the stem and leaves of this West Indian plant, by percolating the ground plant with ether, distilling off the solvent and the volatile oil removed by the solvent, and extracting the residue with hot, dilute alcohol; on cooling, the filtrate deposits rosettes of colourless needles, m.p. 123°, soluble in alcohol, acetone, or chloroform, but sparingly so in dry ether. The alkaloid forms no salts. When heated with water at 160° a volatile base, which is probably a pyridine derivative, is formed, together with an acid and an oil having the odour of anisole.

The base is a temporary depressant of motor and sensory nerve fibres, and of sensory nerve terminations; it depresses the heart's action, and in frogs induces tetanic convulsions of the same nature as those produced by strychnine.

ALKALOIDS OF *NICOTIANA* SPP.

Members of this group of alkaloids have until recently only been found in species of Nicotiana, of which *N. tabacum*, the plant yielding commercial tobacco, exists in a large number of cultural varieties. It has been stated that the chief alkaloid of the group, nicotine, occurs in Indian hemp,[3] but as this product when prepared for smoking is frequently mixed with tobacco, it is probable that the nicotine in this instance was derived from admixed tobacco. It has long been suspected that the alkaloid piturine, which Liversedge obtained from the Australian plant *Duboisia Hopwoodii*,[4] was identical with nicotine, and this was proved to be correct by Rothera.[5]

[1] *Trans. Chem. Soc.* 1901, **79**, 926.
[2] *Ibid.* 1895, **67**, 94; *cf.* Dunstan and Carr, *Proc. Chem. Soc.* 1895, p. 177.
[3] Preobrachensky, *Pharm. Zeit.* 1876, p. 705.
[4] *Chem. News*, 1881, **43**, 124. [5] *Bio-Chem. Journ.* 1910, **5**, 193.

Altogether four alkaloids have been isolated from tobacco :

Nicotine, $C_{10}H_{14}N_2$.	Nicotimine, $C_{10}H_{14}N_2$.
Nicoteine, $C_{10}H_{12}N_2$.	Nicotelline, $C_{10}H_8N_2$.

According to Pictet and Court pyrrolidine and 1-methylpyrroline also occur in tobacco. The quantity of total alkaloids shows great variation, but does not as a rule exceed 6 per cent. in commercial tobacco, and averages about 4 per cent. In 1000 parts of total alkaloid Pictet and Rotschy found 20 of nicoteine, 5 of nicotimine, and 1 of nicotelline.[1]

For the isolation of the total alkaloids (commercial nicotine) the finely powdered tobacco leaves are exhausted with warm water and the extract concentrated, made alkaline by addition of a slight excess of lime or caustic soda, and steam-distilled. The distillate is neutralised, evaporated to a small bulk, made alkaline, and the liberated alkaloid shaken out with ether. The residue left after removal of the ether by distillation is dried in a current of hydrogen.[2]

Commercial nicotine is generally made from midribs of tobacco leaves which are removed in preparing tobacco for smoking. For use as an insecticide large quantities of " tobacco extract," which is merely an aqueous extract of waste tobacco, are manufactured, and this material is a convenient source of tobacco alkaloids.

Estimation. Tobacco is no longer employed therapeutically, but its content of " nicotine " (total alkaloids) is important in ascertaining the suitability of raw tobacco for the preparation of smoking tobacco, although this constituent is less important from this point of view than are the readiness with which the leaves burn, their aroma, content of moisture, &c. This estimation has also acquired great importance recently in view of the use of tobacco and tobacco extracts as agricultural insecticides. The Department of Agriculture of the United States of America some years ago instituted an inquiry into methods for the estimation of nicotine in tobacco, with the result that the process devised by Kissling [3] was recommended

[1] *Berichte*, 1901, **34**, 696. [2] Laiblin, *Annalen*, 1879, **196**, 130.
[3] *Zeit. Anal. Chem.* 1882, **21**, 64, 383 ; 1895, **34**, 413; 1896, **35**, 309, 731.

for adoption, although there are certain objections to it as regards concordance of the results obtained by different chemists using the same material. Thus in the case of a tobacco powder the determination of nicotine by five different chemists gave amounts varying from 0·53 to 0·81 per cent., and for the same tobacco extract percentages varying from 2·2 to 4·24.[1] This method is, however, that most commonly employed in practice, and is carried out in the following way :

The finely powdered tobacco is dried at a temperature not greater than 60°, and 20 grm. of the dry material are mixed with 10 c.c. of alcoholic soda made by dissolving 6 grm. of sodium hydroxide in 40 c.c. of water and diluting to 100 c.c. with 90 per cent. alcohol. This mass is extracted in a Soxhlet apparatus for five hours with ether, the solvent distilled off, and the residue mixed with 50 c.c. of 0·4 per cent. soda solution and steam-distilled. The distillate is titrated with *N*-sulphuric acid, using cochineal or phenacetolin as indicator.

In the case of tobacco extracts 5 grm. of the extract are mixed with 10 c.c. of alcoholic soda as above and enough pure ground calcium carbonate added to form a moist mass free from lumps. This is then packed in a Soxhlet apparatus and the rest of the process carried out as above. The question has been investigated recently by R. M. Chapin, of the U.S. Department of Agriculture, who suggests an improved form of Bertrand and Javillier's process,[2] which, from the point of view of the examination of tobacco extracts, has the merit of not including in the " nicotine " pyridine bases, should these have been added to the extract. The process is equally applicable to tobacco, the alkaloids having been extracted by Kissling's method. The directions given by Chapin [3] may be summarised thus. Enough extract to contain 1 to 2 grm. of nicotine is weighed out, and washed into a 500 c.c. round-bottomed flask, 1 to 1·5 grm. of solid paraffin, one or two pieces of pumice-stone, and excess of caustic soda solu-

[1] *U.S. Dept. Ag., Chem. Div., Bull.* No. 101 of 1910.
[2] *Bull. Sci. pharmacol.* 1909, **16**, 7.
[3] *Bull.* 133, *Bur. Anim. Ind., U.S. Dept. Agric.*, 1911.

tion added. This mixture is distilled in a current of steam and the distillate collected in 10 c.c. of dilute (1 to 4) hydrochloric acid, the flask containing the mixture being heated to keep the contents to a low volume without allowing the separation of solid matter. Distillation is continued until the distillate gives no opalescence with a drop of silicotungstic acid solution in presence of a drop of dilute hydrochloric acid, care being taken that the mixture in the flask remains strongly alkaline to the end. The distillate, which should still be acid, is diluted to a convenient known volume, thoroughly mixed, and then filtered, the first portion being rejected. An aliquot portion containing about 0·1 grm. nicotine is mixed with 3 c.c. of dilute (1 to 4) hydrochloric acid for each 100 c.c. of liquid, and 1 c.c. of a 12 per cent. solution of silicotungstic acid added for each 0·01 grm. of nicotine supposed to be present, and the mixture stirred thoroughly and set aside eighteen hours. The precipitate should then be completely crystalline, and when stirred should settle rapidly, indicating absence of pyridine bases. It is filtered and washed with cold water containing 1 c.c. of strong hydrochloric acid per litre, until the washings give no precipitate with a dilute aqueous solution of nicotine. The wet paper and precipitate are transferred to a platinum crucible, dried at a gentle heat, then carbonised, and finally ignited, this being completed by exposure during 5 to 10 minutes in the flame of a Teclu burner or blow-pipe. The weight of the residue multiplied by 0·114 gives the weight of nicotine in the aliquot part taken for analysis. If greater accuracy is required the nicotine silicotungstate may be collected in a Gooch crucible, washed as described, dried at 125°, and weighed ; this salt when anhydrous contains 10·12 per cent. of nicotine ; it is deliquescent, and the crucible containing it should be enclosed in a stoppered weighing bottle during cooling and weighing.

Nicotine, $C_{10}H_{14}N_2$. The alkaloid when pure is a colourless oil, b.p. 246·1°/730·5 mm. (*decomp.*), D_4^{10} 1·0180, $[\alpha]_D^{20}$ −166·39°,[1] with a pyridine-like odour and unpleasant burning taste ; it may be distilled unchanged with steam, in hydrogen, or under reduced pressure.

[1] *Cf.* Ratz, *Monats.* 1905, **26**, 1241.

Nicotine is miscible with water in all proportions below 60° and above 210°.[1] On admixture of water with nicotine heat is evolved, and a dihydrate formed.[2] The salts are dextrorotatory, easily soluble in water, and do not crystallise easily; the hydrochloride, B.HCl, has $[\alpha]_D + 102{\cdot}2°$; the sulphate, $B_2.H_2SO_4$, $[\alpha]_D + 84{\cdot}8°$, and acetate, $[\alpha]_D + 110{\cdot}29°$.

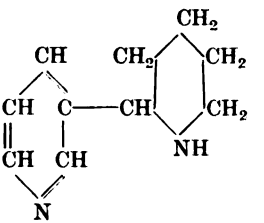
When aqueous solutions of nicotine hydrochloride or sulphate are heated in sealed tubes at 180°–250° they become optically inactive.[3] The platinichloride is a yellow microcrystalline substance of indefinite melting-point. The picrate, $B.2C_6H_2(NO_2)_3OH$, forms short prisms, m.p. 218°, and is characteristic.

Nicotine may be detected by the formation with aqueous solutions of mercuric chloride of a white crystalline precipitate, by the black precipitate formed under similar conditions with potassium platinic iodide, and the crystalline periodide formed when solutions of the base in ether are mixed with iodine dissolved in ether. The appearance and melting-point of the picrate are characteristic. These reactions are of importance as distinguishing nicotine from coniine, with which base the tobacco alkaloid is likely to be confounded.

Constitution. The presence of a pyridine nucleus in nicotine was established by Huber,[4] Weidel,[5] and Laiblin,[6] who, using different oxidising agents, obtained from the base nicotinic acid (β-pyridinecarboxylic acid). Further evidence of this was afforded by the ready formation of a hexahydronicotine by reduction of the base by sodium and amyl alcohol.[7] The empirical formula of nicotine may therefore be extended thus, $C_5H_4N.C_5H_{10}N$, and most of the recent work has been devoted to the determination of the nature of the $C_5H_{10}N$ residue. The empirical composition of this group is identical with that of piperidine, and the behaviour of

[1] Hudson, *Zeit. phys. Chem.* 1904, **47**, 113.
[2] Tsakalotos, *Bull. Soc. chim.* 1909 [iv], **5**, 397.
[3] Pictet and Rotschy, *Berichte*, 1900, **33**, 2353.
[4] *Annalen*, 1867, **141**, 271.
[5] *Ibid.* 1873, **165**, 328.
[6] *Berichte*, 1877, **10**, 2136.
[7] Liebricht, *ibid.* 1886, **19**, 2587.

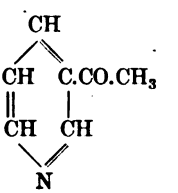
nicotine in certain reactions is well explained if it be assumed to be an α-piperidyl-β-pyridine, thus :



and for a long time this view of its structure was commonly accepted. Laiblin,[1] however, found that zinc nicotine chloride when distilled with lime gave a mixture of pyridine, methylamine, and pyrrole : the formation of the two latter substances from a partially reduced dipyridyl is inexplicable. Later Blau and Herzig and Meyer observed that nicotine when heated with hydriodic acid at 300° gave off a molecule of methylamine, so furnishing evidence of the existence of the group : $N.CH_3$, and the dipyridyl formula was finally disposed of by Blau, who prepared $\alpha : \beta$-dipiperidyl and showed that it was not identical with hexahydronicotine.[2] The reaction which has afforded most information regarding the structure of the side-chain of nicotine is that of bromine on the base, which has been investigated by Pinner.[3] The derivatives obtained in this reaction may be grouped as follows :

In acetic acid.	*In hydrobromic acid at* 100°.
↓	↓
Dibromoxydehydronicotine.	Dibromodioxydehydronicotine.
↓	↓
Dibromocotinine, $C_{10}H_{10}Br_2ON_2$.	Dibromoticonine, $C_{10}H_8Br_2O_2N_2$.

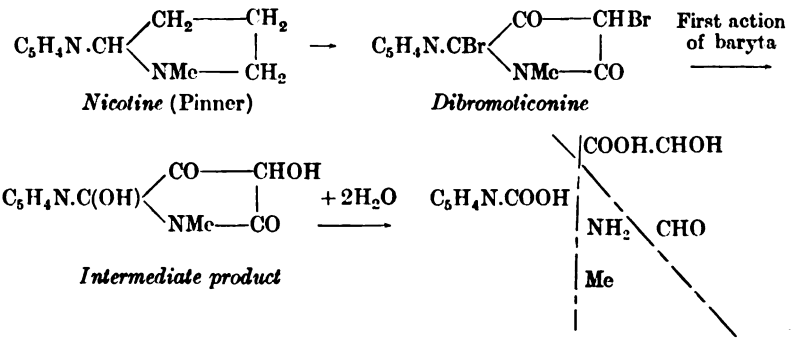
Dibromocotinine when warmed with alkalis furnished methylamine, oxalic acid, and β-methylpyridyl ketone.



[1] *Annalen*, 1879, **196**, 172. [2] *Berichte*, 1891, **24**, 326 ; 1893, **26**, 628, 1029.
[3] *Ibid.* 1892, **25**, 2816 ; 1893, **26**, 292, 769.

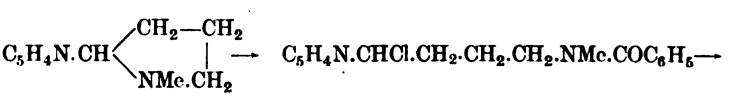
Dibromoticonine when warmed with baryta water at 100° gave methylamine, malonic acid, and β-pyridinecarboxylic acid.

These decomposition products showed that in all probability the side-chains of nicotine, dibromocotinine, and dibromoticonine consist of a series of three primary carbon atoms ending in a group : $N.CH_3$, and the difficulty experienced in reducing nicotine further than the hexahydro derivative makes it probable that the side-chain is closed, *i.e.* that it is a N-methylpyrrolidine, as represented in the formula given below. On this view of the structure of nicotine the formation of these decomposition products may be represented thus : [1]



The product COOH.CHOH.CHO by intramolecular change gives rise to malonic acid, $COOH.CH_2.COOH$.

Etard [2] observed that when benzoyl chloride reacted with nicotine a benzoyl derivative was formed which he regarded as formed by the replacement of an imino hydrogen atom by benzoyl. Pinner, however, showed that Etard's substance was derived from an isomeride of nicotine, which he named *meta*nicotine (*iso*nicotine), and whose formation he explained in the following way : [3]



$C_5H_4N.CH : CH.CH_2.CH_2.NMe.CO.C_6H_5.$

*Benzoyl*meta*nicotine* (*β-Pyridyl-N-methylbutyleneamine*)

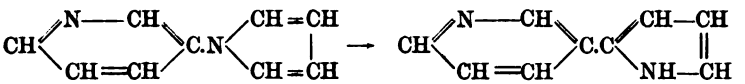
[1] Pinner, *loc. cit.* *Berichte*, 1894, 27, 1056, 2861.

[2] *Compt. rend.* 1893, 117, 170, 278.

Löffler and Kober[1] have shown that *meta*nicotine can be reconverted into nicotine.

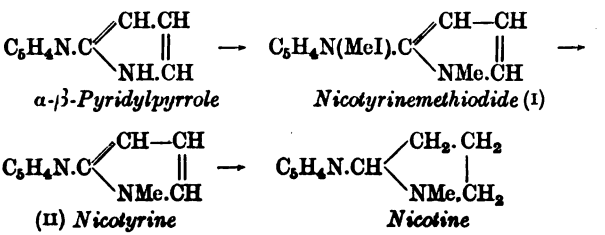
Pinner's formula explains equally well Blau's observation[2] that nicotine furnishes on reduction both a hexahydride and an octohydride, the latter being formed by the opening and reduction of the pyrrolidine ring. It also accounts for Pictet and Genequand's observation[3] that nicotine itself with methyl iodide forms nicotine methiodide, whilst nicotine hydriodide with this reagent gives *iso*nicotine methiodide, and that the latter on oxidation yields trigonelline (*see* p. 16).

The validity of Pinner's nicotine formula has been established by the synthesis of this alkaloid, accomplished by Pictet and collaborators.[4] Pictet and Crepieux found that when the pyridine amide of mucic acid is distilled it yields N-β-pyridylpyrrole, and the vapour of this at a red heat undergoes intramolecular change, yielding α : β-pyridylpyrrole, thus :



N-β-Pyridylpyrrole *α-β-Pyridylpyrrole*

The latter yields a potassium derivative, which reacts with methyl iodide, giving N-methyl-α : β-pyridylpyrrolemethiodide (I), which is identical with nicotyrine methiodide. Nicotyrine (II) can be obtained from nicotine by gently oxidising the latter with silver oxide or alkaline ferricyanides. Pictet and Rotschy found that nicotyrine methiodide on distillation with lime yielded nicotyrine. The latter is very difficult to reduce to nicotine :



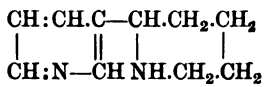
α-β-Pyridylpyrrole *Nicotyrinemethiodide* (I)

(II) *Nicotyrine* *Nicotine*

[1] *Berichte*, 1909, **42**, 3431. [2] *Loc. cit.* [3] *Berichte*, 1897, **30**, 2117.
[4] *Ibid.* 1895, **28**, 1911 ; 1898, **31**, 2018 ; 1900, **33**, 2355 ; 1904, **37**, 1225.

but this was eventually effected by Pictet and Rotschy with the formation of tetrahydronicotyrine, which proved to be identical with inactive nicotine, obtained by heating solutions of natural nicotine hydrochloride or sulphate in sealed tubes at 180°–250°. The synthetic base was resolved into the optical antipodes by fractional crystallisation of the *d*-ditartrate, and in this way *l*-nicotine identical with the natural alkaloid was obtained. The *d*-nicotine simultaneously prepared had b.p. 245·5°–246·5°/729 mm. D_4^{10} 1·0171 and $[\alpha]_D^{20} + 163·17°$.

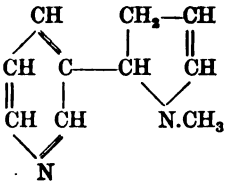
Nicotimine, $C_{10}H_{14}N_2$. This isomeride of nicotine was isolated by Pictet and Rotschy [1] from crude nicotine by treating the latter with nitrous acid, which converts nicotimine into the crystalline nitroso-compound, from which the alkaloid was regenerated as a colourless alkaline oil, b.p. 250°–255°, soluble in water. The hydrochloride, platinichloride, aurichloride, and mercurichloride are crystalline; the picrate forms thick prisms, m.p. 163°. Pictet [2] has suggested that nicotimine contains two pyridine nuclei, and is represented by the following formula:



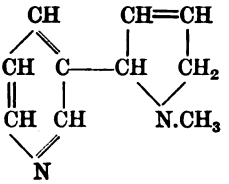
Nicotimine (Pictet)

Nicoteine, $C_{10}H_{12}N_2$. In addition to the foregoing, tobacco contains two alkaloids which are not volatile in steam and remain in the aqueous tobacco extract when this is steam-distilled, viz. nicoteine and nicotelline.[3] The former, separated by extraction with ether, is a colourless alkaline liquid, b.p. 266°–267°, $D_4^{12·5}$ 1·0778, $[\alpha]_D - 46° 41'$, miscible with water or ether, and furnishes well-crystallised lævorotatory salts: the picrate has m.p. 165°. Nicoteine forms a dimethiodide, is oxidised by nitric acid to nicotinic acid, and reacts as a pyrrole derivative, whence Pictet has suggested that it has the following constitution (I),[4] since on heating with silver oxide in water it yields dihydronicotyrine (II).

[1] *Berichte*, 1901, **34**, 696.
[2] *Arch. Pharm.* 1906, **244**, 375.
[3] Pictet and Rotschy, *Berichte*, 1901, **34**, 696.
[4] *Arch. Pharm.* 1906, **244**, 375.



(I) *Nicoteine*



(II) *Dihydronicotyrine*

When reduced with sodium in alcohol no nicotine is formed.

Nicotelline, $C_{10}H_8N_2$. This base, after the removal of nicoteine, is extracted from the aqueous liquid by chloroform, and on adding light petroleum to the latter crystallises out in colourless needles, m.p. 147°–148°, b.p. above 300°; its aqueous solution is neutral to litmus. The alkaloid yields a sparingly soluble di-chromate, does not decolorise acid permanganate, and appears not to be a pyrrole derivative.

Physiological Action of Tobacco Alkaloids

Nicotine is highly toxic. According to Mayor[1] the *lævo*-modification (natural nicotine) is twice as toxic as the *d*-form, and the physiological effects produced are also somewhat different. Nicotine affects both the central and peripheral nerves, increases the activity of the secreting glands, and causes constriction of the blood-vessels. It at first raises and then causes a fall in blood-pressure. It induces contraction of the stomach-walls, causing nausea and vomiting. The respiration is at first rapid and shallow, then somewhat deeper, but eventually becomes slower, and if not interrupted by convulsions gradually becomes weaker, death resulting finally from paralysis of the respiration.

Nicoteine appears to be more poisonous than *l*-nicotine.

The use of tobacco in medicine has ceased, but in recent years nicotine has been recommended for hypodermic injection in tetanus, and the salicylate as a remedy for certain skin affections.

[1] *Berichte*, 1904, **37**, 1233.

III. ALKALOIDS WITH DIHETEROCYCLIC NUCLEI

ALKALOIDS OF THE SOLANACEÆ

THE name "solanaceous alkaloids" should, strictly speaking, be applied to all the alkaloids obtained from solanaceous plants, but it has long been the practice to restrict it to the group of alkaloids dealt with in this section.

In this restricted sense the "solanaceous alkaloids" include nine members, and possibly one or two others not yet fully characterised. The names and formulæ assigned to these alkaloids are as follows:

Apoatropine and *Belladonnine*, $C_{17}H_{21}O_2N$.
Atropine and *Hyoscyamine*, $C_{17}H_{23}O_3N$.
nor-*Hyoscyamine*, $C_{16}H_{21}O_3N$.
pseudo-*Hyoscyamine*, $C_{17}H_{23}O_3N$.
Meteloidine, $C_{13}H_{21}O_4N$.
Scopolamine (*Hyoscine*), $C_{17}H_{21}O_4N$.
Tropacocaine, $C_{15}H_{19}O_2N$. (*See under* Coca, p. 109.)

The members of the group present several features in common; thus they are all esters of tropic, atropic, tiglic, or benzoic acid, yielding on hydrolysis one of these acids together with a basic alcohol such as tropine, *pseudo*-tropine, *nor*-tropine, scopoline, or teloidine. The alkaloids all yield characteristic and usually well-crystallised aurichlorides, which are extremely useful in defining and distinguishing the various members of the group. Their most characteristic property is, however, their mydriatic action; that is, the power of producing dilatation of the pupil of the eye when their aqueous solutions are applied to the conjunctiva. Only three of these alkaloids, atropine, hyoscyamine, and scopolamine, are used to any considerable extent in medicine.

The quantities of total alkaloids in the chief plants of this group are given in the following table:

Name of plant	Part of plant	Total alkaloids per cent.	Constituents	References
Atropa Belladonna	Leaves	0·15–0·60 av. 0·40	Chiefly hyoscyamine	—
	Roots	0·1–0·7 av. 0·50	,, ,,	Old roots may contain a little atropine (Gadamer)
	Seeds	0·831	,, ,,	—
	Whole plant	0·23–1·08	,, ,,	—
Datura spp.				
D. arborea	Leaves	0·44	Chiefly scopolamine, some hyoscyamine	Kircher, *Arch. Pharm.* 1905, **243**, 309; 1906, **244**, 66
	Seeds	—		
	Stems	0·23	in young stems, and roots	
D. fastuosa var. *niger*	Fruits	0·202	—	Andrews, *Trans. Chem. Soc.* 1911, **99**, 1876
	Leaves and branches	0·119	Scopolamine alone or with hyoscyamine	
	Roots	0·101		
var. *flor cærul. plen.*	Seeds	0·254	,, ,,	Schmidt, *Arch. Pharm.* 1906, **244**, 66
var. *flor alb. plen.*	Seeds	0·223	,, ,,	
D. Metel [1]	Fruits	0·12	Usually chiefly scopolamine; occasionally a little hyoscyamine or atropine	Kircher, *loc. cit.*; Andrews, *loc. cit.*; Schmidt, *Arch. Pharm*, 1910, **248**, 641
	Leaves	0·25–0·55		
	Roots	0·1 –0·22		
	Seeds	0·23–0·50		
D. meteloides [1]	Whole plant	0·4	Scopolamine, 0·13; atropine, 0·03; meteloidine, 0·07	Pyman & Reynolds, *Trans. Chem. Soc.* 1908, **93**, 2077
D. quercifolia	Leaves	0·42	Scopolamine and hyoscyamine	Kircher, *loc. cit.*
	Seeds	0·29		
D. Stramonium	Leaves	0·2 –0·45	Chiefly hyoscyamine	Feldhaus, *Arch. Pharm.* 1905, **243**, 328
	Roots	0·21–0·25	Hyoscyamine and scopolamine	
	Seeds	0·2 –0·48	Chiefly hyoscyamine	Andrews, *loc. cit.*
				Umney, *Pharm. Journ.* 1903 [iv], **15**, 492
Duboisia myoporoides [1]	Roots	—	Hyoscyamine, scopolamine, ψ-hyoscyamine	Merck, *Journ. Soc. Chem. Ind.* 1897, **16**, 515
Hyoscyamus spp.				
H. albus	Leaves	0·21–0·56	Hyoscyamine and scopolamine	
	Roots	0·1 –0·14		
	Seeds	0·16		
H. muticus	Leaves	1·4	Hyoscyamine	Dunstan & Brown, *Trans. Chem. Soc.* 1899 **75**, 72; 1901, **79**, 71
	Leaves and stems	0·6	,,	
	Seeds	0·87–1·34	,,	
	Stems	0·6	,,	Gadamer, *Arch. Pharm.* 1898, **236**, 704
H. niger	Leaves	0·045–0·08	Chiefly hyoscyamine with some scopolamine and atropine	Umney, *loc. cit.*
	Roots	0·15–0·17		
	Seeds	0·06–0·10		
	Tops	0·07–0·10		
H. reticulatus	Seeds	0·082	Hyoscyamine and possibly other alkaloids	*Bull. Imp. Inst.* 1911, **9**, 115
	Whole plant	0·116–0·240		
Scopolia carniolica (*S. atropoides*, *S. Hladnikiana*)	Rhizomes	0·43–0·51	Hyoscyamine, with possibly a trace of scopolamine	Dunstan & Chaston, *Pharm. Journ.* 1889 [iii], **20**, 461
				Ransom, *ibid.* p. 462
S. japonica [1]	Leaves	0·18	,	Schmidt and Henschke, *Arch. Pharm*, 1888 [iii], **26**, 185
				Watanabe, *Abst. Chem. Soc.* 1911, ii, 427

Carr and Reynolds (*Trans. Chem. Soc.* 1912, **101**, 946) have shown that these plants and also *Mandragora vernalis* contain *nor*hyoscyamine (p. 80).

The foregoing list is not exhaustive, but it includes all the plants which are or may be employed in the manufacture of these alkaloids; it may, however, be mentioned that traces of hyoscyamine or a similar substance have been observed in the lettuce [1] and the potato plant.

Atropine rarely, if ever, occurs as such in plants. This alkaloid is generally made from hyoscyamine, and therefore the plants richest in hyoscyamine and free from other alkaloids form the best sources of this substance. One of the best raw materials is *Hyoscyamus muticus*, which contains hyoscyamine only.[2] Much atropine is also stated to be made from hyoscyamine obtained from *Scopolia* rhizome. Scopolamine is usually obtained from one of the species of *Scopolia*, although a considerable quantity is doubtless also prepared from the residual liquors obtained in the preparation of hyoscyamine for atropine manufacture from other solanaceous plants. The mother liquors of atropine extraction from belladonna do not furnish scopolamine (L. Merck).

Preparation. The process employed for extracting these alkaloids depends to some extent on the material used, but the following method given by Guareschi is with slight modification generally applicable:

The material, reduced to a fine powder, is percolated with cold 90 per cent. alcohol (the "ordinary" methylated spirit supplied duty free in the United Kingdom, freed from excess of water by treatment with quicklime, answers well), the percolate being concentrated by distilling off the solvent, preferably under reduced pressure. The residual liquid is treated with a little chalk to neutralise the free acids, the mixture being allowed to stand for twenty-four hours. It is then filtered, made slightly acid by the admixture of dilute (0·5 per cent.) sulphuric acid, and shaken out with light petroleum or ether to remove fat, resin, &c. The clarified liquid is made just cloudy by addition of ammonia solution and again set aside for twenty-four hours, whereby a certain amount of a resinous

[1] Dymond, *Journ. Chem. Soc.* 1892, **61**, 90.
[2] Dunstan and Brown, *Journ. Chem. Soc.* 1899, **75**, 72, and 1901, **79**, 71

impurity is removed. The liquid may now be made distinctly alkaline with ammonia solution, when the mixed alkaloids will be precipitated as a white, amorphous powder, which, after washing with a little distilled water, may be dried by pressure, dissolved in alcohol, decolorised with animal charcoal, if necessary, and the alkaloids fractionally crystallised by the addition of water to the alcoholic solution, when they separate in the following order: atropine (if present), hyoscyamine, scopolamine. The fractions so obtained should then be recrystallised in like manner until they approximate in melting-point to the pure alkaloid.

For the isolation of the alkaloids on a small scale for purposes of investigation the following method gives good results: The finely ground material is exhausted by percolation with cold alcohol and the solvent distilled off under reduced pressure until practically the whole has been removed. The semi-solid extract is agitated with several small quantities of warm water and finally with 0·5 per cent. sulphuric acid. These aqueous and acid extracts, which now contain the whole of the alkaloids, are mixed and filtered, and the filtrate shaken with ether to remove oil, resin, and non-alkaloidal impurities. The clarified aqueous liquid is made distinctly alkaline with ammonia solution and shaken out with successive portions of chloroform until all the alkaloids have passed into that solvent. The total chloroform extract is now washed once with a little water, dried over anhydrous sodium sulphate, and the solvent finally distilled off under reduced pressure at a temperature not exceeding 40°. The residue obtained is usually gummy, and when hyoscyamine is the predominant constituent, as in *Hyoscyamus muticus*, this residue, on solution in chloroform and addition of a few drops of light petroleum, deposits impurities containing a little alkaloid, and on further addition of petroleum deposits crystals of hyoscyamine. In any case, by dissolving the residue in a slight excess of very dilute sulphuric acid, filtering and shaking out once with ether, small further quantities of impurities are removed. On adding to this solution ammonia solution in slight excess and shaking out several times with ether and then with chloroform, a

partial separation of the alkaloids is effected; purification may be completed by fractional crystallisation of the aurichlorides. For this purpose the two portions are dissolved separately in a slight excess of dilute hydrochloric acid, and the aurichlorides precipitated in fractions by adding solution of gold chloride. These fractions are recrystallised from hot water containing a little hydrochloric acid and the process repeated until fractions of constant melting-point are obtained. Atropine aurichloride separates as an oil, but becomes crystalline on standing, and on recrystallisation melts at 136°. It liquefies when heated in water. Hyoscyamine aurichloride is usually precipitated in crystalline form, and when pure melts at 162°. *l*-Scopolamine aurichloride is also precipitated as a rule in crystals, and when recrystallised till pure melts at 198°.[1]

Estimation of the Total Alkaloids of Solanaceous Plants

As already indicated, the solanaceous plants yielding hyoscyamine and scopolamine are of great importance as drugs, or as sources of atropine and the other alkaloids of this group. Certain members of this group of plants are recognised in the various national pharmacopœias, and in most cases the official galenical preparations made from them are "standardised," *i.e.* at certain stages in their manufacture the preparations are assayed for alkaloids by prescribed processes and then concentrated or diluted until their alkaloidal contents agree with prescribed standards. Some of the principal official assay processes for these drugs and their preparations are as follow:

The crude drugs of this class recognised in the *British Pharmacopœia* are henbane leaves (*Hyoscyamus niger*), belladonna leaves and roots (*Atropa Belladonna*), and stramonium leaves and seeds (*Datura Stramonium*). The Pharmacopœia does not prescribe methods for the assay of the crude drugs. The following processes devised by

[1] For further information on the isolation, purification, and identification of these alkaloids, *see* Dunstan and Chaston, *Pharm. Journ.* 1889 [iii], **20**, 461; Dunstan and Brown, *Trans. Chem. Soc.* 1899, **75**, 72; 1901, **79**, 71; Andrews, *ibid.* 1911, **99**, 1871; Carr and Reynolds, *ibid.* 1912, **101**, 957.

Dunstan and Ransom,[1] and subsequently slightly modified,[2] give good results with all solanaceous plants containing alkaloids of this group:

Roots. Twenty grammes of the finely ground roots are exhausted in a Soxhlet extractor or similar apparatus with a mixture of chloroform and dry alcohol in equal parts. The solution is shaken with water (25 c.c.), when the natural alkaloidal salts pass into the water, which is run into a second separator. The agitation with water (25 c.c.) is repeated, and the separated aqueous liquid added to the first quantity. The 50 c.c. of aqueous solution are shaken once with a little chloroform and the latter discarded. Ammonia solution in slight excess is now added, and the liberated alkaloids extracted by shaking with several portions of chloroform, each portion after use being run into a tared flask. From the combined chloroform liquors the solvent is distilled off and the residue dried at 100° and weighed.

Leaves, stems, fruit capsules, fruits, or seeds. Twenty grammes of the finely powdered material are exhausted by dry alcohol and the solvent distilled off under reduced pressure, leaving a semi-solid residue. The latter is washed several times with small quantities of warm water, and finally with dilute (0·1 per cent.) sulphuric acid, and the aqueous and acid washings decanted and filtered into a separating funnel, where they are washed with ether to remove non-alkaloidal impurities. The purified, slightly acid liquid is now rendered slightly alkaline with ammonia solution, and the alkaloids extracted by shaking several times with chloroform. The total chloroform solution is washed with a little water, dried over fused, anhydrous sodium sulphate, the solvent distilled off under reduced pressure, and the residue dried in a vacuous desiccator and weighed.

Pharmacopœial methods. The following solanaceous drugs are recognised in the Pharmacopœia of the United States (8th Revision):

[1] *Pharm. Journ.* 1883-84 [iii], **14**, 623; 1885 [iii], **16**, 237, 238, 777.

[2] Dunstan and Brown, *Trans. Chem. Soc.* 1899, **75**, 72; 1901, **79**, 71 Andrews, *ibid.* 1911, **99**, 1871.

belladonna leaves and roots, henbane leaves and flowering tops, *Scopolia carniolica* rhizomes, and stramonium leaves. For all these the same method of assay is prescribed by the United States Pharmacopœia, with the exception that in the case of henbane 25 grm. of drug are taken for assay in place of the 10 grm. prescribed in the other four cases.

Ten grammes of the drug (25 grm. in the case of henbane) in No. 60 powder are mixed with 50 c.c. of a mixture of chloroform (1 volume) and ether (4 volumes), and set aside ten minutes in a stoppered Erlenmeyer flask. Two cubic centimetres of ammonia solution (sp. gr. 0·958 at 25°) and 3 c.c. of distilled water are then added and the flask shaken at frequent intervals during one hour. The contents of the flask are then transferred to a small percolator having its lower end obstructed by a plug of cotton-wool, and the liquid which passes through is collected in a separating funnel containing 6 c.c. of normal sulphuric acid diluted with 20 c.c. of distilled water. The ground drug remaining in the percolator is packed in firmly with a glass rod and the percolation continued by washing out the flask with first 10 and then 5 c.c. portions of the chloroform-ether mixture, and adding the washings to the percolator until in all 50 c.c. have been used. The separator is then shaken well during one minute, and the acid liquid run off into a second separator. The extraction is repeated twice, using each time 10 c.c. of the diluted sulphuric acid. The combined acid liquids are made distinctly alkaline with ammonia solution (sp. gr. 0·958) and the liberated alkaloids extracted by shaking with 15, 15, and 5 c.c. portions of chloroform in turn, each portion of chloroform as used being run into a beaker, which is then heated on a water-bath till the solvent has disappeared. The residue is dissolved in 3 c.c. of ether, which is allowed to evaporate completely. The residue is dissolved in 3 c.c. of $N/10$ sulphuric acid, five drops of cochineal or iodeosin test solution added, and the number (n) of c.c. of $N/50$ potassium hydroxide solution required to neutralise the excess of acid noted. The percentage of alkaloids present is given by the formula

$(3 - n/5) \times 0{\cdot}287$. The United States Pharmacopœia stipulates that the drugs named shall contain the following minimum percentages of total alkaloids when assayed by the above process: belladonna roots, 0·45 per cent.; belladonna leaves, 0·3 per cent.; henbane leaves and tops, 0·08 per cent.; scopolia rhizome, 0·5 per cent.; stramonium leaves, 0·25 per cent.

The drugs of this class recognised in the German Pharmacopœia V. are stramonium leaves, henbane herb, and belladonna leaves. For belladonna leaves the following method of assay is prescribed: Twenty grammes of finely powdered leaves are placed in a medicine bottle with 120 grm. of ether, and, after shaking, 5 grm. of 15 per cent. sodium hydroxide solution and 5 grm. of water are added, and the whole frequently shaken during one hour. The ethereal layer is filtered off and two-thirds of the ether distilled from 60 grm. of the filtrate. The cold concentrated solution is placed in a separating funnel, the flask washed out three times, using 5 c.c. of ether each time, and finally with 10 c.c. of dilute hydrochloric acid (1 : 49 of water), all these washings being added to the separator, which is then shaken during two minutes. The acid liquid is run into a second separator and the extraction repeated twice, using 5 c.c. of diluted hydrochloric acid each time. The combined acid liquids are made distinctly alkaline with sodium carbonate solution, and the alkaloids extracted by shaking during two minutes with 5 c.c. of chloroform, and repeating this operation three times, the chloroform solutions (in all 20 c.c.) being run into a separator to which 20 c.c. of $N/100$ hydrochloric acid are added and sufficient ether to make the ether-chloroform mixture float on the acid. The funnel is shaken during two minutes, and the acid liquid filtered into a 200 c.c. flask, the extraction being repeated three times in the same way, using 10 c.c. of distilled water each time, these being also filtered into the flask. The filter is washed until the total filtrate measures 100 c.c. To this enough ether to form a layer 1 cm. deep, and 10 drops of iodeosin solution are added, and $N/100$ potassium hydroxide solution is run in with continual agitation until the watery layer acquires a distinct bright red colour. At least 9·6 c.c. of

$N/100$ potassium hydroxide solution should be required for belladonna leaves corresponding to 0·3 per cent. of total alkaloid. For henbane leaves 10 c.c. of $N/100$ hydrochloric acid are used in the final extraction, and 7·6 c.c. of $N/100$ potassium hydroxide solution should be required to neutralise the excess of acid, corresponding to 0·07 per cent. of total alkaloid. No assay process is given for stramonium leaves.

Assay of Galenical Preparations

The British Pharmacopœia, 1898, gives the following process for liquid extract of belladonna: Ten cubic centimetres of the extract are mixed in a separator with 10 c.c. of chloroform, 50 c.c. of water, and a distinct excess of ammonia solution (sp. gr. 0·959), and the whole shaken. The chloroformic solution is withdrawn and the extraction with chloroform repeated twice. The mixed chloroformic solutions are then extracted twice, using on each occasion 5 c.c. of diluted sulphuric acid (sp. gr. 1·094) mixed with 10 c.c. of warm water. The mixed acid solutions are shaken once with 3 c.c. of chloroform, and then made distinctly alkaline with ammonia solution, and the alkaloids extracted by shaking three times with chloroform, using 10 c.c. each time. The mixed chloroformic solutions are shaken once with 5 c.c. of water containing a drop of ammonia solution, and are then run into a tared dish, the solvent allowed to evaporate, and the residue dried below 100° and weighed. The residue is then dissolved in 10 c.c. of $N/10$ hydrochloric acid and the number of c.c. (n) of $N/100$ sodium hydroxide solution required to neutralise the excess of acid, in presence of tincture of cochineal as indicator, determined. The *percentage* of alkaloids present is given by the formula $(100 - n) \times 0{\cdot}0287$. The liquid extract should contain 0·75 grm. of alkaloids in 100 c.c. The alcoholic extract of belladonna of the British Pharmacopœia, and also the tincture, are made from the liquid extract and may be assayed in like manner. The former should contain 1 per cent. and the latter 0·048 to 0·052 grm. of alkaloid in 100 c.c. No assay

process is prescribed for the green extract of belladonna, or henbane, or stramonium extract.

The United States Pharmacopœia (8th. Rev.) gives the following processes for (1) extracts, (2) liquid extracts, and (3) tinctures prepared from belladonna, henbane, scopolia, and stramonium :

(1) *Extracts.* Five grammes of the extract (2 grm. in the case of scopolia extract, or 10 grm. in the case of henbane extract) are dissolved in a mixture of distilled water 10 c.c., alcohol 5 c.c., ammonia solution (sp. gr. 0·958 at 25°) 2 c.c., and chloroform 20 c.c., and transferred to a separator, a little alcohol being used for washing out the beaker. The separator is shaken during thirty seconds, the chloroform withdrawn, and the extraction repeated twice, using 10 c.c. of chloroform each time. The mixed chloroformic solutions are extracted first with 5 c.c. of *N*-sulphuric acid mixed with 10 c.c. of distilled water, and then with 1 c.c. of *N*-sulphuric acid diluted with 10 c.c. of water. The combined acid liquids are filtered into a separator through cotton-wool, about 10 c.c. of distilled water being used for washing; they are made alkaline with ammonia solution and the alkaloids extracted by shaking three times with 15, 10, and 10 c.c. of chloroform, evaporating the chloroformic solution to dryness on the water-bath, dissolving the residue in 3 c.c. of ether, and again evaporating to dryness. This final residue is then dissolved in 5 c.c. of $N/10$ sulphuric acid and titrated back with n c.c. of $N/50$ potassium hydroxide solution, using cochineal or iodeosin test solution as indicator. The percentage of alkaloids is given by the formula $(5 - n/5) \times 0{\cdot}0287 \times 100/w$, where w is the weight of extract used.

The United States Pharmacopœia prescribes the following percentages of alkaloids in the extracts named :

Extract of belladonna leaves, 1·4 per cent.
Extract of henbane leaves, 0·3 per cent.
Extract of scopolia, 2·0 per cent.
Extract of stramonium, 1·0 per cent.

(2) *Fluid Extracts.* In principle the method is that of the British

Pharmacopœia, but differs in details. Ten cubic centimetres of fluid extract (50 c.c. in the case of fluid extract of henbane) are mixed with 10 c.c. of distilled water, 2 c.c. of ammonia solution (sp. gr. 0·958 at 25°), and 20 c.c. of chloroform, and shaken during one minute. The chloroformic solution is withdrawn into a second separator (II) and the extraction repeated twice, using 10 c.c. of chloroform each time. The combined chloroformic solutions in separator II are now extracted with 8 c.c. of *N*-sulphuric acid mixed with 20 c.c. of distilled water by shaking together for one minute. The acid layer is filtered into a clean separator (III), 10 c.c. of distilled water being used to wash separator II and the filter, the washings being added to separator III. To the latter 4 c.c. of ammonia solution (sp. gr. 0·958 at 25°) are added and the alkaloids extracted by shaking for several minutes, first with 20 c.c. of chloroform and then twice, using 10 c.c. of chloroform each time. The combined chloroformic solutions are run into a beaker and the solvent evaporated on the water-bath until the residue is quite dry. The latter is dissolved in 5 c.c. of $N/10$ sulphuric acid, five drops of cochineal or iodeosin test solution added as indicator, and the excess of acid determined by titration with n c.c. of $N/50$ potassium hydroxide solution. The percentage of alkaloids is given by the formula $(5 - n/5) \times \frac{0{\cdot}0287 \times 100}{n'}$, where n' is the number of cubic centimetres of extract used.

The fluid extracts of this group in the United States Pharmacopœia should contain the following quantities of total alkaloids expressed in grammes per 100 c.c.: belladonna, 0·4; henbane, 0·075; scopolia, 0·5; stramonium, 0·25.

(3) *Tinctures.* For these products the process described in the preceding paragraphs for fluid extracts is used, 100 c.c. of the tincture being first evaporated on the water-bath to 10 c.c. In this case the formula for calculating the percentage of alkaloids becomes $(5 - n/5) \times 0{\cdot}0287$, n' being 100. The tinctures of this group in the United States Pharmacopœia contain the following quantities of alkaloids expressed in grammes per 100 c.c.: belladonna, 0·03; henbane, 0·007; stramonium, 0·025.

The German Pharmacopœia (5th Edit.) gives the following method for belladonna and henbane extracts: Three grammes of extract are mixed with 5 grm. of water, 5 grm. of dry alcohol, and when solution is complete 70 grm. of ether and 5 c.c. of sodium carbonate solution are added, and the whole shaken occasionally during one hour. The ethereal solution is filtered, 50 grm. collected, and two-thirds of the ether distilled off. The concentrated ethereal solution, when cold, is put into a separator, together with (*a*) 5 c.c. of ether and (*b*) 10 c.c. of 1 per cent. hydrochloric acid, both used first to wash out the distilling flask, and the whole shaken during two minutes. The acid solution is run into a second separator (II) and the extraction repeated twice, taking 5 c.c. each time of the diluted hydrochloric acid. The combined acid liquids are mixed with 5 c.c. of chloroform, made alkaline with sodium carbonate solution, and the whole shaken during two minutes, and the extraction repeated three times, using 5 c.c. of chloroform each time. To the combined chloroform solutions 20 c.c. $N/100$ hydrochloric acid are added (10 c.c. in the case of henbane extract) and sufficient ether to make the chloroform-ether mixture float on the acid, and the whole shaken during two minutes. The acid liquid is filtered into a 200 c.c. flask and the extraction repeated three times, using 10 c.c. of distilled water each time, and each quantity of water being filtered into the flask. The filter is washed with distilled water till the filtrate measures 100 c.c. To this enough ether is added to form a layer 1 cm. deep, then 10 drops of iodeosin test solution, and the excess of acid titrated with $N/100$ potassium hydroxide solution. The percentage of alkaloids is given by the formula $n \times 0{\cdot}1445$, where n is the number of c.c. of $N/100$ potassium hydroxide solution used. For belladonna extract n should be equal to 9·6 (= 1·5 per cent. of alkaloids), and for henbane extract n should be 6·5 (= 0·5 per cent. total alkaloids).

Atropine, $C_{17}H_{23}O_3N$. It is probable that this alkaloid never occurs in more than traces in solanaceous plants, and its isolation from stramonium seeds by Mein [1] and later by Geiger and Hesse [2] was probably due to the fact that the hyoscyamine present was

[1] *Annalen*, 1833, **6**, 67. [2] *Ibid.* 1833, **5**, 43; **6**, 44; **7**, 269.

converted into atropine by the agents used in the process of extraction. Commercially the alkaloid is obtained by treating hyoscyamine, extracted from the plants by a process such as that already described (p. 50), with dilute alkali, when it undergoes isomerisation to atropine.[1] Atropine is best crystallised by adding water to its solution in alcohol. It was subsequently investigated by Liebig, who assigned to it its present formula, and was later shown by von Planta [2] to be identical with daturine obtained from stramonium fruits.[3]

The alkaloid crystallises in colourless, elongated prisms, m.p. 115·5°, sublimes unchanged when heated rapidly, is readily soluble in alcohol (1 in 1·46 at 25°) or chloroform (1 in 1·56 at 25°), less soluble in ether (1 in 16·6 at 25°) or hot water (1 in 86·7 at 80°), and sparingly so in cold water (1 in 450 at 25°). The aqueous solution is bitter to the taste, alkaline to litmus, and oxidises, depositing resinous decomposition products, on exposure to air.

Atropine is optically inactive when pure, but the commercial alkaloid is usually slightly lævorotatory, owing to the presence of hyoscyamine.

Atropine causes dilatation of the pupil of the eye like other alkaloids of this group; hence the term "mydriatic alkaloids." A drop or two of an aqueous solution, containing 1 part of atropine in 130,000 parts of water, when introduced into the eye of a cat is sufficient to produce this effect. This property may be used for the detection of atropine, but the test should be applied with very great care. When warmed with sulphuric acid and a small crystal of potassium dichromate, atropine develops a bitter-almond odour. Evaporated to dryness on the water-bath with concentrated nitric acid, it gives a residue which becomes violet on adding a drop or two of sodium hydroxide solution in alcohol. Atropine does not form a mercurichloride, but with a solution of mercuric chloride gives a yellow to red precipitate of mercuric oxide. A crystal of

[1] Will and Bredig, *Berichte*, 1888, **21**, 2797; *cf.* Gadamer, *Arch. Pharm.* 1901, **239**, 294.
[2] *Ibid.* 1850, **74**, 245.
[3] *Cf.* Pesci, *Gazzetta*, 1882, **12**, 59.

atropine with a few drops of sulphuric acid and 1 drop of cresol gives a pink colour, whilst hyoscyamine gives a brown colour and scopolamine remains colourless.[1] The aurichloride (*see below*) affords the most certain method of identifying the alkaloid.

The salts of atropine are mostly crystalline and soluble in water. The sulphate, $B_2.H_2SO_4.H_2O$, occurs in commerce as a colourless crystalline powder, m.p. 189·9° (188° when free from hyoscyamine), soluble in water (1 in 0·38) or alcohol (1 in 3·7), and sparingly so in chloroform (1 in 620) or ether (1 in 2140), in each case at 25°. This salt is that usually employed in medicine. The platinichloride, $B_2.H_2PtCl_6$, is readily soluble in dilute hydrochloric acid and consequently is not precipitated when atropine hydrochloride is added to platinic chloride solution containing free hydrochloric acid. On evaporation it is obtained in monoclinic crystals, m.p. 207°–208°. The aurichloride, $B.HAuCl_4$, separates as an oil, and solidifies while still hot to a crystalline mass, which may be rapidly recrystallised from water containing hydrochloric acid. The crystals melt at 136°, or below 100° when heated under water. This salt and the picrate, m.p. 175°–176°, are well adapted for the identification of the alkaloid, since the aurichlorides and picrates of the other alkaloids of this group melt at different temperatures.

The reactions and constitution of atropine are discussed later (p. 67).

Apoatropine (*Atropamine*), $C_{17}H_{21}O_2N$. This anhydride of atropine was first obtained by Pesci[2] as a product of the action of nitric acid on atropine and was subsequently prepared by Merck,[3] Hesse,[4] and others through the action of various dehydrating agents upon atropine or hyoscyamine. It was also isolated under the name atropamine by Hesse[5] from belladonna root and regarded by him as isomeric with Pesci's base, the identity of the two being

[1] For other reactions, *see* Reichard, *Chem. Zeit.* 1904, **28**, 1048.
[2] *Gazzetta*, 1881, **11**, 538; 1882, **12**, 60.
[3] *Arch. Pharm.* 1891, **229**, 134; 1893, **231**, 110.
[4] *Annalen*, 1892, **271**, 124; 1893, **277**, 290. [5] *Annalen*, 1891, **261**, 87

finally established by Merck.[1] Apoatropine crystallises in prisms, m.p. 60°; it is slightly soluble in water, but readily dissolves in the ordinary solvents. The salts crystallise well, but are unstable in sunlight, the hydrochloride in thin plates, m.p. 237°, and the aurichloride in needles, m.p. 110°. The base and its salts are optically inactive and are not mydriatic. When apoatropine is heated alone, or evaporated with strong hydrochloric acid, &c., it partly passes into the isomeric belladonnine (*see below*), and is partly decomposed into tropine (p. 66) and atropic acid (p. 65).

A partial synthesis of apoatropine has been brought about by Ladenburg[2] through the esterification of tropine by atropic acid in the usual manner. Apoatropine is therefore atropyltropëine.

Belladonnine, $C_{17}H_{21}O_2N$. This isomeride of apoatropine was first obtained by Hübschmann[3] from henbane berries (*Hyoscyamus niger*). It was examined in a purer condition by Kraut and later by Merling,[4] who assigned to it the formula given above, which was confirmed by Hesse,[5] who stated further that on heating at 120° to 130° hyoscyamine passes into atropine, then into apoatropine, and finally into belladonnine. On heating apoatropine with hydrochloric acid at 85°–100° during eight hours in sealed tubes, belladonnine and some tropine are formed; whilst on heating at 140° during sixteen hours, BELLATROPINE, $C_8H_{15}O_2N$, colourless prisms, is produced. On allowing a solution of atropine or hyoscyamine in sulphuric acid to stand for a short time, belladonnine is formed.[6] Hesse therefore regards belladonnine as produced by isomerisation of the tropine portion of the apoatropine molecule, the tropine residue being converted into the isomeric bellatropine, so that belladonnine is atropylbellatropëine.

Belladonnine is an uncrystallisable, resinous base insoluble in

[1] *Loc. cit.*
[2] *Annalen*, 1883, **217**, 102.
[3] *Jahresberichte*, 1858, p. 376.
[4] *Berichte*, 1884, **17**, 381.
[5] *Annalen*, 1891, **261**, 87; 1892, **271**, 128; 1893, **277**, 295
[6] Hesse *loc. cit.*

water, but easily soluble in alcohol, ether, or chloroform. The platinichloride, m.p. 229°, and the aurichloride, m.p. 120°, are both amorphous.

Hyoscyamine, $C_{17}H_{23}O_3N$. This, the most commonly occurring alkaloid of the group, is an isomeride of atropine, and is the chief alkaloidal constituent of *Atropa Belladonna*, *Datura Stramonium*, *Hyoscyamus* spp., &c. The best source is *Hyoscyamus muticus* (*see* Table, p. 49). The preparation has been described already. It was first obtained by Geiger and Hesse[1] from henbane (*Hyoscyamus niger*), and its hydrolysis into a base and an acid was first observed by Höhn and Reichardt.[2] The formula now accepted for the alkaloid was first given by Ladenburg,[3] who also showed that it was a physical isomeride of atropine.

Hyoscyamine crystallises from dilute alcohol in long silky needles, m.p. 108·5°, and is lævorotatory in solution, $[\alpha]_D$ — 20·75°, — 22° in 50 per cent. alcohol;[4] it is readily soluble in benzene, chloroform, or alcohol, less so in ether or cold water.

The ordinary salts of hyoscyamine are crystalline. The sulphate, $B_2.H_2SO_4$, m.p. 206° (*dry*), crystallises in needles from alcohol, is bitter to the taste, neutral, and readily soluble in water. According to the United States Pharmacopœia, the anhydrous salt melts at 198·9°. The hydrobromide, B.HBr, m.p. 151·8°, forms prisms; both these salts are deliquescent. The aurichloride, $B.HAuCl_4$, m.p. 162°, crystallises in golden-yellow leaflets from dilute hydrochloric acid; unlike atropine aurichloride, it does not melt when heated under water. This salt is less soluble in water containing hydrochloric acid than atropine aurichloride, from which it may be separated by fractional crystallisation. The platinichloride, m.p. 206°, is somewhat soluble in dilute hydrochloric acid, and is obtained by spontaneous evaporation of solutions of hyoscyamine hydrochloride and platinic chloride; it forms orange prisms. The picrate, m.p. 161°–163°, is crystalline.

[1] *Annalen*, 1833, **7**, 270. [2] *Ibid.* 1871, **157**, 93.
[3] *Ibid.* 1880, **206**, 282.
[4] Carr and Reynolds, *Trans. Chem. Soc.* 1910, **97**, 1329.

Hyoscyamine and its salts cause dilatation of the pupil of the eye like atropine, and its colour reactions are almost identical with those of the latter alkaloid. Hyoscyamine is readily converted into the racemic modification, atropine, by melting or by the addition of small quantities of alkali to an alcoholic solution. This method is said to be that generally employed in the manufacture of atropine from hyoscyamine. The same change is brought about by sodium carbonate and slowly by ammonia.[1]

When heated with acids or alkalis, hyoscyamine undergoes hydrolysis into tropine and tropic acid. It is probable that the hyoscyamine is in the first place converted by these reagents into atropine, and that it is really this alkaloid which is hydrolysed. According to Gadamer,[2] when hyoscyamine is hydrolysed with cold water the products are inactive tropine and lævorotatory tropic acid, a substance which has been shown to racemise with great rapidity. Ladenburg and Hundt [3] found that by the esterification of *inactive* tropine by *lævo*tropic acid a *l*-atropine not identical with hyoscyamine was produced, but Amenomiya has shown [4] that Ladenburg and Hundt's *d*- and *l*-atropines were probably mixtures of atropine with *d*- and *l*-hyoscyamines. He separated *dl*-tropic acid into the *d*- and *l*- forms by crystallisation of the quinine salt and then esterified these with tropine in 5 per cent. hydrochloric acid, and in this way obtained *d*- and *l*-hyoscyamines having the following properties:

—	M.p. of aurichloride	$[\alpha]_D$ of hydrochloride	M.p. of alkaloid
Natural *l*-hyoscyamine	158°–159°	− 25·07°	108°
Synthetic *l*-hyoscyamine	158°–159°	− 23·15°	103°
Synthetic *d*-hyoscyamine	158°–159°	+ 24·12°	106°

[1] Will, *Berichte*, 1888, **21**, 1717; Gadamer, *ibid.* p. 1829; Will and Bredig, *ibid.* p. 2797.
[2] *Arch. Pharm.* 1901, **239**, 294.
[3] *Berichte*, 1889, **22**, 2590.
[4] *Arch. Pharm.* 1902, **240**, 498.

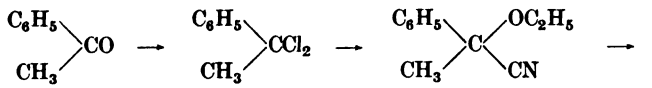
Constitution of Atropine and Hyoscyamine

Atropine is readily hydrolysed when warmed with alkalis or dilute acids or even with water.[1] By heating it with concentrated hydrochloric acid in a closed tube at 130°, or with baryta water at 60°, it is completely resolved into the base *tropine*, $C_8H_{15}ON$, and *tropic acid*, according to the following equation:[2]

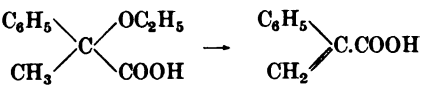
$$\underset{\textit{Atropine}}{C_{17}H_{23}O_3N} + H_2O = \underset{\textit{Tropine}}{C_8H_{15}ON} + \underset{\textit{Tropic acid}}{C_9H_{10}O_3}.$$

At higher temperatures the tropic acid first produced loses a molecule of water, forming atropic acid, $C_9H_8O_2$.

Atropic acid, $C_9H_8O_2$. The constitution of atropic acid has been determined by Ladenburg and Rugheimer's synthesis of this acid from acetophenone.[3] The ketone was first converted into α-dichloroethylbenzene by treatment with phosphorus pentachloride, and this product, by the action of potassium cyanide in alcohol, into ethoxycyanoethylbenzene, which on hydrolysis gave ethylatrolactic acid. By the action of strong hydrochloric acid this substance furnished atropic acid, melting, like that derived from the solanaceous alkaloids, at 106·5°, and boiling at 267° with some decomposition. This series of changes may be represented as follows:



Acetophenone *α-Dichloroethylbenzene* *Ethoxycyanoethylbenzene*



Ethylatrolactic acid *Atropic acid*

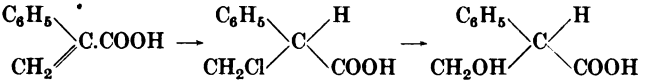
Tropic acid, $C_9H_{10}O_3$. By the action of hypochlorous acid

[1] Gadamer, *Arch. Pharm.* 1901, **239**, 294.

[2] Kraut, *Annalen*, 1863, **128**, 280; 1865, **133**, 87; 1868, **148**, 236; Lossen, *ibid.* 1864, **131**, 43; 1866, **138**, 230.

[3] *Berichte*, 1880, **13**, 376, 2041.

atropic acid furnishes a chlorohydratropic acid, which when warmed in aqueous solution passes into tropic acid, thus :



Atropic acid *Chlorohydratropic acid* *Tropic acid*

The acid crystallises in prisms and melts at 117°. The *dl*-acid thus obtained can be separated into the optically active forms by crystallisation of the quinine salts.[1]

Tropine, $C_8H_{15}ON$. This base, which is produced as already described, by the hydrolysis of several of the solanaceous alkaloids, forms colourless plates, m.p. 63°, b.p. 233°, soluble in water, ether, alcohol, or benzene. Its aqueous solution is strongly alkaline, and readily absorbs carbon dioxide from the air. The salts crystallise well ; the hydrochloride in plates, the picrate in yellow needles. The aurichloride forms golden-yellow needles, m.p. 210° (*decomp.*), whilst the platinichloride forms orange-coloured monoclinic needles, m.p. 198°.

The base contains a hydroxyl group, and readily undergoes esterification with organic acids in the ordinary way. The esters so formed are, after the suggestion of Ladenburg, called *tropēines*. A considerable number of these have been prepared,[2] and a few of them have found application in medicine in place of atropine and hyoscyamine. The following are the more important :

Tropyltropēines, $C_{17}H_{23}O_3N$. Three of these have been prepared by the combination respectively of *inactive*, *dextro*-, and *lævo*-tropic acids with *inactive* tropine ; the first is identical with atropine, the two latter are the *d*- and *l*-hyoscyamines, prepared by Amenomiya (*see* p. 64). The first and third synthetic alkaloids correspond in character and behaviour with the natural alkaloids, and, like them, exert a strong mydriatic action. *l*-Hyoscyamine is the most active and *d*-hyoscyamine the least active of the three (*see* p. 89).

[1] Ladenburg and Hundt, *Berichte*, 1889, **22**, 2590.

[2] *See especially* Jowett and Pyman, *Trans. Chem. Soc.* 1909, **95**, 1020.

Atrolactyltropēine (*pseudo*atropine), *α*-Hydroxy-*α*-phenylpropionyltropēine, $C_{17}H_{23}O_3N$. Considerable interest attaches to this substance since atrolactic acid is isomeric with tropic acid. It forms brilliant needles, m.p. 119°, and is more strongly mydriatic than homatropine (*see below*).

α-Hydroxy-β-phenylpropionyltropēine, $C_{17}H_{23}O_3N$, isomeric with the foregoing, crystallises in rosettes of needles, m.p. 89°–90°. It is more strongly mydriatic than homatropine (*see below*).

Atroglyceryltropēine, $C_{17}H_{23}O_4N$, crystallises in rectangular oblong plates, m.p. 124°–125°, is less mydriatic than the foregoing alkaloids, but more active than homatropine.

Benzoyltropēine, $C_{15}H_{19}O_2N$, crystallises in shining plates, m.p. 58°, and is mydriatic, but less so than homatropine.

Phenylglycollyltropēine (*Homatropine*), $C_{16}H_{21}O_3N$. This is the most important of the artificial tropēines and is largely used in medicine in the form of its salts as a substitute for atropine. It crystallises in transparent prisms, m.p. 95·5° to 98·5°. The hydrobromide, colourless crystalline powder, m.p. 213·8°, the hydrochloride, and the salicylate are used in medicine. They are freely soluble in water. The aurichloride, $B.HAuCl_4$, forms prisms, and is sparingly soluble in water. Homatropine is a powerful mydriatic, but its effect is more transient than that of atropine. It is also less toxic.

Homatropine is distinguished from atropine by not giving the violet coloration on treatment with nitric acid, followed by alcoholic potassium hydroxide.

Constitution of Tropine. The problem of assigning to this base a constitution capable of affording a satisfactory explanation of its many and diverse reactions is one of great difficulty, and has only been successfully solved by the long-continued investigations of many chemists, prominent among whom are Ladenburg, Merling, and Willstätter. The complexity of the problem may be better understood when it is recalled that in some reactions tropine behaves as a comparatively simple pyridine derivative, yielding such substances as dibromopyridine and ethylpyridine; in others

as an aromatic compound, *e.g.* when it gives rise to benzyl bromide. It is impossible within reasonable limits to give an exhaustive historical account of the various investigations, results of which have gradually led up to our present knowledge of the constitution of tropine ; attention will, therefore, be principally directed to those reactions which form the basis upon which the now generally accepted formula of Willstätter rests.

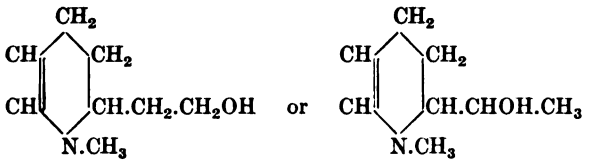
Tropine readily suffers dehydration by the action of strong sulphuric or hydrochloric acid, forming a new base,[1] TROPIDINE, $C_8H_{13}N$, an oily, strongly alkaline liquid, b.p. 162°, having a coniine-like odour. It combines with two atoms of bromine, and with one molecule of each of the halogen acids, but is not reduced by nascent hydrogen. Like tropine, it is a tertiary base. The methiodide when heated with potassium hydroxide yields TROPILENE, $C_7H_{10}O$, and dimethylamine, the latter affording evidence of the existence of the group $=N.CH_3$ in tropidine and consequently in tropine.

By the action of bromine on tropidine Ladenburg[2] found that two substances could be produced, viz. methyldibromopyridine and $\beta\beta$-dibromopyridine.

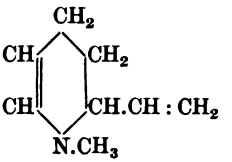
When hydriodic acid reacts with tropine at temperatures above 150° tropidine results, but at lower temperatures an intermediate iodo-compound, $C_8H_{14}NI.HI$, is formed, which is the hydriodide of a base in which an atom of iodine replaces the —OH group of tropine ; by the reduction of this substance with nascent hydrogen, dihydrotropidine results, which, as already mentioned, cannot be obtained directly from tropidine. This reduced product is of interest, since, on distillation, its hydrochloride loses a molecule of methyl chloride and gives rise to nor*hydrotropidine*, $C_7H_{13}N$, and this in turn furnishes α-ethylpyridine by distillation with zinc dust.[3]

The results so far recorded are those upon which Ladenburg chiefly founded his formulæ representing tropine and tropidine :[4]

[1] Ladenburg, *Annalen*, 1883, **217**, 117.
[2] Ladenburg, *Berichte*, 1887, **20**, 1647.
[3] *Ibid.* p. 144.
[4] *Loc. cit.*



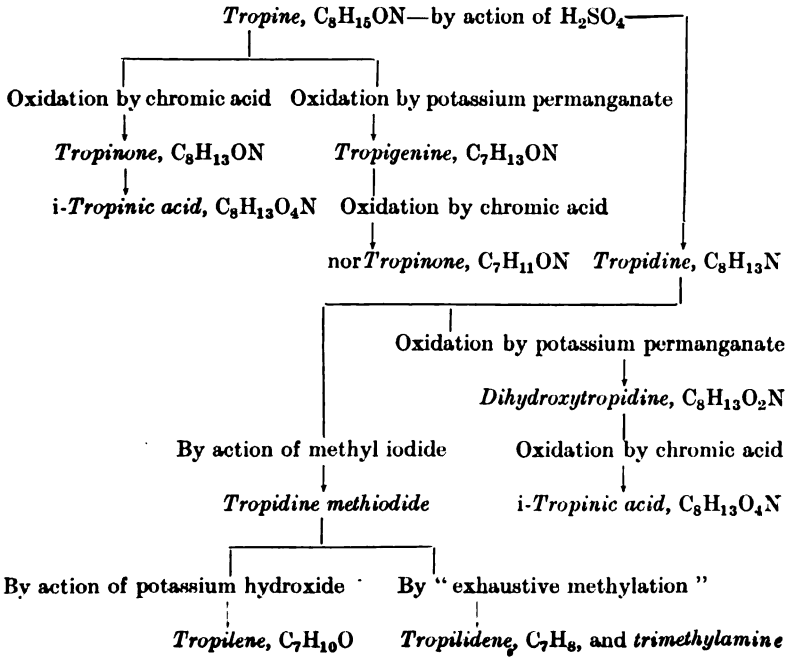
Tropine (Ladenburg)



Tropidine (Ladenburg)

The inadequacy of these formulæ became evident when the oxidation products of tropine were examined.

When acted upon by acidified potassium permanganate, or chromic acid, tropine and tropidine give rise to a series of oxidation products the interrelationships of which are shown in the following scheme, which also gives briefly a view of the effects of " exhaustive methylation " on tropidine :



The most important of these products are the following:

Tropinone, $C_8H_{13}ON$. This substance, first prepared by Willstätter,[1] crystallises in spear-shaped needles, m.p. 41°, b.p. 219°–220° under 714 mm. pressure, dissolves in the ordinary solvents, and is a strong base, liberating ammonia from its salts. It has the properties of a ketone, giving an oxime, m.p. 111°, and a semicarbazone, m.p. 212°. It is a tertiary base; the methiodide reacts violently with potassium hydroxide, producing dimethylamine, and a substance which Merling regarded as a dihydrobenzaldehyde.[2] When reduced by sodium amalgam, tropinone forms, not tropine, but pseudo*tropine*, identical with that obtained by the hydrolysis of benzoyl*pseudo*tropine (*tropacocaine*), occurring naturally in coca leaves (p. 109). When reduced electrolytically or by zinc dust in hydriodic acid, a mixture of tropine and *pseudo*tropine is produced, so that it is possible to convert *pseudo*tropine into tropine by oxidising to tropinone and then reducing.[3]

i-*Tropinic acid*, $C_8H_{13}O_4N$. This oxidation product of tropine and its derivatives, as well as of *pseudo*tropine, is a substance of great importance in this group, and the questions of its constitution and its relation to tropine have given rise to much discussion.[4] It crystallises in small needles, m.p. 248° (*decomp.*), is soluble in water, insoluble in alcohol, and almost insoluble in other media. It is a dibasic acid and yields salts, which are usually well crystallised, both with bases and acids. The formation of this dibasic acid by the oxidation of tropine is not explicable in any simple manner by Ladenburg's formula for tropine, and it was this difficulty which led Merling to propose the formula to be presently discussed (p. 71). By crystallisation of the cinchonine salt, *i*-tropinic acid can be resolved into the *d*- and *l*- forms. The first of these is produced by the oxidation of ecgonine (p. 103).

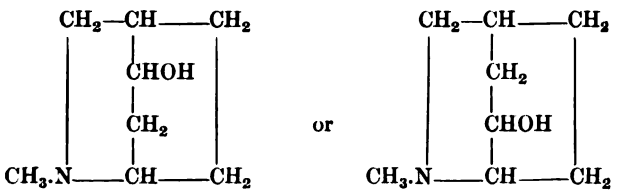
Tropigenine, $C_7H_{13}ON$. This intermediate product of the

[1] *Berichte*, 1896, **29**, 396. [2] *Cf.* Willstätter, *Berichte*, 1898, **31**, 1548.
[3] Willstätter and Iglauer, *Berichte*, 1900, **33**, 1170.
[4] Merling, *Annalen*, 1883, **216**, 348; Willstätter, *Berichte*, 1896, **29**, 398 1897 **30**, 2679.

action of potassium permanganate on tropine is a strong base, which crystallises from ether in colourless needles, m.p. 161°. It sublimes when heated to 100° *in vacuo*, absorbs carbon dioxide from the air, and is liberated from solutions of its hydrochloride by silver oxide, but not by caustic soda. Its relation to tropine is clearly established by the fact that it is a secondary base giving a nitroso-derivative, and that it combines with a molecule of methyl iodide to form tropine methiodide, showing that in its formation the methyl group attached to the nitrogen atom of tropine is replaced by hydrogen.[1]

nor*Tropinone*, $C_7H_{11}ON$. This base bears the same relation to tropigenine as tropinone does to tropine, and results from the oxidising action of chromic acid on tropigenine.[2] It crystallises in long, thin deliquescent needles, m.p. 69°, is readily soluble in water or alcohol, and less so in ether. On reduction with sodium amalgam it forms *pseudo*tropigenine, which corresponds with *pseudo*tropine. It furnishes an oxime, microscopic leaflets, m.p. 181°. As a secondary amine, *nor*tropinone combines with nitric oxide, forming nitroso*nor*tropinone, crystallising in needles, m.p. 121°.

The formation of these oxidation products and, in particular, of the dibasic tropinic acid led Merling [3] to propose a formula for tropine which represented it as a dicyclic system composed of a reduced pyridine and a reduced benzene ring having four atoms of carbon in common.



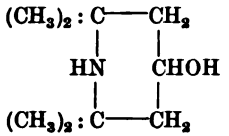
Tropine (Merling)

No very conclusive evidence was forthcoming to decide between these two formulæ, but the first was preferred by Merling on account

[1] Merling, *Annalen*, 1883, **216**, 343; Willstätter, *Berichte*, 1896, **29**, 1579, 1637.

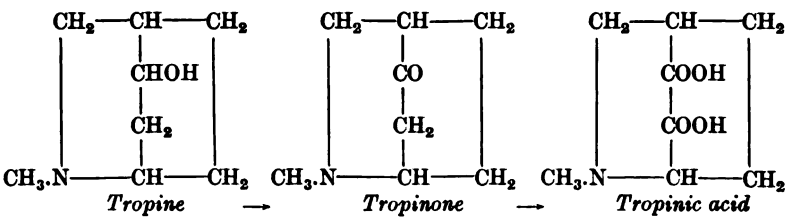
[2] Willstätter, *Berichte*, 1896, **29**, 1581, 1638. [3] *Berichte*, 1891, **24**, 3108.

of its similarity in structure to Fischer's triacetonamine, which in its phenylglycollic ester exhibits mydriatic action; to this base Fischer has assigned the following formula:[1]



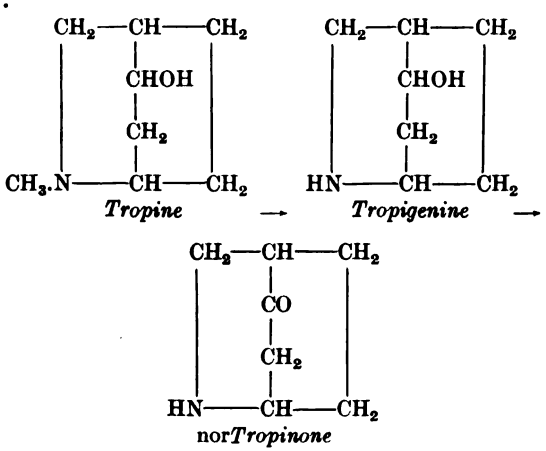
Triacetonamine (Fischer)

On comparing the two formulæ it will be seen that the hydroxyl group is in both cases in the *para* position to the nitrogen atom. Merling's formula for tropine satisfactorily explains many of its typical reactions. Thus the formation of tropinone and tropinic acid by the oxidation of tropine is represented as follows:



Tropine → *Tropinone* → *Tropinic acid*

and in a similar manner may be shown the production of tropigenine and *nor*tropinone by oxidation of tropine with potassium permanganate:

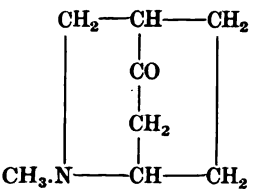


Tropine → *Tropigenine* →

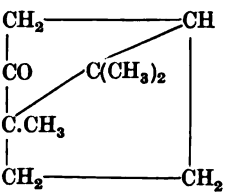
norTropinone

[1] *Berichte*, 1883, **16**, 1604.

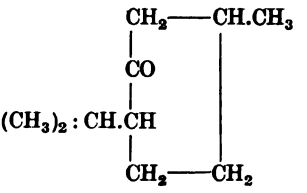
Although Merling's formula satisfactorily accounted for many of the reactions of tropine and its derivatives which at that time had been observed, new facts not in harmony with it were soon brought forward. If Merling's formula for tropinone be compared with those of camphor and menthone it will be seen that the carbonyl group is similarly situated in all three cases, being next to a $-CH_2-$ group. It should, therefore, confer reactivity



Tropinone (Merling)

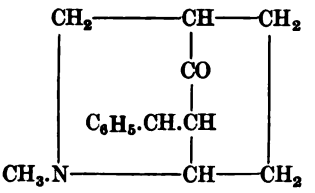


Camphor



Menthone

upon the hydrogen atoms of this group, and it was to be expected that tropinone should condense with benzaldehyde to yield a monobenzylidene derivative of the formula :



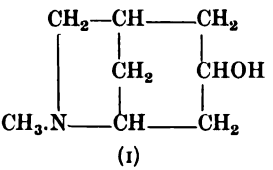
Benzylidenetropinone (Merling)

It was found, however, that in this reaction a dibenzylidenetropinone [1] was formed, and similarly, by condensation of tropinone with ethyl oxalate in presence of sodium ethoxide, a diethyltropinone dioxalate was produced, whilst by the interaction of tropinone

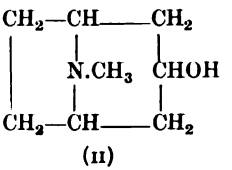
[1] Willstätter, *Berichte*, 1897, **30**, 731, 2679.

with amyl nitrite a dioximinotropinone was obtained. These reactions afford strong evidence of the presence of two methylenic groups contiguous to the carbonyl, *i.e.* that the keto-base, tropinone, must contain the grouping $—CH_2—CO—CH_2—$, while tropine must contain the related group $—CH_2—CHOH—CH_2—$.

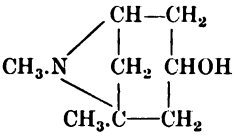
On the basis of these observations, Willstätter suggested three possible formulæ for tropine, thus :



(I)



(II)



(III)

Tropine (Willstätter)

To obtain definite evidence for one of these formulæ Willstätter [1] applied Hofmann's reaction, "exhaustive methylation," to methyltropinate methiodide, when, in addition to trimethylamine and methyl alcohol, he obtained an unsaturated, dibasic, seven-carbon acid, which on reduction took up four atoms of hydrogen, forming pimelic acid. The unsaturated acid must, therefore, be represented by the following formula :

$$COOH—CH=CH—CH=CH—CH_2—COOH \rightarrow$$

Piperylenecarboxylic acid

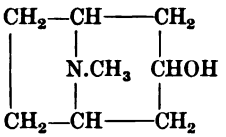
$$COOH—CH_2—CH_2—CH_2—CH_2—CH_2—COOH$$

Pimelic acid

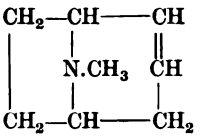
Of the three tropine formulæ given above, only one (II) fulfils this condition and is capable of yielding a seven-carbon open-chain acid of this formula, and this, therefore, is to be preferred as representing the constitution of tropine. The formulæ

[1] *Berichte*, 1898, **31**, 1535, 2498.

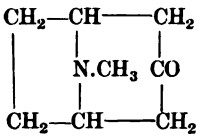
of the chief tropine derivatives must, therefore, be written as follows:



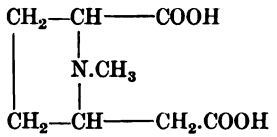
Tropine



Tropidine

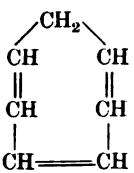


Tropinone

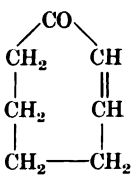


Tropinic acid

Tropilidene and tropilene (*see* p. 69), produced by (1) exhaustive methylation of tropidinemethiodide and (2) the action of potassium hydroxide on the methiodide, respectively, were regarded by Merling as methylenedihydrobenzene and tetrahydrobenzaldehyde respectively. They are regarded by Willstätter as heptacyclic derivatives of the following formulæ:



Tropilidene



Tropilene

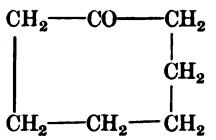
Tropilene readily gives with benzaldehyde a benzylidene derivative and an oxymethylene compound, reactions which clearly establish the existence in its molecule of a $-CH_2-CO-$ group.

Willstätter's view of the constitution of tropine was confirmed by his synthesis of tropidine, tropine, and *pseudo*tropine [1] from the heptacyclic ketone, suberone, as a starting-point. Suberone is a liquid with an odour resembling that of peppermint, obtained by the distillation of the calcium salt of suberic acid, the latter being

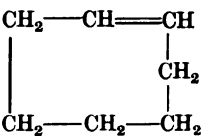
[1] *Berichte*, 1901, **34**, 129, 3163; *Annalen*, 1901, **317**, 204, 267, 307; 1903, **326**, 1, 23.

the chief product of the action of nitric acid upon a large number of naturally occurring substances, such as cork, coco-nut oil, paraffin, stearic and oleic acids. Suberic acid is produced by the electrolytic reduction of glutaric acid,[1] and several syntheses of glutaric acid are on record,[2] so that this is a complete synthesis of tropine and, consequently, of the alkaloids, atropine, hyoscyamine, and their relatives.

The suberone was converted into its oxime, and the latter reduced to suberylamine, which was converted by " exhaustive methylation " into *cyclo*heptene :

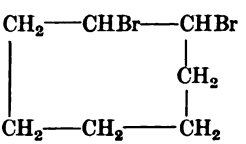


Suberone

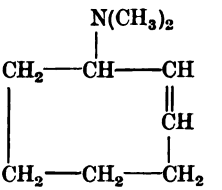


cyclo*Heptene*

The latter was then brominated and the *cyclo*heptene dibromide heated with dimethylamine in benzene, forming dimethylamino-Δ^2-*cyclo*heptene. This was converted by exhaustive methylation and subsequent distillation into the *cyclo*heptadiene identical with

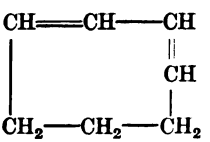


cyclo*Heptene dibromide*

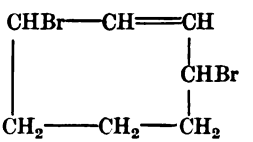


Dimethylamino-Δ^2-cyclo*heptene*

the dihydrotropilidene, obtainable from dihydrotropidine. The latter hydrocarbon was in turn converted into the dibromide and this,



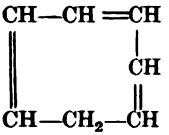
cyclo*Heptadiene*
(*Dihydrotropilidene*)



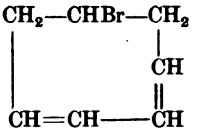
cyclo*Heptadiene dibromide*
(*Dihydrotropilidene dibromide*)

[1] Crum Brown and Walker, *Annalen*, 1891, **261**, 119.
[2] *e.g.* Bottomley and Perkin, *Trans. Chem. Soc.* 1900, **77**, 300.

by heating with quinoline, was transformed into a *cyclo*heptatriene identical with tropilidene (*see* p. 75).

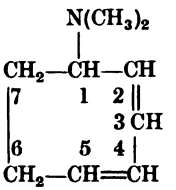


cyclo*Heptatriene*
(*Tropilidene*)



Bromocycloheptadiene
(*Tropilidene hydrobromide*)

On adding hydrogen bromide to a solution of tropilidene in acetic acid, bromo*cyclo*heptadiene was formed. This substance reacts with dimethylamine, forming dimethylamino*cyclo*heptadiene, identical with *a*-methyltropidine, obtained by Merling by the distillation of tropidinemethylammonium hydroxide.[1] To this compound, therefore, the following formula must be ascribed:

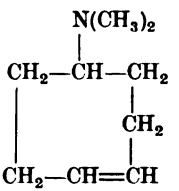


a-Methyltropidine

It had been shown by Hofmann[2] that by the action on hydrochloric acid on dimethylpiperidine, methyl chloride and methylpiperidine result; Merling in re-investigating this reaction[3] found that, not methylpiperidine, but *aa*-dimethylpyrrolidine was formed, a substance with the same composition as Hofmann's supposed base. On the same principle is based Gabriel's synthesis of pyrrolidine from δ-chlorobutylamine and of piperidine from ε-chloroamylamine. The same reaction was applied by Merling when he converted *a*-methyltropidine into tropidine. It appears, therefore, that, as in the reaction of an alkyl haloid with a primary base, the haloid hydrocarbon residue in a molecule may enter into reaction with the basic residue in the same molecule, *i.e. intramolecular*

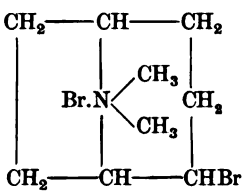
[1] *Berichte*, 1891, **24**, 3108.
[2] *Ibid.* 1881, **14**, 494, 659.
[3] *Annalen*, 1891, **264**, 310.

methylation may occur. Therefore, in the case of a substance represented by the formula given above for α-methyltropidine, if either of the carbon atoms 4 or 5 be chlorinated and the resulting product distilled, "intramolecular methylation" may be expected to occur with the production of tropidine. This method of reproducing tropidine from α-methyltropidine had already been employed by Merling,[1] but on repeating the experiment Willstätter was unable to obtain a pure tropidine, and so had recourse to the use of Δ^4-dimethylamino*cyclo*heptene, which is formed by the reduction of α-methyltropidine with sodium in alcohol.

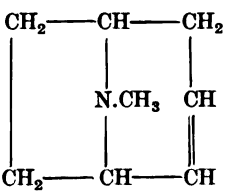


Δ^4-Dimethylaminocycloheptene (α-Methyldihydrotropidine)

This was converted into the dibromide by bromine dissolved in hydrobromic acid, and the latter warmed in ethereal solution, when it changed into bromodihydrotropidine methobromide, which



Bromodihydrotropidine methobromide



Tropidine

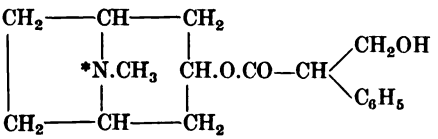
when warmed with alkali lost a molecule of hydrobromic acid, forming tropidinemethobromide. This by the action of potassium iodide passed into the corresponding methiodide, and the latter by digestion with silver chloride gave the methochloride, which on heating furnished tropidine, identical with that obtained from tropine.

This synthetic tropidine was converted into the hydrobromide

[1] *Berichte*, 1891, **24**, 3110.

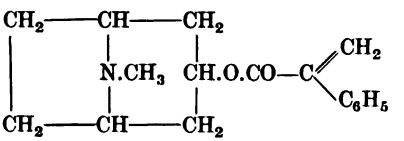
(bromodihydrotropidine) and the solution heated with six times the quantity of 10 per cent. sulphuric acid at 200°–210°, when it passed into *pseudo*tropine,[1] identical with the natural base derived from tropacocaine (p. 109), and since the latter may be converted into tropine by oxidation to tropinone and reduction of the latter by zinc dust and hydriodic acid, this complicated series of reactions affords a complete synthesis of tropine. As tropine had already been converted into atropine and hyoscyamine (p. 66), the complete synthetical production of these naturally occurring alkaloids may also be regarded as accomplished.

Combining the formula given above for tropine with that of tropic acid, it is seen that atropine and hyoscyamine must be represented as follows :



Atropine and *Hyoscyamine*
(dl-*tropyltropëine*) (l-*tropyltropëine*)

whilst apoatropine and belladonnine must be written ·



Apoatropine and *Belladonnine* (dl-*atropyltropëines*)

The nomenclature of tropine and its derivatives has recently been revised both by Ciamician and Silber and by Willstätter, and for convenience in referring to the papers of these authors the following table showing their systems, together with the names in common use, has been compiled :

[1] Willstätter, *Berichte*, 1901, **34**, 3163. *Cf.* Ladenburg, *ibid.* 1902, **35**, 1159.

* In *nor*hyoscyamine (p. 80) this $-CH_3$ group is replaced by —H.

Common names	System of Ciamician and Silber	System of Willstätter
Dihydrotropidine	N.methyltropamine	Tropan
Tropidine	N.methyltropenine	Tropen
Tropine	N.methyltropoline	Tropanol
Tropigenine	Tropoline	Nortropanol
Norhydrotropidine	Tropanine	Nortropan
Tropinone	N.methyltroponine	Tropanone

*nor***Hyoscyamine,** $C_{16}H_{21}O_3N$. Carr and Reynolds have shown [1] that this alkaloid occurs in minute quantity in *Scopolia japonica*, *Datura Metel*, *D. meteloides*, *Duboisia myoporoides*, and *Mandragora vernalis*. Its constitution is established by the following facts: (1) It contains no $=N.CH_3$ group; (2) it forms a nitrosoamine, and therefore contains a $=NH$ group; (3) methyl iodide converts it into hyoscyamine; (4) on hydrolysis it yields tropic acid and *nor*tropine (*nor*tropanol). It is lævorotatory and is racemised to *nor*ATROPINE by dilute alkalis. Both *nor*hyoscyamine and *nor*atropine are mydriatic. It is probable that Merck's ψ-hyoscyamine (*see below*) is identical with *nor*hyoscyamine (*see also* Appendix, p. 449).

*pseudo***Hyoscyamine,** $C_{17}H_{23}O_3N$. This alkaloid, isomeric with atropine and hyoscyamine, was isolated by E. Merck [2] from *Duboisia myoporoides*, and has also been found by Hesse in *Mandragora officinarum* roots (*see* p. 81). It crystallises from a mixture of chloroform and ether in needles, m.p. 133°–134°. It is lævorotatory in solution, $[\alpha]_D$ — 21°. The platinichloride and the picrate were prepared; the latter is crystalline and melts at 220°. When heated with baryta water *pseudo*hyoscyamine is readily hydrolysed into tropic acid and a base, $C_8H_{15}ON$, which is neither tropine nor *pseudo*tropine.[3] According to Carr and Reynolds [4] ψ-hyoscyamine is identical with *nor*hyoscyamine (*see above*).

Hyoscine (*see Scopolamine*, p. 82). The name hyoscine has

[1] *Trans. Chem. Soc.* 1912, **101**, 946. [2] *Arch. Pharm.* 1893, **231**, 117.
[3] *Loc. cit.* [4] *Loc. cit.*

been applied to two distinct substances. It was first used by Höhn and Reichard [1] for the basic hydrolytic product of hyoscyamine, which is now known as tropine. It was subsequently used by Ladenburg [2] for a new amorphous alkaloid stated to be an isomeride of atropine, $C_{17}H_{23}O_3N$, isolated from the mother liquors of hyoscyamine. This was found subsequently by Schmidt,[3] Hesse,[4] and others to be identical with the alkaloid scopolamine, $C_{17}H_{21}O_4N$, obtained by the first-mentioned chemist from the rhizomes of *Scopolia japonica*.[5] Unfortunately the name hyoscine has passed into current commercial use for scopolamine, though the latter name is now adopted in scientific literature. At first hyoscine was used commercially for scopolamine obtained from *Hyoscyamus* spp.,[6] but this is no longer the case; thus the British and United States Pharmacopœias describe "hyoscine" as contained in Hyoscyamus and other solanaceous plants. L. Merck has pointed out [7] that, with the exception of *pseudo*hyoscyamine (*see* p. 80), no alkaloid of the composition $C_{17}H_{23}O_3N$ occurs in the secondary alkaloids of solanaceous plants, so that the existence of hyoscine having the formula $C_{17}H_{23}O_3N$ is still unconfirmed.

Mandragorine, $C_{17}H_{23}O_3N$. An alkaloid to which this name and formula were assigned was isolated by Ahrens [8] from the root of *Mandragora officinarum*, a plant whose sedative properties were well known to the ancients, and which, in the form of "wine of mandragora," was probably the first anæsthetic used in surgical operations.[9] The more recent investigations of Thoms and Wentzel [10] have shown, however, that mandragorine is merely a mixture of hyoscyamine and scopolamine with perhaps a minute quantity of a third alkaloid. Hesse has recently asserted that this root contains, in addition to hyoscyamine and scopolamine, *pseudo*hyoscyamine (*see* p. 80) and a new alkaloid also called mandragorine. This has

[1] *Annalen*, 1871, **157**, 98. [2] *Ibid.* 1880, **206**, 299.
[3] *Arch. Pharm.* 1892, **230**, 207; 1894, **232**, 409.
[4] *Annalen*, 1892, **271**, 120; 1893, **276**, 84.
[5] *Arch. Pharm.* 1890, **228**, 139, 435. [6] *Journ. Soc. Chem. Ind.* 1897, **16**, 515.
[7] *Cf.* L. Merck, *loc. cit.* [8] *Berichte*, 1889, **22**, 2159.
[9] *Asclepiad*, June 1888. [10] *Berichte*, 1901, **34**, 1023.

the composition $C_{15}H_{19}O_2N$, and furnishes a crystalline aurichloride, m.p. 124°–126°; on hydrolysis, tropic acid and a base resembling tropine are formed.[1]

Meteloidine, $C_{13}H_{21}O_4N$, occurs, along with atropine and scopolamine, in *Datura meteloides* (*see* Table on p. 49).[2] An alcoholic extract of the plant, concentrated almost to dryness, was extracted with 1 per cent. hydrochloric acid, the acid solution made alkaline with ammonia, shaken out with chloroform, and the latter solution fractionally extracted with successive portions of dilute hydrobromic acid. Meteloidine hydrobromide was obtained in the first fraction.

Meteloidine crystallises from benzene, in tabular needles, m.p. 141°–142°, $[\alpha]_D$ 0°, is readily soluble in alcohol or chloroform, sparingly so in water, ether, or benzene. The hydrobromide, $B.HBr.2H_2O$, forms chisel-shaped needles, m.p. 250° (*dry*); the aurichloride, $B.HAuCl_4.\frac{1}{2}H_2O$, m.p. 149°–150°, forms short yellow needles from dilute alcohol; the picrate has m.p. 177°–180° and forms hexagonal plates. Meteloidine is physiologically inactive.

On hydrolysis by baryta the alkaloid is resolved into tiglic acid, $CH_3.CH : C(CH_3).COOH$, and a new base, TELOIDINE, $C_8H_{15}O_3N$, which crystallises from boiling acetone diluted with a little water in chisel-shaped needles containing $1H_2O$, m.p. 168°–169° (*dry*). It is not volatile; the hydrochloride, m.p. above 300°, hydrobromide, m.p. 295°, and aurichloride, m.p. 225°, are all crystalline.

l-**Scopolamine** (*Hyoscine*), $C_{17}H_{21}O_4N$. This alkaloid was first isolated and described under this name by E. Schmidt,[3] who obtained it from the rhizome of *Scopolia japonica* and subsequently from that of *Scopolia carniolica*.[4] As already mentioned in the note on hyoscine (p. 80), the same alkaloid had been obtained under the latter name from *Hyoscyamus niger* by Ladenburg, who regarded the new base as isomeric with atropine. It has, however,

[1] *Journ. prakt. Chem.* 1901 [ii], **64**, 274.
[2] Pyman and Reynolds, *Trans. Chem. Soc.* 1908, **93**, 2077.
[3] *Arch. Pharm.* 1890, **228**, 139, 435.
[4] *Cf.* however, Dunstan and Chaston, *Pharm. Journ.* 1889 [iii], **20**, 461.

been shown by Hesse,[1] Schmidt,[2] and L. Merck [3] that it is extremely improbable that any alkaloid, isomeric with atropine or hyoscyamine, is obtainable from *Hyoscyamus niger*. Therefore Ladenburg's hyoscine must have been impure scopolamine.

The occurrence of scopolamine in solanaceous plants is shown in the Table on p. 49. The alkaloid is usually obtained by working up the mother liquors from the preparation of hyoscyamine (*see* p. 50), but *Datura Metel*, which contains scopolamine as its chief constituent, would appear to be a particularly satisfactory material from which to prepare this alkaloid.

The free base crystallises with $1H_2O$ in transparent prisms, m.p. 59°, is soluble in the ordinary solvents and slightly so in water. It is lævorotatory, $[\alpha]_D^{20} - 18°$ in alcohol, $-28°$ in water. The salts crystallise well: the hydrobromide, $B.HBr.3H_2O$, m.p. 193°–194° (*dry*), $[\alpha]_D - 15{\cdot}72°$ in alcohol, $-24°$ to $-25°$ in water (Gadamer),[4] crystallises in rhombic tablets, is readily soluble in water (1 in 1·5 at 25°) or alcohol (1 in 16 at 25°), sparingly in chloroform (1 in 750 at 25°), insoluble in ether. It is bitter and acrid to the taste and is slightly acid to litmus. This salt is that mostly used in medicine. The aurichloride, $B.HAuCl_4$, m.p. 198°, crystallises in yellow prisms, and is sparingly soluble in water containing hydrochloric acid (1 in 510 at 50° for a solution containing 10 c.c. of hydrochloric acid, sp. gr. 1·19, in 1000 c.c. of water). The picrate has m.p. 180°–181°.

i-Scopolamine (*Atroscine*). Scopolamine, like hyoscyamine, is readily transformed by the action of dilute alkalis into an optical isomeride, *i*-scopolamine, the same change being brought about in its salts even by very gentle heating, and for this reason commercial scopolamine hydrobromide invariably contains some of the inactive salt.

Hesse [5] isolated from the scopolamine hydrobromide of commerce

[1] *Annalen*, 1892, **271**, 120; 1893, **276**, 84.
[2] *Arch. Pharm.* 1892, **230**, 207; 1894, **232**, 409.
[3] *Journ. Soc. Chem. Ind.* 1897, **16**, 515.
[4] *Cf.* Carr and Reynolds, *Trans. Chem. Soc.* 1910, **97**, 1330.
[5] *Berichte*, 1896, **29**, 1776.

an optically inactive alkaloid isomeric with scopolamine, which he named ATROSCINE. According to Schmidt [1] this substance was merely *i*-scopolamine, but Gadamer [2] showed that Hesse's atroscine and Schmidt's *i*-scopolamine were respectively di- and monohydrates of the same alkaloid.[3]

i-Scopolamine may be prepared by the action of moist silver oxide, or a very dilute sodium hydroxide solution in alcohol, on *l*-scopolamine, at atmospheric temperature. L. Merck [4] has pointed out that scopolamine hydrobromide from henbane seed has as a rule a rotation of — 24° to — 25°, whilst that from *Scopolia* rhizome has a rotation of — 13·47°, so that *Scopolia* rhizome appears always to contain some *inactive* scopolamine.[5] From such scopolamine hydrobromide, according to Gadamer,[6] the inactive alkaloid can be separated by adding sodium carbonate to the aqueous solution, and extracting with a mixture of chloroform and ether. On rubbing the residue with alcohol and water and cooling, the dihydrate (Hesse's atroscine), rosettes of needles, m.p. 37°–38° (36°–37°, Hesse), forms, whilst "seeding" with the monohydrate (Schmidt's *i*-scopolamine) leads to the separation of the latter form, monoclinic needles, m.p. 56°–57°. The separation of either form can be induced at will by adding a crystal of the desired form to a solution of the alkaloid in alcohol, to which water sufficient to produce cloudiness has been added. The anhydrous alkaloid melts at 82°–83°. The aurichloride has m.p. 208° (*decomp.*); the hydrobromide forms monoclinic crystals, m.p. 180° (*dry*), and gives hydrates with $\frac{1}{2}H_2O$, rhombic tablets, and with $3H_2O$, rhombic crystals.

Scopolamine is mydriatic to about the same extent as hyoscyamine. Its reactions are for the most part like those of atropine and hyoscyamine, but it gives a white precipitate with mercuric chloride. It may best be distinguished from these alkaloids by means of its aurichloride or picrate, m.p. 193°.

When warmed with barium hydroxide, scopolamine is hydrolysed,

[1] *Arch. Pharm.* 1898, **236**, 9, 47. [2] *Ibid.* 1898, **236**, 382.
[3] *Cf.* Hesse, *Annalen*, 1899, **309**, 75; *Journ. prakt. Chem.* 1901 [ii], **64**, 353; 1902 [ii], **66**, 194. [4] *Loc. cit.* [5] *Cf.* Schmidt, *Arch. Pharm.* 1898, **236**, 54.
[6] *Arch. Pharm.* 1898, **236**, 382. *Cf.* Hesse, *Annalen*, 1899, **309**, 75.

yielding tropic acid and a new base, $C_8H_{13}O_2N$, which has been variously named "*pseudo*tropine," "oxytropine," "oscine," and "scopoline," the last name being that now generally adopted. According to Gadamer [1] *l*-scopolamine is slowly hydrolysed by dilute alkalis, yielding scopoline and *l*-tropic acid, whence it would appear to be *l-tropylscopolēine*, *i*-scopolamine (atroscine) being *i-tropylscopolēine*.

The constitution of tropic acid has been discussed already (p. 65).

SCOPOLINE, $C_8H_{13}O_2N$. This substance was probably first obtained by Ladenburg by the hydrolysis of hyoscine. It was prepared by Hesse,[2] who named it "oscine" and assigned to it the foregoing formula. It was subsequently examined by Luboldt.[3] It forms colourless, hygroscopic, prismatic crystals, m.p. 109°, from ether or light petroleum, and boils at 241°–243°. The salts crystallise well.

Like tropine, scopoline contains a hydroxyl group and is readily esterified by acids, forming a series of esters, the scopolēines.[4] When scopoline is esterified with tropic acid, scopolamine is not formed. The product is an amorphous alkaloid, $C_{17}H_{19}O_3N$, which on solution in acids takes up the elements of a molecule of water, forming amorphous salts of a base, not known in the free state, isomorphous with scopolamine. This base is mydriatic, but less so than scopolamine. None of the artificial scopolēines have been used in medicine.

The constitution of scopoline is still unknown. It is a tertiary amine containing an $:NCH_3$ group, and on oxidation with chromic anhydride in sulphuric acid yields scopoligenine, $C_7H_{10}O_2:NH$ (analogous with tropigenine, similarly obtained from tropine, p. 70), pyridinemethosulphate, methylamine, and carbon dioxide. Scopoligenine forms prismatic crystals, m.p. 205°–206°, sublimes at 120°, and is reconverted to scopoline by the action of methyl iodide.

[1] *Arch. Pharm.* 1901, **239**, 294.
[2] *Annalen*, 1892, **271**, 114; 1893, **276**, 84. [3] *Arch. Pharm.* 1898, **236**, 11.
[4] *Merck's Report*, 1894, p. 15; Luboldt, *loc. cit.* p. 33.

Scopoline yields a monoacetyl derivative (*acetylscopolēine*, m.p. 53°) and a benzoyl derivative (*benzoylscopolēine*, m.p. 68°–70°), both of which are crystalline. The alkaloid contains no carbonyl group. On heating with excess of saturated hydrobromic acid at 130°, it yields hydrobromoscopoline hydrobromide, $C_8H_{14}O_2NBr.HBr$, plates, m.p. 202°, and this on reduction furnishes dihydroscopoline, $C_8H_{15}O_2N$ (aurichloride, m.p. 200°–201°), which contains two hydroxyl groups and on oxidation with chromic acid yields a dibasic acid provisionally regarded as a *N*-methylpiperidine—*aa'*-dicarboxylic acid.

On the basis of these results Luboldt,[1] Schmidt and collaborators[2] conclude that scopoline must contain a pyridine nucleus, that the hydroxyl group must lie outside this nucleus, and that this also applies to the second oxygen atom; the latter appears to be present in the form of an ether group, $O\begin{<}\begin{matrix}C= \\ | \\ C=\end{matrix}$ which by the action of hydrobromic acid is converted into $\begin{matrix}HO.C= \\ | \\ Br.C=\end{matrix}$

Tetramethylaminobutane, $N(CH_3)_2.CH_2.CH_2.CH_2.CH_2.N(CH_3)_2$. This diamine was isolated in 1907 by E. Merck from the secondary bases of *Hyoscyamus muticus*, and was investigated by Willstätter and Heubner.[3] It is a colourless liquid, D^{15} 0·7941, b.p. 169°, miscible in all proportions with water, strongly alkaline in reaction, optically inactive, and possesses a pungent acrid taste. The hydrochloride, $C_8H_{20}N_2.2HCl$, forms triangular prisms, m.p. 273° (*decomp.*), the platinichloride, $B.H_2PtCl_6.2H_2O$, prisms, m.p. 234° (*decomp.*), and the aurichloride, golden-yellow prisms, m.p. 206°–207° (*decomp.*), from hot water. The substance is not poisonous to frogs or rabbits in moderate doses. It absorbs two molecules of methyl iodide, forming hexamethyltetramethylenediammonium odide, $MeI.NMe_2.CH_2.CH_2.CH_2.CH_2.NMe_2.MeI$, which on dis-

[1] *Loc. cit.* (*cf.* Willstätter and Hug, *Zeit. physiol. Chem.* 1912, **79**, 146).

[2] *Apoth. Zeit.* 1902, **17**, 592; *Arch. Pharm.* 1905, **243**, 559; 1909, **247**, 79.

[3] *Berichte*, 1907, **40**, 3869.

tillation with silver oxide yields butadiene and trimethylamine. Hexamethyltetramethylenediammonium chloride, identical in all respects with that obtainable from the iodide mentioned above, was prepared by methylating putrescine (1 : 4-diaminobutane), and this on distillation furnished *N*-methylpyrrolidine methochloride. These reactions show that the base from *H. muticus* must be tetramethyldiaminobutane : its occurrence is of interest from the fact that by distillation of its dimethochloride it can so readily be converted into a pyrrolidine derivative, and that hyoscyamine, the chief alkaloid of *H. muticus*, contains a pyrrolidine ring in its nucleus.

Physiological Action of Atropine and the Allied Alkaloids

Atropine. This alkaloid exhibits a very complex physiological action when administered internally. It at first stimulates and eventually depresses the central nervous system, giving rise to hallucinations, a feeling of exaltation, inconsequent and garrulous speech, delirium and convulsions followed by stupor and coma. Death eventually results from asphyxia. As little as 0·1 grm. has proved a fatal dose. Atropine paralyses the peripheral nerve endings and in this way affects the secretory glands, the heart, and organs containing unstriped muscle.

Most of the secretions are decreased by atropine owing to paralysis of the nerve ends. It is to this feature of its action that the dryness of the throat and mouth characteristic of poisoning by atropine is due, and it is for this reason that the alkaloid is used in the later stages of phthisis as a preventive of night-sweating. The kidney is but little affected by atropine and consequently there is little or no change in the secretion of urine after its administration. Atropine paralyses the inhibitory terminations of the vagus in the heart. The heart is sometimes slowed and weakened at first, but is generally quickened as a result of paralysis of the inhibitory fibres in the heart. Respiration becomes quicker and deeper, but eventually slower and shallower, and respiratory failure is the cause of death from large doses. There is often a

marked rise in temperature. Atropine affects all organs containing unstriped muscle, lessening their movements, and consequently is antagonistic in this respect to muscarine and nicotine.

Atropine is principally used in medicine owing to its property of causing dilatation of the pupil of the eye (mydriasis). The dilatation may be induced by internal administration or by application of atropine solutions to the eye. It is due to paralysis of the motor nerve terminations in the circular muscle of the iris. At the same time the accommodation is paralysed as a result of the action of the alkaloid on the nerve endings in the ciliary muscle. This property of atropine and the allied alkaloids has been the subject of many investigations, some of which are of special interest owing to their bearing on the correlation of the constitution of these alkaloids with their physiological action. Mydriasis is caused by atropine, hyoscyamine, scopolamine, ephedrine, and *pseudo*ephedrine among the naturally occurring alkaloids, and by *ac*-tetrahydro-β-naphthylamine, and in view of the great differences in structure shown among these substances, it is at present impossible to say that the property is due to any particular nuclear structure in the active substances. In the case of the atropine group of alkaloids, it appears to be inherent in the tropine residue, since, although tropine does not cause mydriasis when applied directly to the eye, it induces it when administered internally in large doses to a cat. The influence of side-chains in increasing or reducing the mydriatic effect has been thoroughly investigated by Jowett and collaborators, who have prepared and tested about forty tropëines containing very varied acid radicles. The preparation and properties of these tropëines are described in the following papers : Jowett and Hann, *Trans. Chem. Soc.* 1906, **89**, 357 ; Jowett and Pyman, *ibid.* 1907, **91**, 92 ; 1909, **95**, 1020 ; and the correlation of their structure and mydriatic effect is discussed by Jowett and Pyman in a paper contributed to the London Congress of Applied Chemistry, 1909.[1] These authors compared the effect of solutions of the various tropëines by instillation into the conjunctival sacs of cats. The solutions used were

[1] *Proc. 7th Int. Cong. Appl. Chem.* London, 1909.

equivalent in tropine content to 1 per cent. solution of homatropine hydrobromide. As a result of this work they draw the following conclusions, for the conditions specified :

I. Tropēines of aliphatic acids exert no mydriatic effect.

II. The replacement of the benzene residue by that of pyridine in the acyl group of a mydriatic tropēine does not cause the activity to vanish.

III. In tropēines containing a disubstituted benzene ring, those in which the replacing groups occupy the *para* position have the least mydriatic action ; thus *o*- and *m*-hydroxybenzoyl-tropēines are active, but not the *p*-isomeride.

IV. No generalisation as to the relation between the mydriatic action and chemical constitution of the tropēines can be made at present which will explain the observed facts.

Hyoscyamine. The natural alkaloid *l*-hyoscyamine and its *d*-isomeride resemble atropine qualitatively in action, but the former acts much more strongly on the peripheral nerve endings than atropine. *d*-Hyoscyamine (*see* p. 64) has about one-hundredth the mydriatic power of *l*-hyoscyamine and about one-twenty-fifth its power of paralysing the nerve terminations in the heart. It appears likely that the intermediate action on peripheral nerve endings shown by atropine is due to the fact that this, the racemic form of hyoscyamine, is separated in the body into its optical isomerides, and that only the *lævo* form acts on the nerve terminals.[1]

Meteloidine. This alkaloid has no marked physiological action.[2]

Scopolamine (*Hyoscine*). This substance resembles atropine in its action on the peripheral nerve terminals ; it produces mydriasis and paralysis of accommodation more quickly than atropine, but the effect is of shorter duration. Its effects on the central nervous system are quite different from those of atropine ; as a rule it induces a feeling of fatigue and drowsiness, though in many cases there is a short stage of excitement, with giddiness and indistinct

[1] Cushny, *Proc. Amer. Physiol. Soc.* 1903, xiv ; *J. Physiol.* 1904, **30**, 176 ; Laidlaw, *Trans. Chem. Soc.* 1909, **95**, 1969.

[2] Pyman and Reynolds, *Trans. Chem. Soc.* 1908, **93**, 2077.

speech, especially when large doses are used. According to Hug the *l*- form is more active than the *i*- form and is more stable in aqueous solution.

ALKALOIDS OF *ERYTHROXYLON COCA*

The genus *Erythroxylon*, to which the distribution of this group of alkaloids is confined, comprises about eighty species, of which only four or five have been subjected to complete examination. The habitat of these plants is principally the western side of South America, and although several indigenous species occur in India, Africa, and Australia, the latter have at present no economic value, and the attention of coca cultivators is chiefly devoted to three or four kinds derived originally from Bolivia and Peru, viz.:

Erythroxylon Coca, Lam. (Bolivian or Huanuco coca).

Erythroxylon Coca var. *Novo-granatense* (*E. Carthagense*, Jacq).

Erythroxylon Truxillense, Rusby (Peruvian or Truxillo leaves).

This classification of the botanical sources of coca leaves is due to Rusby,[1] and has been fully discussed by Holmes,[2] who adopts it with certain minor modifications.

Commercially, four kinds of coca leaves are known in the London market:

(1) Huanuco or Bolivian. (3) Java.

(2) Truxillo or Peruvian. (4) Ceylon.

According to Rusby, (1) is from *E. Coca*, Lam., (2) and (3) are from *E. Truxillense*, Rusby, and (4) is from *E. Carthagense*, Jacq. Rusby's classification of these leaves, however, is placed in some doubt by the fact that the Peruvian leaves contain a large proportion of cocaine, whilst the Java leaves are stated to contain little or none.[3] It is improbable, therefore, that these two varieties are derived from the same species. Further, commercial consignments of Ceylon leaves are often described as either of "Truxillo character" or "Huanuco character," and samples examined by Professor

[1] *Druggists' Circular and Chemists' Gazette*, November 1900, pp. 220–223. *Pharm. Journ.* January 5, 1901, p. 4, and January 26, 1901, p. 81.

[2] *Cf.* however, de Jong, *Chem. Weekbl.* 1908, **5**, 666.

Greenish recently were indistinguishable from Truxillo leaves, and the same samples examined chemically at the Imperial Institute proved to contain a large proportion of cocaine. It seems likely, therefore, that Ceylon leaves are of the same botanical origin as Peruvian leaves,[1] whilst those of Java are from a distinct species, or at least from a well-marked variety of *E. Truxillense*.

In South America coca leaves are chewed with lime as a stimulant by the natives of that continent, and are largely exported to Europe for use in medicine and for the preparation of cocaine. Crude cocaine is also manufactured in Peru and exported chiefly to Hamburg to be refined. The coca leaves of international trade come principally from Peru and Java, with small quantities from Ceylon.

A large number of alkaloids have been obtained from coca leaves ; they fall naturally into four groups, as follows :

(1) The *cocaines*, which on hydrolysis yield ecgonine, benzoic, cinnamic, or truxillic acid, and methyl alcohol.

Cocaine : Methylbenzoylecgonine.
Cinnamylcocaine : Methylcinnamoylecgonine.
α-Truxilline : Methyl-α-truxilloylecgonine.
β-Truxilline : Methyl-β-truxilloylecgonine.

(2) The pseudo*tropēines* are closely related to the tropēines (p. 66), and are easily hydrolysed into an acid and the basic alcohol *pseudo*tropine, a stereoisomeride of tropine.

Tropacocaine : *Benzoyl*pseudo*tropēine*.

(3) The *acylecgonines* are acyl esters of ecgonine and by hydrolysis furnish this base and an acid.

Benzoylecgonine.

(4) The *hygrines* are volatile alkaloids of simpler structure than the foregoing. They have not been thoroughly investigated.

Hygrine (low boiling).
Cuscohygrine.
β-*Hygrine* (high boiling).

[1] *Bull. Imp. Inst.* 1912, **10**, 37.

The occurrence of these alkaloids in coca leaves from various sources is as follows (the percentages of total alkaloids given are very uncertain, since the methods of estimation are in most cases different, and some of them are of doubtful accuracy):

Commercial Coca Leaves

Geographical source	Total alkaloids per cent.	Chief constituent	Reference
Java	1·0–2·5 (season 1908)	Cinnamyl-cocaine	de Jong, *Teysmannia*, 1910, **21**, 201
	0·6–2·4 (season 1909) 1·22		Hartwich, *Arch. Pharm.* 1903, **241**, 617
Ceylon	0·7–1·6	Cocaine	*Bull. Imp. Inst.* 1912, **10**, 37; and Hartwich, *loc. cit.*
Bolivia	0·7–0·9	Cocaine	Hartwich, *loc. cit.*
Peru	Up to 1·00	Cocaine	Hartwich, *loc. cit.*

Coca leaves grown experimentally in India and examined by Howard [1] contained 0·4 to 0·8 per cent. of alkaloid, largely cocaine. Small quantities of alkaloids have also been found in the leaves of *E. pulchrum* (South America), *E. monogynum* (India), *E. montanum*, *E. laurifolium*, *E. retusum*, *E. areolatum*, and *E. ovatum*.[2] de Jong has pointed out that the nature of the alkaloids in coca leaves varies with the age of the leaves, the youngest leaves being richest in cinnamylcocaine, whilst in the older leaves this is replaced by cocaine or truxilline.[3]

Estimation of Total Alkaloids. For the estimation of the total alkaloids of coca leaves the United States Pharmacopœia (8th Rev.) gives the following process:

Ten grammes of powdered leaves are mixed with 50 c.c. of a mixture of ether (4 vols.) with chloroform (1 vol.), and after ten minutes 2 c.c. of ammonia solution (sp. gr. 0·958 at 25°) are added mixed with 3 c.c. of water, and the whole shaken frequently during one hour. The contents of the flask are now transferred to a small glass percolator plugged at the lower end with cotton-wool and

[1] *Kew Bulletin*, 1889, p. 8. [2] *Loc. cit.* [3] *Rec. Trav. Chim.* 1906, **25**, 233.

inserted in a separator containing 6 c.c. of *N*-sulphuric acid mixed with 20 c.c. of distilled water. When all the liquid has passed through, the powder in the percolator is packed in firmly with a glass rod and the flask is rinsed out into the percolator with 10 c.c. of the ether-chloroform mixture, followed by other small portions of the same menstruum, using 50 c.c. in all. The separator is now shaken for one minute, the acid layer drawn off, and the extraction with diluted sulphuric acid (6 c.c. *N*-acid with 20 c.c. of water) repeated twice, using 10 c.c. each time. The combined acid liquids collected in a second separator are made alkaline with ammonia solution and shaken out with ether, using in succession 25, 20, and 15 c.c. The combined ethereal solutions are collected in a beaker and the solvent allowed to evaporate completely over warm water. The residue is dissolved in 3 c.c. of ether, which is also allowed to evaporate. The residue is then dissolved in 4 c.c. of $N/10$ sulphuric acid and titrated back with $N/50$ potassium hydroxide solution, using cochineal or iodeosin as indicator. The percentage of ether-soluble alkaloids in the leaves is given by the formula $(4 - n/5)0{\cdot}3$, where n is the number of c.c. of $N/50$ alkali used. The percentage should be not less than 0·5.

A critical survey of methods for conducting the assay of coca leaves is given by Bierling, Pape, and Viehover.[1]

For the assay of fluid extract of coca the following process is given in the U.S. Pharmacopœia: Ten cubic centimetres of the extract are mixed with 25 c.c. of ether and 2 c.c. of ammonia solution (sp. gr. 0·958 at 25°) and shaken for one minute. The aqueous layer is drawn off and again shaken with 20 c.c. of ether for one minute. The combined ethereal liquids are shaken first with 5 c.c. of *N*-sulphuric acid diluted with 5 c.c. of water and then with 1 c.c. of *N*-acid diluted with 9 c.c. of water, the acid liquids being in each case run into a second separator, where they are made alkaline with ammonia solution and extracted three times in succession with 20, 15, and 15 c.c. of ether. The residue from the combined ethereal solutions is dissolved in 5 c.c. of $N/10$ sulphuric acid and titrated

[1] *Arch. Pharm.* 1910, **248**, 303.

back with n c.c. of $N/50$ potassium hydroxide solution, using cochineal or iodeosin as indicator. The percentage of alkaloids in the fluid extract is given by the formula $(5 - n/5)0{\cdot}3$. It should be not less than 0·5 grm. per 100 c.c.

The amount of cocaine in coca leaves cannot at present be accurately determined, but various methods are available by which an approximate estimation of the richness in cocaine of the total alkaloid obtained by the above method of estimation may be obtained.[1]

Estimation of Ecgonine. In view of the fact that much of the cocaine of commerce is not obtained directly from the leaves but from ecgonine obtained by the hydrolysis of the secondary alkaloids in the leaves (*see* p. 98), a method for the estimation of ecgonine is of importance. Greshoff recommended the following process: The total alkaloids from 15 grm. of leaves are boiled for one hour in a reflux apparatus with thirty times their weight of dilute hydrochloric acid and an equal volume of water. When cold the solution is filtered and extracted twice in succession with its own volume of ether. The aqueous solution is then evaporated to dryness and the residual ecgonine hydrochloride weighed, after drying at 90°–95°.[2]

Cocaine, $C_{17}H_{21}O_4N$. This alkaloid is believed to be largely prepared by a process devised by Bignon.[3] The finely powdered coca leaves are extracted with a mixture of aqueous sodium carbonate and petroleum, the mixture being gently warmed and continuously agitated, whereby the liberated alkaloids pass into solution in the petroleum. The latter is then drawn off and the remainder pressed from the residue. Dilute hydrochloric acid is added to the filtrate and the crystalline precipitate of crude cocaine hydrochloride filtered off, pressed, and dried. A small quantity of the

[1] For such processes, *see* Grandval and Lajoux, *Journ. Pharm.* 1893 [5], **28**, 102; Garsed, *Pharm. Journ.* 1903 [iv], **17**, 784. *Cf.* de Jong, *Rec. Trav. Chim.* 1906, **25**, 1.

[2] *Pharm. Weekbl.* 1907, **44**, 961. *Cf.* de Jong, *Rec. Trav. Chim.* 1906, **25**, 1, and *Pharm. Weekbl.* 1908, **45**, 42.

[3] Guareschi, *Einführung in das Studium der Alkaloide*, p. 267, or *Jahresberichte*, 1885, 1714. *Cf.* de Jong, *Rec. Trav. Chim.* 1906, **25**, 311.

alkaloid still remains in the mother liquor, and may be obtained by evaporation of the latter. The crude salt so prepared generally contains from 80 to 90 per cent. of cocaine hydrochloride. It is purified by liberating the free base and dissolving this in alcoholic hydrochloric acid, the hydrochloride so precipitated being recrystallised. The mother liquors contain the amorphous alkaloids, which have as such no economic value, and these are converted into cocaine in the following way: The solutions are concentrated by evaporation and heated to the boiling-point with hydrochloric acid during one hour. The reaction mixture is poured into excess of water to precipitate the insoluble truxillic and other acids produced by the hydrolysis, and the filtrate evaporated until ecgonine hydrochloride separates out, this process being facilitated by addition of alcohol and ether. The ecgonine is set free in the usual manner, dried, and digested in molecular quantity with benzoic anhydride for one hour. The excess of benzoic anhydride and the benzoic acid produced are removed by ether, the benzoylecgonine remaining undissolved together with unattacked ecgonine, which should not amount to more than 20 per cent. of the quantity taken. The two bases are separated by washing with a small amount of water, in which ecgonine is very soluble. The purified benzoylecgonine is now mixed with methyl iodide and a solution of potassium hydroxide and methyl alcohol, and the whole boiled for several hours, when cocaine is quantitatively formed, and may be purified as already described.[1] According to Merck the conversion of ecgonine into cocaine may be accomplished in one operation by heating the former with methyl iodide and benzoic anhydride under pressure.[2]

A very large proportion of the cocaine now made is obtained from Java leaves in which the chief alkaloid is cinnamylcocaine, not cocaine itself. In this case the total alkaloids are treated by the process just described for the preparation of cocaine from the secondary bases.

[1] Liebermann and Giesel, *Berichte*, 1888, **21**, 3196. *Cf.* Einhorn and Klein, *ibid.* p. 3335.

[2] *Berichte*, 1885, **18**, 2953.

The crude cocaine exported from Peru is prepared by extracting the finely ground leaves with dilute sulphuric acid. The acid extract is made alkaline with sodium carbonate, and the liberated alkaloids dissolved out by petroleum. From the latter they are re-extracted by dilute sulphuric acid and finally precipitated with sodium carbonate solution, the precipitate being washed with water, pressed, and dried for export. This material contains from 83 to 97 per cent. of cocaine. About 6000 kilogrammes of this product are exported per annum.[1]

Cocaine crystallises from alcohol in monoclinic four- to six-sided prisms, m.p. 98°, and is volatile above 90°. It is lævorotatory, $[\alpha]_D$ −15·8°, slightly soluble in cold water (1 in 600 at 25°), more soluble in hot water (1 in 260 at 80°), readily soluble in alcohol (1 in 5 at 25°), ether, benzene, or light petroleum. The aqueous solution is alkaline to litmus, has a slightly bitter taste, and when applied to the tongue produces a characteristic numbness. The ordinary salts of cocaine are crystalline. The hydrochloride, the salt chiefly used in medicine, crystallises anhydrous from alcohol, in short prisms, m.p. 186°, $[\alpha]_D$ − 71·95° (in 2 per cent. aqueous solution), − 67·5° (in aqueous alcohol). It is readily soluble in water (1 in 0·4 at 25°) or alcohol (1 in 2·6 at 25°), but insoluble in ether or light petroleum. The chromate, $B.H_2CrO_4.H_2O$, is sparingly soluble in water and is precipitated as orange-yellow leaflets, m.p. 127°, when potassium chromate is added to an acid solution of the hydrochloride. The platinichloride, $B_2.H_2PtCl_6$, is crystalline and sparingly soluble in water. Aqueous mercuric chloride gives with a solution of cocaine hydrochloride a bulky precipitate of the mercurichloride, $B.HCl.HgCl_2$, which may be crystallised from alcohol. The nitrate, periodide, $B.HI.I_2$, m.p. 161°, formate, m.p. 42°, and salicylate, which is triboluminescent, have also been used in medicine.

Detection. Cocaine may be detected by the peculiar sensation of numbness which it produces on the tongue, by the characteristics of the derivatives already recorded, and by the decomposition

[1] *Chemist and Druggist*, 1912, **80**, 51.

products resulting from the action of acids and alkalis (*see below*).

The following qualitative reactions are also useful: The alkaloid forms a colourless solution with sulphuric acid, which gives off benzoic acid on warming. A cubic centimetre of a 3 per cent. solution of potassium permanganate gives a crystalline (rectangular plates), violet precipitate with 0·01 grm. of the hydrochloride dissolved in two drops of water.[1] The hydrochloride, heated with a little alcoholic potash, gives off an odour of methyl benzoate. The purity of the hydrochloride may, according to Merck,[2] be roughly gauged by Maclagan's test. (The figures in brackets in the following description are those prescribed in the United States Pharmacopœia for this test.) It consists in dissolving 0·06 grm. (0·1 grm.) of the salt in 60 grm. of water (85 c.c.), adding two drops of 10 per cent. ammonia (four drops of ammonia solution, sp. gr. 0·958 at 25°), and stirring vigorously. After fifteen minutes the mixture should deposit a *crystalline* precipitate of free cocaine; a milky appearance indicates the presence of amorphous alkaloids. If 0·1 grm. of the salt is dissolved in 5 c.c. of water containing three drops of dilute sulphuric acid (sp. gr. 1·067 at 25°), the addition of three drops of $N/10$ potassium permanganate should produce a violet colour lasting at least thirty minutes, indicating the presence of traces only of cinnamylcocaine.[3]

d-Cocaine (iso*Cocaine*). A dextrorotatory isomeride of *l*-cocaine was obtained from coca leaves by Liebermann and Giesel,[4] but is now generally believed to have been produced by the action of alkalis on the *l*-cocaine contained in the leaves. It crystallises in colourless prisms, m.p. 46°, and has a specific rotation $[\alpha]_D + 4{\cdot}5°$ in water. The nitrate is sparingly soluble in water (1·5 in 100 at 20°). This base has since been prepared synthetically from *d*-ecgonine (p. 103).[5]

dl-Cocaine. This was prepared by Willstätter and Bode[6]

[1] *Cf.* Seiter, *Amer. Journ. Pharm.* 1911, **83**, 195, 265.
[2] *Cf.* Günther, *Ber. Pharm. Ges.* 1899, **9**, 38.
[3] *Cf.* Hankin, *Analyst*, 1911, **35**, 2.
[4] *Berichte*, 1890, **23**, 508, 926.
[5] Einhorn and Marquardt, *ibid.* 1890, **23**, 468, 981.
[6] *Berichte*, 1901, **34**, 1457.

from synthetic *dl*-ecgonine. It crystallises from light petroleum in hexagonal plates, m.p. 80°, yields a hydrochloride, m.p. 205°, and differs from the natural *l*-cocaine in giving a sparingly soluble nitrate, m.p. 172°, in which respect it resembles *d*-cocaine. The aurichloride, $B.HAuCl_4.2H_2O$, is crystalline, m.p. 65°–70° or 164°–165° (*dry*).

When heated with mineral acids cocaine is hydrolysed into a new base ecgonine (*see* p. 103), benzoic acid, and methyl alcohol,[1] and a similar change takes place with baryta water. If the alkaloid is boiled with water, methyl alcohol alone is split off and a new base, benzoylecgonine, is produced,[2] thus :

$$\underset{\textit{Cocaine}}{C_{17}H_{21}O_4N} + H_2O = CH_3OH + \underset{\textit{Benzoylecgonine}}{C_{16}H_{19}O_4N}.$$

Benzoylecgonine occurs in coca leaves (p. 101). On hydrolysis by acids or alkalis it yields ecgonine and benzoic acid, thus :

$$\underset{\textit{Benzoylecgonine}}{C_{16}H_{19}O_4N} + H_2O = \underset{\textit{Ecgonine}}{C_9H_{15}O_3N} + C_6H_5.COOH.$$

Cocaine is, therefore, methylbenzoylecgonine.

l-Cinnamylcocaine, $C_{19}H_{23}O_4N$. This alkaloid was isolated by Giesel [3] from Java coca leaves, in which it is the chief alkaloid, and soon afterwards was prepared synthetically by him.

It is practically insoluble in water, but easily soluble in organic solvents. It crystallises best from benzene or light petroleum in rosettes of needles, m.p. 121°, $[\alpha]_D$ — 4·7° in chloroform. The hydrochloride, $B.HCl.2H_2O$, forms long, shining, somewhat flattened needles, m.p. 176° (*dry*), from water. The platinichloride, m.p. 217°, is precipitated amorphous, but crystallises on standing. The aurichloride forms yellow needles, m.p. 156°.

When warmed with hydrochloric acid the base is hydrolysed, furnishing ecgonine, cinnamic acid, and methyl alcohol.

The synthesis of the alkaloid was effected by heating ecgonine

[1] Lossen, *Annalen*, 1865, **133**, 351.

[2] Paul, *Pharm. Journ.* 1887–88 [iii], **18**, 781 ; Einhorn, *Berichte*, 1888, **21**, 47.

[3] *Berichte*, 1889, **22**, 2661.

at 100° with cinnamic anhydride and methylating the resulting cinnamoylecgonine (colourless needles, m.p. 216°).

The isomeric *d*-CINNAMYLCOCAINE, which does not occur in coca, was prepared by Einhorn and Deckers,[1] by the action of cinnamoyl chloride at 150°–160° on *d*-ecgonine methyl ester. It crystallises in prisms, m.p. 68°, $[\alpha]_D + 2°$ in alcohol. The hydrochloride, B.HCl, forms needles, m.p. 186°; the platinichloride, needles, m.p. 208°; and the aurichloride, orange needles, m.p. 164°.

Truxillines, $C_{38}H_{46}O_8N_2$. In 1887 Hesse isolated from Peruvian coca leaves an amorphous alkaloid which he named cocamine;[2] a year later Liebermann[3] examined this material, and by fractionation of its solutions by addition of petroleum proved it to be a mixture of at least two isomeric bases, which he named *α*- and *β*-truxillines. The pure alkaloids have not been obtained from coca leaves owing to the difficulty of separating them, but each has been prepared synthetically.[4]

α-TRUXILLINE (*Cocamine*, *γ-isatropylcocaine*). An amorphous white powder, m.p. 80°, easily soluble except in light petroleum and water. Solutions of the base are lævorotatory, and possess a bitter taste.

When warmed with hydrochloric acid the base undergoes hydrolysis with the production of ecgonine, methyl alcohol, and *α*-truxillic acid (*γ*-isatropic acid), according to the following equation:

$$\underset{\textit{α-Truxilline}}{C_{38}H_{46}O_8N_2} + 4H_2O = \underset{\textit{α-Truxillic acid}}{(C_9H_8O_2)_2} + 2CH_3OH + \underset{\textit{Ecgonine}}{2C_9H_{15}O_3N}.$$

The synthesis of the alkaloid was accomplished by the action of *α*-truxillic anhydride on ecgonine and methylation of the resulting *α*-truxilloylecgonine.

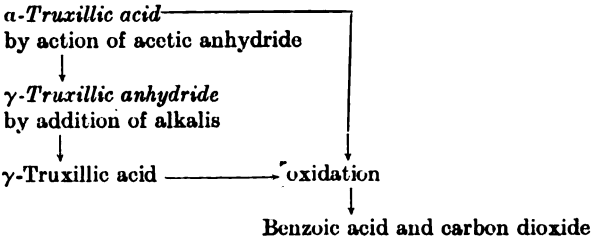
β-TRUXILLINE (iso*Cocamine*, *δ-isatropylcocaine*). This base sinters at 45°, and decomposes above 120°, $[\alpha]_D - 29{\cdot}3°$. It undergoes hydrolysis, furnishing *β*-truxillic acid (*δ*-isatropic acid),

[1] *Berichte*, 1891, **24**, 7. [2] *Ibid.* 1889, **22**, 665.
[3] *Ibid.* 1888, **21**, 2342.
[4] Liebermann and Drory, *ibid.* 1889, **22**, 682.

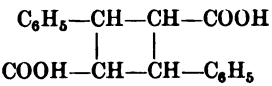
together with ecgonine and methyl alcohol. It also has been synthesised by Liebermann and Drory.[1]

The truxillines are stated to exert little or no local anæsthetic action, but to be cardiac poisons.

TRUXILLIC ACIDS (*Dicinnamic acids*), $(C_9H_8O_2)_2$. This group of isomeric acids has been investigated by Liebermann and collaborators.[2] They all yield cinnamic acid when distilled, but are not attacked by potassium permanganate, and are, therefore, to be regarded as saturated polycinnamic acids. The isomerides are divisible into two pairs of acids, each pair giving the same product when oxidised. These relationships may be concisely exhibited thus :

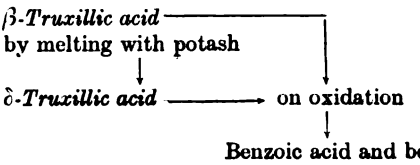


These reactions are accounted for by the following formula, which represents α- and γ-truxillic acids as geometrically isomeric *cis-trans*-tetramethylene derivatives.[3]



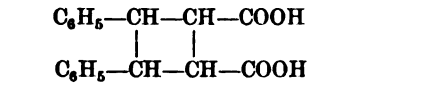
α- and γ-*Truxillic acids* (γ- and ε-*isatropic acids*)

The second pair of isomerides shows the following relationships :



[1] *Loc. cit.*
[2] *Berichte*, 1888, **21**, 2342 ; 1889, **22**, 124, 130, 680, 782, 2240 ; 1890, **23**, 2516.
[3] *Cf.* Riiber, *ibid.* 1902, **35**, 2411, 2908.

and are, therefore, appropriately represented as *cis*-tetramethylene derivatives :



β- and *δ*-*Truxillic acids* (*δ*- and *α*-*isatropic acids*)

The cocaine corresponding to *γ*-truxillic acid (*γ*-truxilline) has been prepared by Liebermann and Drory.[1]

The Table on p. 102 gives the principal characters and reactions of these acids.

Methylcocaine (*Ethylbenzoylecgonine*). This base was isolated by Günther [2] from commercial cocaine, by dissolving the latter in an alcoholic solution of hydrogen chloride and fractional precipitation with ether, the new alkaloid being precipitated last. It melts at 110°, and possesses the same physiological properties as cocaine ; further, it yields an aurichloride and a platinichloride closely resembling the corresponding salts of that base. It is probable that it results from the use of ethyl alcohol as a solvent in the commercial preparation of cocaine from ecgonine, but it is stated by Günther to be isomeric, not identical, with cocaethyline (ethylbenzoylecgonine) prepared synthetically by esterifying benzoylecgonine with ethyl alcohol.[3]

Benzoylecgonine, $C_9H_{14}(CO.C_6H_5)O_3N$. This acyl ester of ecgonine was isolated about the same time by Skraup in Austria and Merck in Germany from Peruvian coca leaves. It was subsequently prepared by Paul [4] by the action of water on cocaine (*see* p. 98).

It was prepared synthetically by Liebermann and Giesel [5] from ecgonine by the action of benzoic anhydride.

It crystallises from water with $4H_2O$ in needles, m.p. 86° or 195° (*dry*), and dissolves readily in alkaline liquids, forming salts. The aurichloride forms yellow shining plates. When benzoyl-

[1] *Loc. cit.* [2] *Chem. Soc. Abstr.* 1899, i. 963.
[3] Merck, *Berichte*, 1885, **18**, 2954 ; Einhorn, *ibid.* 1888, **21**, 48.
[4] *Pharm. Journ.* 1887-88 [iii], **18**, 781. [5] *Berichte*, 1888, **21**, 3196.

Name of acid	Formula	Crystalline form	Melting-point	Product of action of acetic anhydride	Product of action of oxidising agents	Product of action of conc. H_2SO_4
α-Truxillic	$C_{18}H_{16}O_4$	Colourless needles	274°	γ-Truxillic anhydride, m.p. 191°	Benzoic and acetic acids	Truxone, $(C_9H_6O)_n$. m.p. 289°
β-Truxillic	$C_{18}H_{16}O_4$	Colourless needles	206°	δ-Truxillic anhydride, m.p. 161°	Benzil and benzoic acid	—
γ-Truxillic	$C_{18}H_{16}O_4$	Colourless needles	228°	γ-Truxillic anhydride, m.p. 191°	Benzoic and acetic acids	—
δ-Truxillic	$C_{18}H_{16}O_4$	Long needles	174°	δ-Truxillic anhydride	Benzil and benzoic acid	—

ecgonine is boiled with dilute hydrochloric acid it is hydrolysed into ecgonine and benzoic acid. When methylated by any of the ordinary methods it furnishes cocaine, and with other aliphatic alcohols yields a series of homologues of cocaine: of these the ethyl ester (cocaethyline), m.p. 108°–109°, the propyl ester (cocapropyline), m.p. 78°–79·5°, and the *iso*butyl ester, m.p. 61°–62°, among others, have been prepared.

***l*-Ecgonine,** $C_9H_{15}O_3N.H_2O$. This substance was first obtained by Lossen in 1862 [1] as the final basic hydrolytic product of the action of acids on cocaine, and is obtainable in like manner from several of the alkaloids occurring with cocaine (*see above*). It crystallises from dry alcohol in monoclinic prisms, m.p. 198° (*decomp.*), is soluble in water, sparingly so in alcohol, insoluble in most organic liquids; the solutions are lævorotatory. Ecgonine forms salts both with bases and acids; the hydrochloride crystallises in rhombs, m.p. 246°; the aurichloride, $B.HAuCl_4$, forms yellow prisms; and the platinichloride, red needles, m.p. 226°. The base is a tertiary amine.

It is readily esterified in presence of hydrogen chloride, and in this way various alkylecgonines have been prepared. The most important of these is the methyl ester, which was obtained by Einhorn and Klein in 1888 in the form of the hydrochloride crystallising with $1H_2O$ in colourless prisms, m.p. 212° (*decomp.*). When benzoylated this furnishes cocaine. Ecgonine also reacts with acid chlorides and anhydrides to form acyl derivatives: thus by the action of benzoic anhydride, benzoylecgonine (*see* p. 101) is produced, and cinnamoyl-, *iso*valeroyl-, anisoyl-, and truxilloyl- ecgonines have been similarly prepared; these in turn by esterification with methyl alcohol furnish the corresponding cocaines.

***d*-Ecgonine.** This isomeride of ecgonine was first obtained by Einhorn and Marquardt [2] by the action of concentrated potassium hydroxide solution on ecgonine, and is formed when the cocaines are hydrolysed by alkalis. It crystallises from dry alcohol in tablets, m.p. 254°: the hydrochloride forms monoclinic prisms, m.p. 236°,

[1] *Annalen*, 1865, **133**, 351. [2] *Berichte*, 1890, **23**, 468, 981.

$[\alpha]_D$ + 1·6°; the aurichloride, $B.HAuCl_4$, has m.p. 220° (*decomp.*). It forms a series of esters with alcohols and acids like those yielded by *l*-ecgonine, and from it *d*-cocaine has been prepared (p. 97).

***dl*-Ecgonine.** This was prepared by Willstätter and Bode by the reduction of tropinecarboxylic acid.[1] It forms rhombic crystals, m.p. 251° (*decomp.*), and yields a hydrochloride, $B.HCl.\frac{1}{2}H_2O$, crystallising in slender needles, m.p. 149° (*dry, decomp.*), and an aurichloride, glistening needles, m.p. 213°. On benzoylation and methylation it yields *dl*-cocaine (p. 97).

Constitution of Ecgonine

The facts recorded in the foregoing paragraphs furnish evidence of the existence of a hydroxyl and a carboxyl group in the molecule of ecgonine, so that it must be regarded as a hydroxycarboxylic acid.

Einhorn observed[2] that by the action of phosphorus oxychloride and other dehydrating agents ecgonine loses a molecule of water, forming anhydroecgonine, $C_9H_{13}O_2N$. The latter probably occurs in coca leaves; it crystallises from alcohol in needles, m.p. 235°, is unsaturated, and combines with two atoms of bromine; it still contains the —COOH group of the parent base, and readily esterifies with methyl and ethyl alcohols. Ethyl anhydroecgonine has been observed in ecgonine residues obtained in working up the secondary alkaloids of coca leaves,[3] and is probably formed in this process. It has b.p. 130°–132°/11 mm., $[\alpha]_D$ — 51° 33′, and yields an aurichloride, m.p. 124°. When heated with hydrochloric acid at 280° it loses a molecule of carbon dioxide with the formation of tropidine (*see* p. 68), thus establishing a close relationship between tropidine, anhydroecgonine, and ecgonine, the two latter being in the light of this observation respectively the carboxylic acids of tropidine and hydroxytropidine.[4] By the action

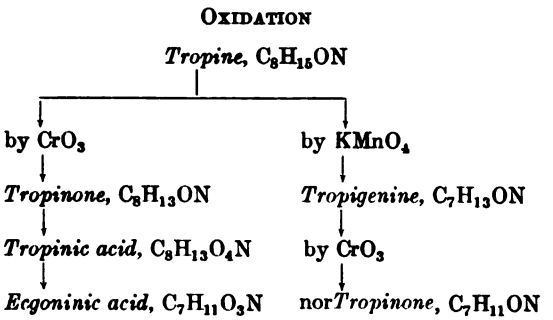
[1] *Berichte*, 1901, **34**, 1457.
[2] *Ibid.* 1887, **20**, 1221.
[3] Liebermann, *ibid.* 1907, **40**, 3602.
[4] Einhorn, *ibid.* 1890, **23**, 1338.

of chromic anhydride in acetic acid on ecgonine the following substances are formed : [1]

Tropinone, $C_8H_{13}ON$ (*see* p. 70).
Tropinic acid, $C_8H_{13}O_4N$ (*see* p. 70).
Ecgoninic acid, $C_7H_{11}O_3N$.

Ecgoninic acid crystallises from benzene in colourless needles, m.p. 93°, and has been shown by Willstätter and Bode to be a *N*-methylpyrrolidone-2-acetic acid,[2] and this has been confirmed by Willstätter and Hollander's [3] synthesis of the acid.

When ecgonine is treated with permanganate in acid solution a new base, *nor*ecgonine, $C_8H_{13}O_3N$, differing from the parent substance by : CH_2, is the principal product. It stands in the same relation to ecgonine as the similarly produced tropigenine does to tropine (p. 70), and like its analogue is a secondary base, and must, therefore, have been produced by the oxidation of a methyl group attached to nitrogen. It crystallises in long needles, m.p. 233°, is very soluble in water, and gives a characteristic aurichloride, m.p. 211°, crystallising in yellow needles.[4] The close relationship shown by these reactions to exist between ecgonine and tropine is made more evident if the behaviour of the two bases under the same treatment is exhibited as follows :



[1] Liebermann, *Berichte*, 1890, **23**, 2518 ; 1891, **24**, 606 ; Willstätter and Müller, 1898, **31**, 178.
[2] *Berichte*, 1901, **34**, 519.
[3] *Ibid.* p. 1818.
[4] Einhorn, *Berichte*, 1888, **21**, 3031.

Ecgonine, $C_9H_{15}O_3N$

by CrO_3 → *Tropinone*, $C_8H_{13}ON$ → *Tropinic acid*, $C_8H_{13}O_4N$ → *Ecgoninic acid*, $C_7H_{11}O_3N$ (*N-methylpyrrolidone-2-acetic acid*)

by $KMnO_4$ → nor*Ecgonine*, $C_8H_{13}O_3N$

DEHYDRATION

Tropine, $C_8H_{15}ON$ → *Tropidine*, $C_8H_{13}N$

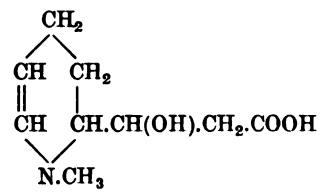
Ecgonine, $C_9H_{15}O_3N$ → *Anhydroecgonine*, $C_9H_{13}O_2N$

EXHAUSTIVE METHYLATION

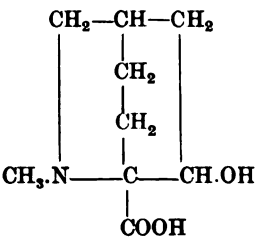
Tropidine, $C_8H_{13}N$ → *Tropilidene*, C_7H_8 (cyclo*Heptatriene*)

Anhydroecgonine, $C_9H_{13}O_2N$ → *c*-cyclo*Heptatrienecarboxylic acid*,[1] $C_8H_8O_2$

It will be seen that ecgonine and its derivatives differ from tropine and its derivatives throughout by CO_2, so that the former probably stands to the latter in the relation of a carboxylic acid. The formulæ assigned at various times to tropine by Ladenburg, Merling, and Willstätter have been suitably modified to represent ecgonine; thus the formulæ I and II given below are based on the tropine formulæ of Ladenburg and Merling respectively:



Ecgonine
(Einhorn after Ladenburg)

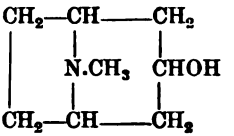


Ecgonine
(Einhorn and Tahara after Merling)

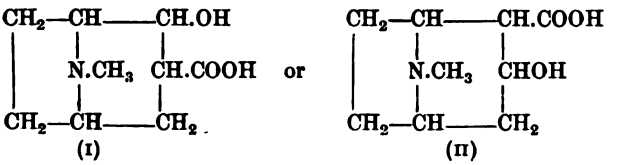
There are two possible formulæ for ecgonine derivable from

[1] Einhorn and Friedländer, *Berichte*, 1893, **26**, 1482. *Cf.* Willstätter and Müller, *ibid.* 1898, **31**, 2498, 2655.

Willstätter's representation of tropine (p. 74), which may be written thus : [1]

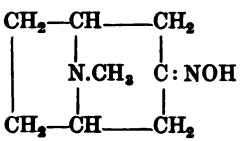


Tropine

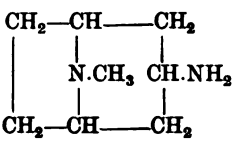


Ecgonine

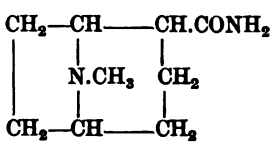
Formula II explains the formation of tropinone from ecgonine better than formula I; further, when ecgonine ethyl ester is reduced by sodium in alcohol it yields hydroecgonidine, $C_9H_{15}O_2N$, and the amide corresponding to this on oxidation by sodium hypobromite yields *iso*tropylamine, isomeric with tropylamine (or *pseudo*tropylamine) obtained by the reduction of tropinoneoxime, but not identical with either; it follows, therefore, that the amino-group in the latter amines must occupy a position different from that in the former, thus :



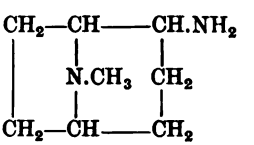
Tropinoneoxime



Tropylamine and pseudo*Tropylamine*



Hydroecgonidineamide



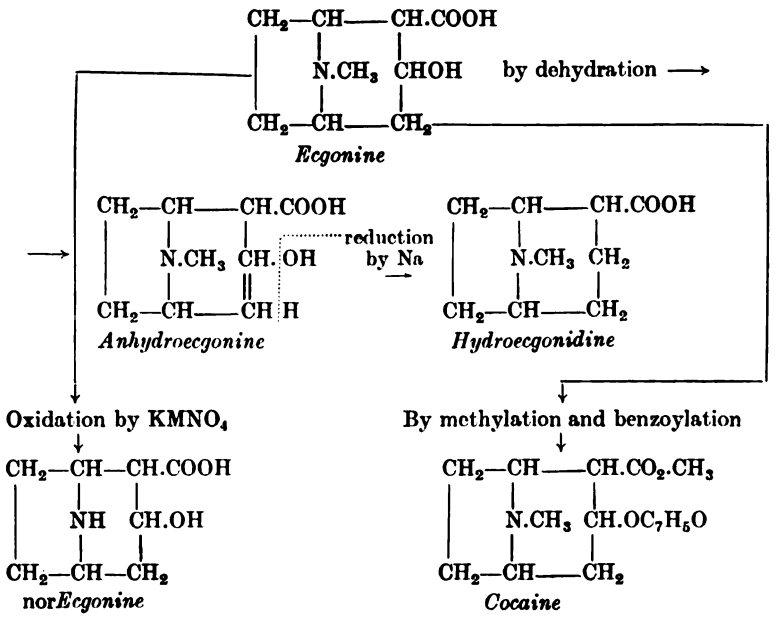
iso*Tropylamine*

The position assigned to the hydroxyl group in formula II explains (1) the ease with which ecgonine loses a molecule of water,

[1] Willstätter, *Berichte*, 1897, **30**, 2679 ; 1898, **31**, 1534, 2655.

forming anhydroecgonine, this change taking place between the —CHOH group and the neighbouring —CH_2 group ; (2) Willstätter and Müller's observation [1] that an unstable acid showing the characteristic behaviour of a β-ketonic acid precedes the formation of tropinone, when ecgonine is oxidised by chromic acid.

Accepting this view of the constitution of ecgonine, the formulæ of its derivatives and of cocaine must be written as follows :

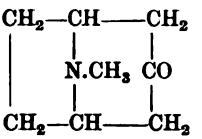


The conversion of tropinone into ecgonine has been accomplished by Willstätter and Bode.[2] For this purpose sodium tropinone was treated with carbon dioxide and sodium, by which it was converted into sodium tropinonecarboxylate. This on reduction with sodium in alcohol yielded chiefly ψ-tropinecarboxylic acid, but also afforded some *dl*-ecgonine (*see* p. 104). This was methylated and then benzoylated, and yielded *dl*-cocaine (*see* p. 97). The latter has not yet been deracemised. As tropinone

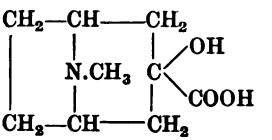
[1] *Berichte*, 1898, **31**, 1212, 2655. [2] *Ibid.* 1901, **34**, 1457.

can be prepared from tropine obtained synthetically (*see* p. 75) the synthesis of *dl*-cocaine is complete.

α-ECGONINE is the name given to a synthetically prepared base, isomeric with ecgonine, and derived from tropine. It differs from the former in the position of the carboxyl group. It was prepared by Willstätter[1] by the addition of hydrocyanic acid to tropinone, and subsequent hydrolysis of the cyanohydrin so formed. It must, therefore, be represented by the following formula:



Tropinone



α-Ecgonine

It occurs in brilliant snow-white crystals, m.p. 305° (*decomp.*), and is readily soluble in water or aqueous alcohol. The benzoyl derivative, m.p. 209°, is crystalline, and on methylation gives *α*-cocaine, a base crystallising in prisms, m.p. 87°, and yielding an aurichloride, m.p. 222° (*decomp.*), crystallising in leaflets. It is bitter to the taste, but does not cause the local anæsthesia characteristic of cocaine.

Tropacocaine (*Benzoyl*pseudo*tropeïne*), $C_{15}H_{19}O_2N$, was discovered by Giesel[2] in Java coca leaves, and has since been found in Peruvian coca.[3] It crystallises in needles, m.p. 49°, is insoluble in water, but soluble in alcohol, ether, or dilute ammonia, the last-named solvent being that usually employed in the separation of the base from the accompanying alkaloids. Its alcoholic solution is strongly alkaline and is optically inactive. The hydrochloride forms needles, m.p. 283° (*decomp.*), and the hydrobromide leaflets. The aurichloride separates in minute yellow needles, m.p. 208°, from hot aqueous solutions.

When heated with hydrochloric acid or baryta water the alkaloid

[1] *Berichte*, 1896, **29**, 2216. [2] *Ibid.* 1891, **24**, 2336.
[3] Hesse, *Journ. prakt. Chem.* 1902 [ii], **66**, 401.

undergoes hydrolysis with the formation of benzoic acid and pseudo*tropine*,[1] thus :

$$C_{15}H_{19}O_2N + H_2O = C_6H_5COOH + C_8H_{15}ON.$$
*Benzoyl*pseudo*tropëine* *Benzoic acid* pseudo*Tropine*

*pseudo*TROPINE, $C_8H_{15}ON$. This base is isomeric with tropine (p. 66), and since it furnishes on oxidation the same products as the latter, and, like it, gives tropidine when dehydrated, it is regarded as a stereoisomeride. It crystallises in colourless tablets or prisms, m.p. 108°, b.p. 240°, is miscible with water, ether, or alcohol, is strongly alkaline in reaction and optically inactive. The hydrochloride forms hygroscopic needles ; the aurichloride crystallises in brilliant yellow plates, m.p. 225° (*decomp.*). *pseudo*Tropine readily esterifies with organic acids, furnishing a series of derivatives, which from their analogy with the tropëines have been called pseudo-*tropëines*, but, unlike the former, exert no mydriatic action.

*Mandelyl*pseudo*tropëine* (pseudo*Homatropine*), $C_{16}H_{21}O_3N$, is a thick uncrystallisable oil, toxic but non-mydriatic.

*Tropyl*pseudo*tropëine*, $C_{17}H_{23}O_3N$, crystallises in colourless needles, m.p. 86°. It irritates the conjunctiva of the eye, but produces no mydriasis.

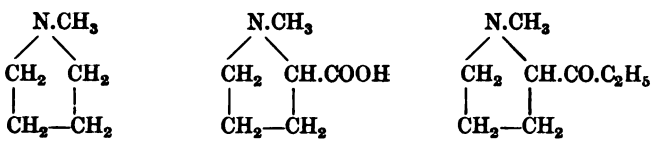
Tropine and *pseudo*tropine are mutually convertible ; thus each alone gives tropinone on oxidation in chromic acid, and this in turn on reduction yields a mixture of tropine and ψ-tropine, which can be separated by means of the picrates, that of ψ-tropine being much the more soluble in water.[2] By the action of sodium amyl-oxide on tropine, Willstätter has shown that *pseudo*tropine is produced,[3] and this has been confirmed by Barrowcliff and Tutin,[4] who also support Willstätter's view that the relation between tropine and ψ-tropine is that of *cis-trans*-isomerism.[5] The synthesis of ψ-tropine has been described already (p. 75).

[1] Liebermann, *Berichte*, 1891, **24**, 2338.
[2] Willstätter, *ibid.* 1900, **33**, 1167. *Cf.* however, Ladenburg, *ibid.* 1902, **35**, 1159. [3] *Berichte*, 1896, **29**, 936.
[4] *Trans. Chem. Soc.* 1909, **95**, 1970.
[5] *Cf.* Willstätter, *Annalen*, 1901, **317**, 204 ; 1903, **326**, 1.

Hygrines. This group of coca alkaloids was discovered by Lossen [1] in an ethereal extract of a slightly alkaline percolate of Peruvian coca leaves, this being the method used for the preparation of cocaine. The base was purified by conversion into its crystalline oxalate, which was recrystallised until pure, decomposed by potash, and the liberated alkaloid isolated by steam distillation. Liebermann and his pupils [2] re-investigated Lossen's supposed homogeneous base, and observed that it could by distillation under reduced pressure be separated into high-boiling (*see below*) and low-boiling hygrine fractions.

HYGRINE, $C_8H_{15}ON$, b.p. 92°–94°/20 mm., 111°–113°/50 mm., or 193°–195°/760 mm., D_4^{17} 0·940, $[\alpha]_D$ — 1·3°, is a colourless, strongly alkaline liquid, which absorbs carbon dioxide from the air and decomposes on exposure to light. It forms an aurichloride and a characteristic picrate, the latter crystallising in yellow needles, m.p. 148°. When oxidised by chromic acid hygrine yields hygrinic acid, $C_6H_{11}O_2N$. When heated alone or with strong sulphuric acid the latter loses carbon dioxide, and gives *N*-methylpyrrolidine, $C_5H_{11}N$.

Both hygrinic acid and hygrine are tertiary amines, and hygrine gives a crystalline oxime, m.p. 116°–120°. On the basis of these results the following formulæ were assigned to hygrinic acid and hygrine:



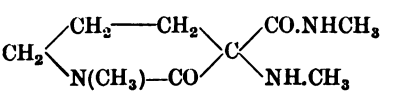
N-*Methylpyrrolidine* *Hygrinic acid* *Hygrine*

These formulæ are confirmed by Willstätter's synthesis of hygrinic acid [3] by the following series of reactions: trimethylene bromide was converted into ethylbromopropylmalonate by condensation with ethylsodiomalonate, and this product bromi-

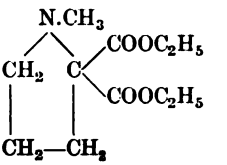
[1] *Annalen*, 1862, **121**, 374.

[2] *Berichte*, 1889, **22**, 675; 1891, **24**, 407; 1893, **26**, 851; 1895, **28**, 578; 1896, **29**, 2050; 1897, **30**, 1113. [3] *Ibid.* 1900, **33**, 1160.

nated with the formation of ethyl $a\delta$-dibromopropylmalonate, $CH_2Br.CH_2.CH_2.C.Br(CO_2C_2H_5)_2$, which reacts with ammonia and amines, forming cyclic amides derived from pyrrolidine and piperidine; thus with methylamine the chief product of the reaction is a substance of the formula (I), with a small quantity of ethyl *N*-methylpyrrolidine-2 : 2-dicarboxylate (II).



(I)



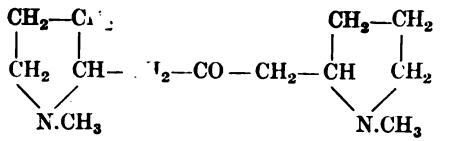
(II)

The latter on hydrolysis lost ethyl alcohol and carbon dioxide, and formed hygrinic acid, which is, therefore, *N*-methylpyrrolidine-2-carboxylic acid (*see formula, p.* 111).

β-Hygrine. This, the second fraction of Lossen's hygrine, was shown by Liebermann [1] to have the composition, $C_{14}H_{24}ON_2$. It decomposes when distilled under ordinary pressure, but boils at 215° under 50 mm. pressure, and has relative density 0·982 at 18°. It forms an aurichloride of the formula, $C_{14}H_{24}ON_2.2HAuCl_4$, and combines with two molecules of methyl iodide, forming a colourless crystalline dimethiodide. When oxidised by chromic acid it yields a small quantity of hygrinic acid.

Cuscohygrine. This third hygrine was first recognised by Liebermann and Cybulski [2] in "Cusco" leaves, whose botanical origin is unknown. It has the formula, $C_{13}H_{24}ON_2$, boils at 185° under 32 mm. pressure, has a relative density 0·9767 at 17°, and is optically inactive. It is miscible with water and forms a soluble hydrate, $C_{13}H_{24}ON_2.3\frac{1}{2}H_2O$, m.p. 40°, and with carbon dioxide forms an unstable carbonate. The alkaloid forms crystalline salts with acids, and has been shown to contain two tertiary nitrogen atoms, and yields hygrinic acid on oxidation with chromic acid. Liebermann regards it as having the following formula :

[1] *Berichte*, 1889, **22**, 675 ; 1895, **28**, 580. [2] *Ibid.* 1895, **28**, 578.



Physiological Action of Coca Alkaloids

Cocaine, the most important of the coca alkaloids, has a bitter taste, is mydriatic, produces local anæsthesia, and is highly toxic.

After absorption, or when taken internally, cocaine acts chiefly on the central nervous system, causing delusions, impaired vision, and paralysis of various kinds ; large doses induce convulsions, and death occurs from paralysis of the respiratory centre.

Cocaine is chiefly used in medicine as a local anæsthetic. At first it was employed almost entirely in minor surgical operations on the eye, throat, nose, &c., but in recent years its use has been largely extended in surgery, anæsthesia of deep-seated tissues being produced by the injection of cocaine solutions in special ways. The anæsthesia is of short duration. Cocaine produces little effect when applied to unbroken skin.

When applied to mucous membrane the alkaloid also causes contraction of the blood-vessels, and the part affected becomes pallid. To enhance this effect and to prevent excessive absorption of the alkaloid, it is sometimes used with adrenaline.

Applied to the eye, cocaine induces not only local anæsthesia but also partial dilatation of the pupil and partial paralysis of accommodation, but these effects are not produced in the same manner as by atropine.

d- and *dl*-Cocaines exert the same action as natural *l*-cocaine.

a-Cocaine (p. 109) has nothing in common with cocaine in physiological action.

Cocaine Substitutes. The importance of cocaine in surgery has led to many attempts to replace it by substances that are less toxic. From this point of view the efforts made to correlate chemical

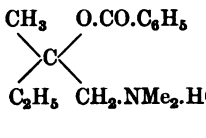
structure with local anæsthetic action are of importance, and have been discussed by Jowett and Pyman.[1] They point out that this property is shown by alkamine esters of widely different structure, but possessing the following characters:

(1) The acyl group may be benzoyl or a substituted aromatic residue.

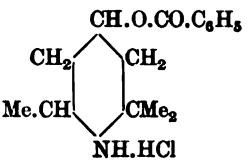
(2) The amino group may be secondary or tertiary or be associated with simple or bridged ring complexes.

(3) The alcohol group may be primary, secondary, or tertiary, and may separate the acyl and amino groups by a chain of two or three carbon atoms.

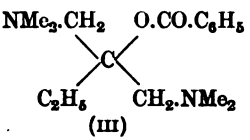
Among the numerous synthetic alkamine esters that have been introduced and used as cocaine substitutes are stovaine (I), β-eucaine (II), and alypine (III):



(I)

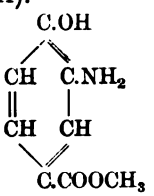


(II)

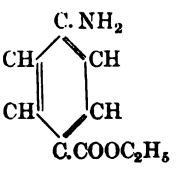


(III)

The property of producing local anæsthesia is also shown by other products than alkamine esters, *e.g.* methyl acetylsalicylate, and the esters of aminoaromatic acids, and several of these are used as cocaine substitutes, *e.g.* new-orthoform (I), anæsthesine (II), and propasine (III).

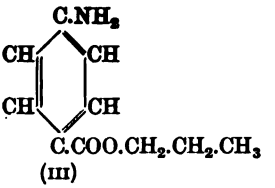


(I)



(II)

[1] *Proc. 7th Int. Congr. Appl. Chem.* Lond. 1909.



(III)

Of the other alkaloids in coca leaves the most interesting is tropacocaine, which resembles cocaine in general in its action, produces local anæsthesia more rapidly, is less poisonous, and causes less dilatation of the pupil of the eye. Benzoylecgonine and ecgonine are comparatively inert. The truxillines have very little anæsthetic effect, but are stated to be cardiac poisons.

ALKALOIDS OF *PUNICA GRANATUM*

The root bark of *Punica Granatum* (pomegranate), employed as an anthelmintic, was investigated by Tanret,[1] who isolated from it four alkaloids. A fifth, *iso*methylpelletierine, was obtained by Piccinini.[2]

Pelletierine, $C_8H_{15}ON$.
Pseudopelletierine, $C_9H_{15}ON$.
iso*Pelletierine*, $C_8H_{15}ON$.
Methylpelletierine, $C_9H_{17}ON$.
iso*Methylpelletierine*, $C_9H_{17}ON$.

The finely ground bark mixed with slaked lime is exhausted with chloroform. From the solution the free bases are extracted with dilute hydrochloric acid. The acid liquid is made alkaline with sodium bicarbonate, whereby methylpelletierine and pseudopelletierine are set free, and can be removed by agitation with chloroform. On distilling off the latter a residue of the mixed alkaloids is obtained, which can be separated into its constituents by conversion into the mixed sulphates and fractional precipitation with sodium bicarbonate, the methylpelletierine separating in the earlier fractions. The remaining alkaloids can be obtained from the

[1] *Compt. rend.* 1878, **86**, 1270; 1879, **88**, 716; 1880, **90**, 696.
[2] *Gazzetta*, 1899, **29**, ii. 311.

original residue by addition of soda solution and extraction with chloroform. The chloroformic extract is then dissolved in dilute sulphuric acid, when pelletierine sulphate separates, of which more is obtained by evaporation under reduced pressure. From the crude sulphates so prepared the free bases are liberated by soda solution and purified by distillation in a current of steam.

According to Ewers [1] the root bark contains 0·63 to 0·72 per cent. of alkaloids, of which nearly half is pelletierine and *iso*pelletierine. Stem bark contains 0·52 per cent. of alkaloids. Methods of estimation are given by Ewers [2] and in the German Pharmacopœia (5th Edition), 1910.

Pelletierine, $C_8H_{15}ON$. The free base is an oily liquid, b.p. 195°/760 mm. or 125°/100 mm., D_0^0 0·988, $[\alpha]_D + 8°$, which absorbs oxygen in air, becoming dark-coloured and resinous. It is soluble in cold water (1 in 23), more so in alcohol, ether, or chloroform, is alkaline to litmus, and readily forms crystalline salts with acids. The sulphate has $[\alpha]_D - 30°$. Pelletierine solutions are precipitated by the usual alkaloidal reagents with the exception of platinic chloride. With sulphuric acid and potassium dichromate it gives an intense green coloration. The alkaloid is an active vermifuge.[3]

***iso*Pelletierine,** $C_8H_{15}ON$. This isomeride is also liquid, b.p. 195°. It closely resembles pelletierine in chemical, physical, and physiological properties, but differs from it in being optically inactive.[3]

Methylpelletierine, $C_9H_{17}ON$. An oily liquid, b.p. 215°, readily soluble in alcohol, ether, or chloroform, and slightly soluble in water (1 in 25 at 12°). The hydrochloride has $[\alpha]_D + 22°$.[3]

***iso*Methylpelletierine,** $C_9H_{17}ON$. This base was found by Piccinini in the higher boiling fractions of crude pseudopelletierine. It is an oily liquid, b.p. 114°–117°/26 mm., of strongly alkaline reaction, miscible with water in all proportions. The picrate melts at 152°–153°; the aurichloride, $B.HAuCl_4$, forms orange-yellow

[1] *Arch. Pharm.* 1899, **237**, 49. [2] *Loc. cit.*
[3] Tanret, *loc. cit.*

rosettes, m.p. 115°–117°; whilst the hydrochloride is a viscous syrup.

The alkaloid gives a semicarbazone, m.p. 169°, in large transparent crystals, soluble in alcohol, but insoluble in ether. The nitrogen atom is present as : $N.CH_3$.

Pseudopelletierine, $C_9H_{15}ON$ (*N-Methylgranatonine*). This, the best-known alkaloid of the group, was isolated by Tanret in 1879.[1] It crystallises from light petroleum in anhydrous, prismatic tablets, m.p. 48°, b.p. 246°, $[\alpha]_D$ 0°, dissolves readily in ether, alcohol, or chloroform, less readily in light petroleum. Pseudopelletierine is a strong base and gives well-crystallised salts : the hydrochloride, B.HCl, forms rhombohedra; the platinichloride, $B_2.H_2PtCl_6$, forms reddish needles; and the aurichloride is a yellowish crystalline substance. The picrate is readily soluble in water. The base is precipitated by all the ordinary alkaloidal reagents, and with chromic acid gives an intense green coloration.

Constitution. The alkaloid behaves with methyl iodide as a tertiary base, forming pseudopelletierine methiodide, colourless cubes, m.p. above 280°. It does not react with nitrous acid to give a nitroso-compound, so that the nitrogen atom appears to be tertiary, probably in the form : $N.CH_3$.

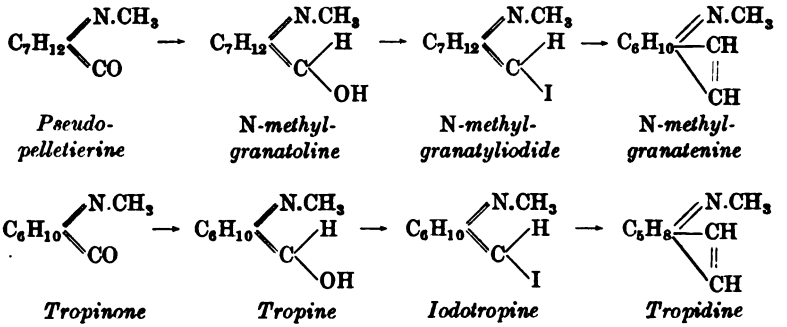
It forms an oxime crystallising in tablets, m.p. 128°, and, therefore, contains a carbonyl group. On reduction the alkaloid is converted into its secondary alcohol, *N*-methylgranatoline, $C_9H_{17}ON$.

$$\underset{\substack{\textit{Pseudopelletierine}\\(\text{N-}\textit{Methylgranatonine})}}{C_9H_{15}ON} + H_2 = \underset{\text{N-}\textit{Methylgranatoline}}{C_8H_{15}(CHOH)N}.$$

This crystallises from light petroleum in fine needles, melting at 100°, and distils at 251°. It forms a monobenzoyl derivative, and when heated with hydriodic acid gives *N*-methylgranatyliodide, $C_9H_{16}NI$: the latter on longer heating with the reagent loses a molecule of hydriodic acid and forms the unsaturated *N*-methylgranatenine, $C_9H_{15}N$. This series of changes may be represented thus :[2]

[1] *Loc. cit.*

[2] Ciamician and Silber, *Berichte*, 1892, **25**, 1601 ; 1893, **26**, 156, 2740.



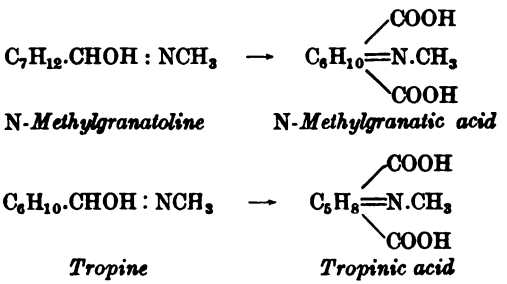
On comparing this series of changes with those brought about by the same means in the tropine group, it is evident that a close parallelism can be traced which suggests that pseudopelletierine is a next higher homologue of tropinone.

This similarity in behaviour is also shown in the conversion of *N*-methylgranatoline into *nor*granatonine by the prolonged action of hydriodic acid and phosphorus: [1]

$C_7H_{12}(CHOH):NCH_3 \rightarrow C_7H_{12}.CH_2:NH$
N-Methylgranatoline — *nor Granatonine*

$C_6H_{10}(CHOH):NCH_3 \rightarrow C_6H_{10}.CH_2:NH$
Tropine — *nor Hydrotropidine*

Similarly *N*-methylgranatoline by oxidation with permanganate furnishes a dibasic acid of the formula, $CH_3.N:C_6H_{10}(COOH)_2$, *N*-methylgranatic acid.



Further, by destructive distillation of *nor*granatonine hydro-

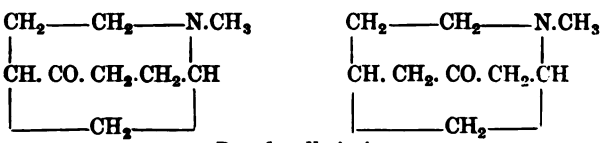
[1] Ciamician and Silber, *Berichte*, 1894, **27**, 1851.

chloride, *a*-propylpyridine is formed, just as *nor*hydrotropidine furnishes *a*-ethylpyridine.[1]

That pseudo pelletierine contains the grouping $-CH_2-CO-CH_2-$, the recognition of which, as has already been pointed out, necessitated the change from Merling's to Willstätter's formula for tropine, has been proved by Piccinini's observation that the alkaloid reacts with two molecules of amyl nitrite to form a di*iso*nitroso compound.[2]

The close similarity in reaction exhibited by pseudopelletierine and its derivatives to tropinone and its products has led to the representation of the former alkaloid by formulæ derived from those at various times adopted for tropine.[3]

Finally, Piccinini's proof that pseudopelletierine must contain the grouping $-CH_2-CO-CH_2-$ led this author to modify Ciamician and Silber's formula thus :

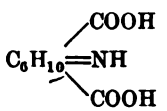


Pseudopelletierine

(Ciamician and Silber) (Piccinini)

and the validity of the latter appeared to be established by the following reactions.[4]

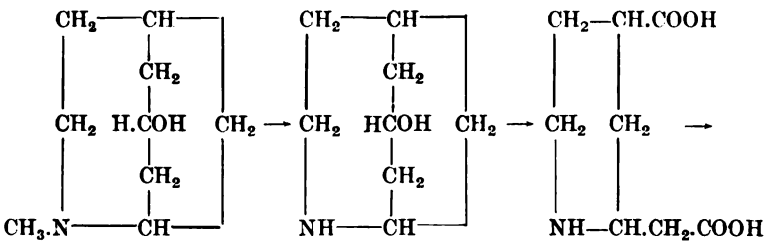
When *N*-methylgranatoline is oxidised by permanganate the methyl group attached to the nitrogen atom is replaced by hydrogen, as in the conversion of tropine into tropigenine, furnishing granatoline ; the latter on further oxidation gives granatic acid, which, since it is the lower homologue of the *N*-methylgranatic acid already mentioned, must be represented thus :

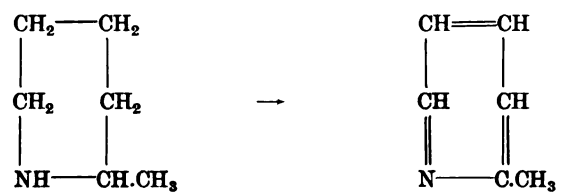


Granatic acid.

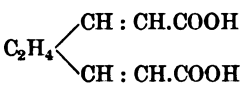
[1] Ciamician and Silber, *Berichte*, 1896, **29**, 482.
[2] *Gazzetta*, 1899, **29**, i. 408 ; ii. 115.
[3] *Cf.* Ciamician and Silber, *Berichte*, 1894, **27**, 2860 ; 1896, **29**, 482.
[4] *Loc. cit.*

This when heated at 150° with mercuric acetate and acetic acid yields a methylpyridinecarboxylic acid, which by distillation furnishes α-methylpyridine. These reactions are explained by Piccinini's formula thus:

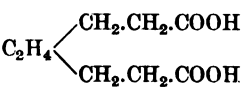




Piccinini has, however, observed that by "exhaustive methylation" of dimethyl methylgranatate,[1] and treatment of the dimethyl ester of dimethylgranatenic acid thus produced with potash, trimethylamine is split off, with the formation of homopiperilenedicarboxylic acid, which on reduction furnishes suberic acid:

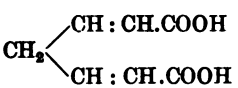


Homopiperilenedicarboxylic acid

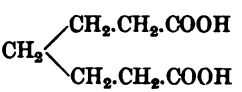


Suberic acid

Under like conditions tropinic acid furnishes piperilenedicarboxylic acid, which on reduction furnishes pimelic acid:



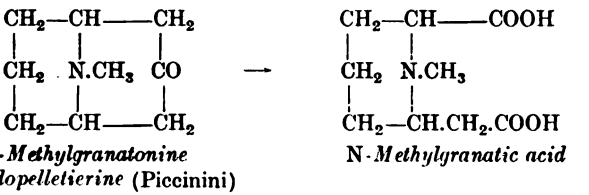
Piperilenedicarboxylic acid



Pimelic acid

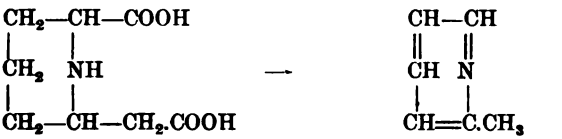
[1] *Gazzetta*, 1899, 29, ii. 104.

Piccinini has, therefore, adopted the following formula (I) for pseudopelletierine,[1] which, as will be seen, is derived from Willstätter's tropinone formula (p. 75) by change of a heptacyclic to an octocyclic ring. The chief derivatives of the parent alkaloid and their formation may be represented in the following way:



N-Methylgranatonine
Pseudopelletierine (Piccinini)

N-Methylgranatic acid



Granatic acid

α-Methylpyridine

Physiological Action of Pomegranate Bark Alkaloids

Pomegranate root bark is official in the British and United States Pharmacopœias, but is now little used in medicine. The active constituents are believed to be pelletierine and *iso*pelletierine, which, according to Schroeder, are highly toxic to tapeworms and explain the use of the bark as a vermifuge. Crude mixtures of the tannates and sulphates of the alkaloids have been employed in medicine under the names pelletierine tannate and pelletierine sulphate. The former is official in the United States Pharmacopœia. The pelletierine sulphate of the French Codex is chiefly composed of pelletierine and *iso*pelletierine sulphates.

ALKALOID OF *CYTISUS SCOPARIUS*

Under the name "broom tops" the herbaceous branches of the common broom, *Cytisus scoparius*, were at one time used to a

[1] *Real. Accad. Lincei.* 1899 [v], **8**, ii. 219. *Cf.* Willstätter and Veraguth, *Berichte*, **1905**, **38**, 1984.

considerable extent in medicine. From this material Stenhouse [1] isolated the alkaloid sparteine. "Lupinidine," obtained from yellow lupin seeds, is identical with sparteine.[2] According to Chevalier broom tops yield 0·23 to 0·68 per cent. of sparteine, depending on the season of collection, being richest in March and poorest in August after flowering.[3]

Sparteine, $C_{15}H_{26}N_2$. The alkaloid is prepared by extracting ground broom tops with dilute sulphuric acid, concentrating the extract, adding excess of alkali, and distilling the liberated alkaloid in a current of steam. The distillate is exactly neutralised with hydrochloric acid, evaporated to dryness, and the residue distilled over solid potash. The distillate is finally purified by redistillation in a current of hydrogen.

Sparteine is a colourless oil, D^0 1·034, D^{20} 1·0196, $[\alpha]_D^{21}$ — 16·42° in alcohol, b.p. 188° under 18 mm. pressure or 325° in hydrogen under 754 mm. pressure. It has a bitter taste, an odour recalling that of aniline, and is sparingly soluble in water (1 in 328 at 22°), but readily so in alcohol, chloroform, or ether. The base is strongly alkaline, and is monoacidic to litmus and phenolphthalein, but diacidic to methyl orange. It forms well-crystallised salts and behaves as a diacidic base. The sulphate, $B.H_2SO_4.5H_2O$, $[\alpha]_D^{15}$ — 22·12° in water, forms transparent columnar crystals soluble in 1·1 of water at 25°, or 2·4 of alcohol at 25°. This salt is used in medicine and is official in the United States, French, and Japanese Pharmacopœias. The platinichloride, $B.H_2PtCl_6.2H_2O$, m.p. 243·5° (*decomp.*), forms rhombic prisms from dilute hydrochloric acid; and the aurichloride, $B.HAuCl_4$, m.p. 175°–184° (*decomp.*), is a crystalline precipitate. The picrate, m.p. 208°, forms glancing yellow needles from boiling alcohol.

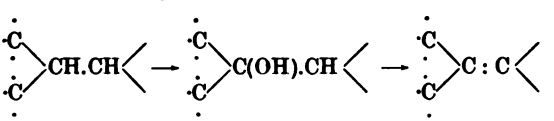
Reactions and Constitution. According to Jorissen [4] sparteine is distinguished from other alkaloids by giving a bulky red precipitate when hydrogen sulphide is passed through sulphur suspended

[1] *Journ. Chem. Soc.* 1852, **4**, 216.
[2] Willstätter and Marx, *Berichte*, 1904, **37**, 2351.
[3] *Compt. rend.* 1910, **150**, 1069. [4] *J. Pharm. Chim.* 1911 [vii], **4**, 251–52

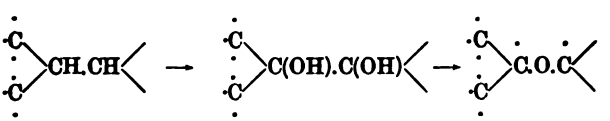
in a solution of the base in ether. Coniine gives an orange and atropine a yellow precipitate under these conditions.

Moureu and Valeur [1] pointed out that both the nitrogen atoms in sparteine are basic and tertiary, and that neither has a methyl group attached to it. Further, they showed that the alkaloid is saturated, since it is unaffected by reducing agents or by permanganate, and for these reasons they suggested that it probably contains two or more saturated closed chains. Similar conclusions were reached by Wackernagel and Wolffenstein,[2] who suggested that sparteine was a dicyclic base containing both a pyridine and a pyrrolidine ring.

Willstätter and Marx,[3] by oxidising sparteine sulphate with chromic acid, obtained SPARTYRINE, $C_{15}H_{24}N_2$, together with OXYSPARTEINE, $C_{15}H_{24}ON_2$, already obtained by Ahrens, and a third base, $C_{15}H_{24}O_4N_2$. Spartyrine, m.p. 153°–154°, $[\alpha]_D^{18\cdot5}$—25·96°, is crystalline, yields a crystalline hydrochloride and platinichloride, and contains an ethylenic linking : it appears to be formed by such a change as the following in a portion of the sparteine molecule :



Oxysparteine, m.p. 87·5°, b.p. 209° under 12·5 mm., $[\alpha]_D^{18}$ —10·04°, the same authors suggested, is formed, not by the further oxidation of spartyrine, but by an extension of the process by which spartyrine is produced, thus :

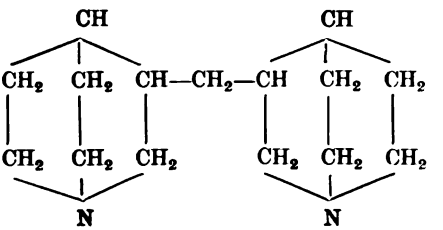


Further insight into the constitution of sparteine is due chiefly to Moureu and Valeur, and has been obtained mainly by a study of its degradation by " exhaustive methylation."

When sparteine is treated with methyl iodide in methyl alcohol

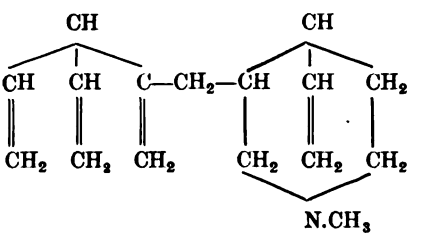
[1] *Compt. rend.* 1903, **137**, 194.
[2] *Berichte*, 1904, **37**, 3238. *Cf.* Willstätter and Marx, *ibid.* 1904, **37**, 2351.
[3] *Ibid.* 1905, **38**, 1772.

it yields two stereoisomeric monomethiodides [1] distinguished by the α-methiodide, having a lower solubility in water and a lower specific rotation than the α′-isomeride. The former on treatment with silver hydroxide gives sparteinemethylammonium hydroxide, which on heating yields methylsparteine, $N:C_{15}H_{25}NCH_3$, and this on repetition of the treatment furnishes in turn dimethylsparteine and sparteinetrimethylammonium hydroxide. The latter on heating breaks down into trimethylamine and hemisparteilene, $C_{15}H_{23}N$. Moureu and Valeur explain these reactions by the following formula for sparteine, which accounts for the stereoisomerism of the two monomethiodides by the symmetry of the molecule: [2]



Sparteine

When dimethylsparteine reacts with excess of methyl iodide a dimethiodide is formed which with moist silver hydroxide gives tetramethylsparteineammonium hydroxide, $C_{15}H_{24}Me_2N_2(MeOH)_2$, and this on distillation yields trimethylamine and methylhemisparteilene, which from its mode of formation must have the following structure if Moureu and Valeur's formula for sparteine is accepted:



Methylhemisparteilene

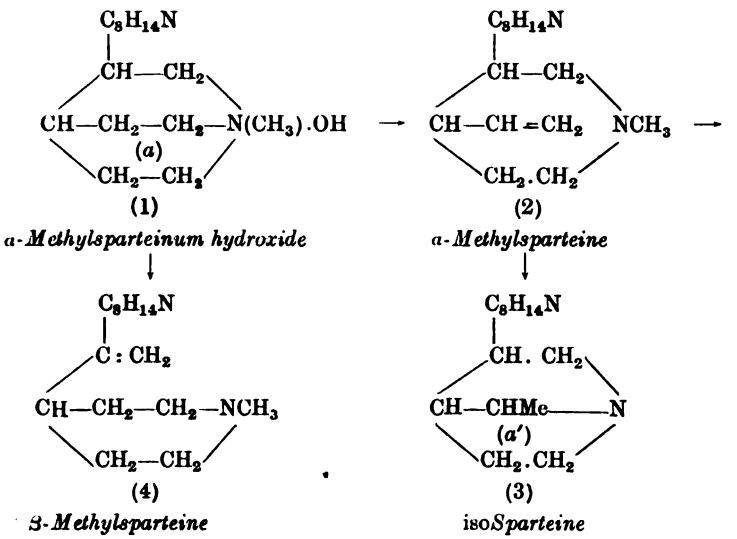
[1] *Compt. rend.* 1905, **140**, 1601, 1645.

[2] *Ibid.* 1905, **141**, 117, 261, 328; 1907, **145**, 815. *Cf.* however, 1912, **154**, 309, and Germain. *Gazzetta*, 1912, **42**, i. 447.

By exhaustive methylation of methylhemisparteilene the hydrocarbon sparteilene, $C_{15}H_{20}$, is obtained in which the same change has taken place in the second ring as took place in the first ring in the formation of methylhemisparteilene.[1]

Moureu and Valeur have also shown that in the action of silver hydroxide on sparteine α-methiodide two methylsparteines, distinguished as α- and β-, are produced, and that the dihydriodide of the former when heated with water at 125° is partly converted into the methiodide of a new base, *iso*sparteine, b.p. 177·5° under 16·5 mm., $[\alpha]_D$ — 25·01° in alcohol, which, like sparteine, is a saturated ditertiary base.[2]

These changes are assumed to take place thus :



that is, the formation of *iso*sparteine involves the opening of the piperidine ring (*a* in formula 1) by the rupture of the bridge, and its subsequent reclosing to form a pyrrolidine ring (*a'* in formula 3). The reverse change occurs when *iso*sparteinemethosulphate is heated with baryta ; under these conditions this substance passes into the

[1] *Compt. rend.* 1912, **154**, 161.
[2] *Ibid.* 1907, **145**, 929, 1184, 1343 ; 1908, **146**, 79 ; 1911, **152**, 386, 527.

corresponding methylhydroxide, which at 100° *in vacuo* is converted into α-methylsparteine.[1]

Physiological Action. Sparteine closely resembles coniine in its physiological action. It appears to exert very little effect on the central nervous system, but paralyses the motor nerve terminations and the sympathetic ganglia. It also causes greater depression of the heart's action than coniine, and is less active in increasing arterial tension when injected into a vein. It is poisonous, but less so than coniine. Broom tops were used in medicine chiefly as a diuretic, this action being due, not to the sparteine they contain, but to a neutral substance, scoparin, also present in the plant.

[1] Valeur, *Compt. rend.* 1908, **147**, 127, 864, 1318.

IV. QUINOLINE GROUP

ALKALOIDS OF *CINCHONA* SPECIES

THIS group of natural alkaloids occurs in the various species of the two Rubiaceous genera, *Cinchona* and *Remijia*, indigenous to the eastern slopes of the Andes between the latitudes 10° N. and 20° S. Cinchona is found on an average from 5000 to 8000 feet above sea-level, the highest limit being 11,000 and the lowest 2500 feet. It is uncertain whether the antipyretic properties of the barks of these plants were known to the natives before the advent of the Spaniards, but it was generally believed at the commencement of the eighteenth century that this was the case, as is shown by Arrot, who travelled in South America in 1737.[1] Humboldt, however, was informed at Loxa in 1807 that the natives regarded cinchona bark as a very dangerous drug, and that the *Cascarilleros*, who collected it for export to Europe, were convinced that the only purpose for which it could be employed was the dyeing of cloth. Similar statements were made by Pöppig in 1830 and by Spruce in 1860, whilst Markham in 1862 observed that the native doctors never used cinchona bark. The bark was first employed in Europe in 1639, and its introduction is described by Chifflet in a pamphlet published at Brussels in 1653; two years later it was sold in England under the name "Jesuits' powder," and was prescribed by Brady at Cambridge about 1658 and by Willis in London about 1660. It first appears in the London Pharmacopœia published in 1677 under the name of *Cortex Peruanus*. Excellent summaries of the history of cinchona will be found in Flückiger and Hanbury's *Pharmacographia* (p. 338)[2] and in a paper by Mr. D. Howard.[3]

The genus *Cinchona* was established by Linnæus in 1742, and

[1] *Phil. Trans.* 1737, **40**, 81.
[2] Macmillan & Co., London, 1874.
[3] *Journ. Soc. Chem. Ind.* 1906, **25**, 97.

the tree now known as *Cinchona officinalis* was described by him in 1753. Soon after the introduction of the drug into Europe the demand for it became so great that there was some prospect of a total extinction of the plants in South America, and attention was directed to the possibility of cultivating the trees in other countries. This was attempted in India, Ceylon, Jamaica, Australia, and Java, but was only thoroughly successful from the first in India and Ceylon, though of late years the cultivation has declined in these countries and has enormously increased in Java, so much so that the latter is now the most important cinchona district in the world, a position which is chiefly the result of the long-continued chemical and botanical investigations carried out under the auspices of the Dutch Government. In the various cinchona gardens, in order to secure a continuous supply of bark without destroying the trees, new methods have been introduced from time to time, such as stripping off portions and covering the wounds with moss, whereby a formation of new bark is produced known as "renewed bark," which generally contains a larger proportion of alkaloids than that due to natural growth. In Java it was found that the outer bark could be shaved off in small pieces periodically without inflicting injury on the tree. In recent years these methods of harvesting have been supplemented by "coppicing," bark being stripped from the cut branches.

The first attempts at cinchona cultivation both in India and Java were made with *Cinchona succirubra*, because it was found to be the hardiest of the known species, and this advantage was considered to outweigh the smallness of its yield in quinine. Subsequently a variety of *Cinchona Calisaya* was discovered by Ledger, the bark of which gave a far higher yield of quinine than any of the known cinchonas, but the plant was more difficult to rear than *C. succirubra*, and therefore did not find favour with Indian planters. In Java it is raised by grafting seedlings upon a young stock of the hardier *succirubra*, the latter being almost entirely cut away when the graft becomes well established. Young trees grown in this way are at first planted rather thickly, and after three years are

coppiced, this process being continued yearly until the increasing girth of the stems renders necessary the removal of a certain number of the trees, which are uprooted, and the whole of the bark from both root and stem stripped off. The remainder are treated by the process already described until the trees become mature, when they are all uprooted, stripped of bark, and a fresh plantation formed.

In recent years attention has been more and more devoted to the selection of cinchonas for cultivation, on the basis of the richness of the bark in quinine, and to the production of hybrids which will combine the qualities of rich bark, resistance to disease, and large yield. Much of the bark which now comes on the market is of the " hybrid " or " Ledger " kinds.

As an indication of the extent to which Java has now obtained control of the cinchona bark it may be mentioned that in 1910, of 22,469 cwt. of bark imported into the United Kingdom, 17,908 cwt. came from Java.

The varieties chiefly cultivated in Java are shown by the statement made in the *Report of the Java Government Cinchona Undertakings* for 1909 that out of a total area of 1513 bouws, 1050 were occupied by *C. Ledgeriana*, 85 by hybrids, 239 by *C. robusta*, and 135 by *C. succirubra*. The total bark harvest in these plantations in 1909 was 1,787,809 half-kilogrammes, of which 872,983 half-kilogrammes were exported to Europe. Of the bark exported, 586,080 half-kilogrammes were " Ledger " and " hybrid " bark containing on the average the equivalent of 7·54 per cent. of quinine sulphate ; the rest was made up of *C. succirubra*, *C. robusta*, and *C. pitayensis* barks.

A similar preference for " Ledgeriana " and " hybrid " barks is shown by the figures for the Bengal Government Plantations in 1910–11 :

Varieties grown	Number in plantation	Bark harvested
Ledgeriana	2,095,652	500,900 lb.
Hybrid No. 1	159,232	
Hybrid No. 2	78,828	
Cinchona officinalis	93,985	
Cinchona succirubra	117,120	

The only alkaloids of practical importance belonging to the quinine group are :

1. *Quinine.*
2. *Quinidine.*
3. *Cinchonine.*
4. *Cinchonidine.*

But in addition to these over twenty other alkaloids have been isolated from various species of Cinchona and from cuprea bark.

The names and formulæ of the alkaloids of this series are as follows :

CINCHONINE AND ITS ISOMERIDES, $C_{19}H_{22}ON_2$.

Cinchonine. *Homocinchonidine.*
Cinchonidine. *Cinchonicine.*

DIHYDROCINCHONINES, $C_{19}H_{24}ON_2$.

Cinchotine (*Hydrocinchonine*).
Hydrocinchonidine (*Cinchamidine*).
Cinchonamine.

HYDROXYCINCHONINE, $C_{19}H_{22}O_2N_2$.

Cupreine.

ALKALOIDS OF THE FORMULA $C_{19}H_{24}O_2N_2$.

Quinamine. *Conquinamine.*

METHOXYCINCHONINES, $C_{20}H_{24}O_2N_2$.

Quinine. *Quinidine.* *Quinicine.*

ALKALOIDS OF THE FORMULA $C_{20}H_{26}O_2N_2$ (*Methoxydihydrocinchonines*) :

Hydroquinine. *Hydroquinidine.*

ALKALOIDS OF THE FORMULA $C_{22}H_{26}O_4N_2$:

Chairamine. *Chairamidine.*

Conchairamine. *Conchairamidine.*

ALKALOIDS OF THE FORMULA $C_{23}H_{26}O_4N_2$:

Cusconine. *Concusconine.* *Aricine.*

VARIOUS ALKALOIDS:

Dicinchonine, $C_{38}H_{44}O_2N_4$.
Diconquinine, $C_{40}H_{46}O_4N_4$.
Paricine, $C_{16}H_{18}ON_2$.
Javanine
Cuscamine
Cuscamidine
Cusconidine

} Of undetermined composition.

Estimation of Alkaloids in Cinchona Barks

A great number of processes have been devised for the determination of the total alkaloids in cinchona barks, presenting as a rule the common feature of liberating the alkaloids by admixture of the bark with some basic substance and subsequent extraction with a suitable solvent. Methods for the approximate estimation of the more important alkaloids separately usually depend on the different solubilities of the periodides, sulphates, tartrates, or hydriodides of the chief cinchona bases.

In the earlier processes dilute acids were employed as extracting liquids, but the use of such solvents has now been abandoned because of the difficulty of obtaining the alkaloids free from the colouring matter simultaneously extracted.

British Pharmacopœia (1898). The dried bark of *Cinchona succirubra* is the only cinchona bark official in this Pharmacopœia, and the following process for its assay is prescribed: Twenty grammes of the bark in No. 60 powder are mixed with 6 grm. of slaked lime and the whole moistened with 20 c.c. of water and set aside for two hours. The mass is then transferred to a flask, fitted with a reflux condenser, and boiled with 130 c.c. of "benzolated amyl alcohol" (benzene 3 vols., amyl alcohol 1 vol.) during thirty minutes. The solvent is decanted through a filter into a separator, and the boiling with the same quantity of solvent repeated twice. The

contents of the flask are finally turned out on the filter and washed with fresh portions of the solvent till exhausted, all the liquors being collected in the separator. The thoroughly mixed liquors while still warm are shaken (1) with 2 c.c. of diluted hydrochloric acid (sp. gr. 1·052) mixed with 12 c.c. of water; (2) with water acidified with dilute hydrochloric acid, fresh portions being used until alkaloid is no longer extracted. The mixed acid liquors are then exactly neutralised with dilute ammonia solution and concentrated to 16 c.c. To this 1·5 grm. of sodium potassium tartrate dissolved in 3 grm. of water are added, the mixture stirred well and set aside one hour. The precipitated tartrates of quinine and cinchonidine are collected on a tared filter, washed with water, dried at 100°, and their weight n determined. The combined percentage of these two alkaloids in the bark is given by the formula $n \times 0{\cdot}8 \times 5$.

The mother liquor and washings are then treated with ammonia solution in slight excess, and the precipitate of "other alkaloids" collected on a tared filter, washed, dried, and its weight n' determined. The percentage of "other alkaloids" in the bark is equal to $5n'$. The percentage of "total alkaloids" in the bark is equal to $5(0{\cdot}8n + n')$. The "total alkaloids" should be between 5 and 6 per cent., of which not less than half should be quinine and cinchonidine.

For "liquid extract of cinchona bark" the same Pharmacopœia prescribes the following process: Five cubic centimetres of the extract are mixed with 25 c.c. of water in a glass separator, 30 c.c. of "benzolated amyl alcohol" added and 15 c.c. of potassium hydroxide solution (sp. gr. 1·058), and shaken together repeatedly. The alkaline layer is drawn off and the extraction repeated with a fresh quantity (30 c.c.) of benzolated amyl alcohol. The two alcoholic extracts are combined, shaken with a little water, and the alkaloids extracted by shaking twice with warm diluted hydrochloric acid, using 30 c.c. each time (1 vol. acid, sp. gr. 1·052, 5 vols. water). The two acid liquors are mixed, 10 c.c. of chloroform added and enough ammonia solution to make the mixture alkaline, and the whole shaken. The chloroformic solution is drawn off and the extraction repeated twice,

using 10 c.c. of chloroform each time. The solvent is allowed to evaporate from the combined chloroformic extracts contained in a tared dish and the residue dried at 110° and weighed. The weight multiplied by 20 gives the weight in grammes of total alkaloids in 100 c.c. of the extract. It should amount to 5 grm.

The same process is used for the "tincture of cinchona," of which 10 c.c. are used for assay. The tincture should contain between 0·95 and 1·05 grm. of total alkaloids in 100 c.c., whilst "compound tincture of cinchona" should contain half this amount of total alkaloids.

United States Pharmacopœia (8th Rev.). This recognises (1) cinchona bark which may be derived from *C. Ledgeriana, C. Calisaya, C. officinalis*, or hybrids of these; and (2) red cinchona bark derived from *C. succirubra*. The same assay process is prescribed for both. Cinchona bark must contain 5 per cent. of total alkaloids, of which 4 per cent. must be ether-soluble; red cinchona bark must contain 5 per cent. of total alkaloids.

Fifteen grammes of cinchona bark in No. 80 (or finer) powder are mixed in a flask with 250 c.c. ether and 50 c.c. chloroform, 10 c.c. of ammonia water (sp. gr. 0·958 at 25°) added, and the whole shaken frequently, or, if possible, continuously, during five hours. Fifteen cubic centimetres of distilled water are then added, and the flask shaken till the powder separates easily. Two hundred cubic centimetres of the clear supernatant liquid (10 grm. of bark) are transferred to a separator and the alkaloids extracted by shaking in turn with (1) 15 c.c. *N*-sulphuric acid, (2) 5 c.c. *N*-sulphuric acid and 5 c.c. of water, and (3) 5 c.c. of water. The combined acid liquids are filtered into a measuring cylinder and the filter washed with enough water to make the filtrate up to 50 c.c. after mixing.

Of this, 25 c.c. are assayed for total alkaloids by shaking in a separator with 25 c.c. of a mixture of chloroform (3 vols.) and ether (1 vol.) and 5 c.c. of ammonia water. The chloroform-ether layer is withdrawn and the extraction continued, using first 20 c.c. of chloroform-ether mixture and finally 10 c.c. of chloroform. The combined chloroform-ether solutions are run into a tared flask, the

solvent allowed to evaporate on a water-bath, the residue dissolved in 3 c.c. of ether and re-dried. It is finally dried at 110°, and its weight *n* determined. The percentage of total alkaloids in the bark is given by the formula 20*n*.

The second 25 c.c. are assayed for ether-soluble alkaloids (quinine, quinidine, and cinchonidine) by the same method, using for extraction 25 c.c. of ether in one operation, 5 c.c. of ether being used to rinse out the separator.

The same Pharmacopœia gives the following process for the "liquid extract of cinchona" in which the "ether-soluble alkaloids" are determined: Ten cubic centimetres of the extract are shaken with 100 c.c. of ether, 25 c.c. of chloroform, and 10 c.c. of ammonia water at intervals during ten minutes. After separation, 66 c.c. of the clear supernatant liquid (5 c.c. of extract) are transferred to a separator, using 5 c.c. of ether to wash out the measure, and shaken in turn with (1) 10 c.c. *N*-sulphuric acid, (2) 5 c.c. *N*-sulphuric acid and 5 c.c. of water, and (3) 5 c.c. water. The combined acid liquids are then mixed with 25 c.c. of ether, made alkaline with ammonia water, the temperature being kept below 25°, shaken thoroughly for two minutes, the ether withdrawn, and the aqueous liquid rejected, the separator being rinsed out with 5 c.c. of ether. The ethereal solution and the rinsings are run into a tared flask, the solvent distilled off, and the residue dried at 110° and weighed. The weight multiplied by 20 gives the number of grammes of ether-soluble alkaloids in 100 c.c. of the extract, which should be not less than 4.

For the "tincture of cinchona" the United States Pharmacopœia prescribes the same process as for the liquid extract, 50 c.c. of the tincture being evaporated to 10 c.c. on the water-bath, 10 c.c. of diluted alcohol being used to wash the concentrated tincture into the flask. The tincture should contain 0·75 grm. of ether-soluble alkaloids in 100 c.c.

German Pharmacopœia (1910). The bark of *Cinchona succirubra* is official in this Pharmacopœia and is required to contain at least 6·5 per cent. of total alkaloids, assayed by a process similar in principle to that of the United States Pharmacopœia for total

alkaloids. The alkaloidal residue dissolved in $N/10$-hydrochloric acid is determined by titration with $N/10$-potash in presence of hæmatoxylin, 1 c.c. of $N/10$-hydrochloric acid being taken as equal to 0·0309 grm. of total alkaloids.

Estimation of Quinine

From 1 to 5 grm. of total alkaloids extracted by the United States Pharmacopœia method from the bark may be used for the estimation of the chief alkaloids. For the estimation of quinine it should be exactly neutralised with $N/10$-sulphuric acid and the resulting liquid diluted with water until it contains 1 part by weight of total alkaloid in 70 parts by weight of solution. The latter is heated to 90° during five minutes, then cooled to 15° and set aside at this temperature during thirty minutes, when crystals of quinine sulphate will separate if the total alkaloids contained more than 8 per cent. of quinine. The crystals are collected on a tared filter and washed with cold water until the filtrate weighs 90 grm. for each gramme of total alkaloids taken. The crystals are dried at 100° and weighed. The weight requires correction for the solubility of quinine sulphate in water at 15°, and for this purpose 0·12 per cent. of the weight of the filtrate and washings should be added to the weight of quinine sulphate found.

Estimation of Cinchonidine, Cinchonine, and Quinidine

For the satisfactory estimation of the remaining bases it is necessary to start with about 5 grm. of the total alkaloids from which the quinine should be separated by the foregoing process. To the filtrate a slight excess of soda solution is added and the alkaloids shaken out with chloroform, which is distilled off and the residue dissolved in sufficient dilute sulphuric acid to produce exact neutrality (*Solution A*). A saturated solution of sodium potassium tartrate is then added, the mixture allowed to stand at 15° for one hour and frequently stirred ; the precipitate is collected on a tared filter, washed with as little water as possible, the filtrate

and washings being collected in a graduated beaker and measured. The *cinchonidine tartrate* is dried at 105° and weighed, 0·00083 grm. being added to the weight for each cubic centimetre of filtrate.

The filtrate is evaporated on the water-bath to its original volume (*Solution A*), clarified by addition of a drop of acetic acid, a saturated neutral solution of potassium iodide added, and the liquid frequently stirred during two hours at 15°. The precipitated *quinidine hydriodide* is collected with the same precautions as before. The weight obtained should be corrected by the addition of 0·00077 grm. for each cubic centimetre of filtrate.

The liquid is now made just alkaline with soda solution and the precipitate extracted with chloroform, the latter distilled off and the residue dried and weighed as cinchonine, the weight being corrected by the deduction of 0·00052 grm. for each cubic centimetre of the original liquid (*Solution A*), and 0·00066 grm. for each cubic centimetre of the filtrate from the quinidine estimation. The cinchonine residue will also contain any amorphous alkaloids present, and for the removal of these it may be washed with dilute alcohol (sp. gr. 0·94), the insoluble matter being purified cinchonine, which should again be weighed.

The process here outlined is a modified form of de Vrij's method,[1] recommended by Allen[2] as specially suitable for East Indian barks, and he has considerably shortened and improved it by substituting titration for gravimetric determination of the alkaloidal salts. Thus the cinchonidine tartrate is washed into a beaker with boiling water, a drop of phenolphthalein added, and the mixture titrated with $N/20$-soda, each cubic centimetre of which corresponds to 0·0147 grm. of cinchonidine. In the same manner the quinidine hydriodide solution is washed into the titration vessel with dilute potassium iodide solution and the estimation carried out as before, 1 c.c. of $N/20$-soda being equivalent to 0·0162 grm. of quinidine. The results thus obtained are, however, less accurate than those got gravimetrically.

[1] *Pharm. Journ.* 1871 [iii], **2**, 642.
[2] *Commercial Organic Analysis*, 4th ed. vol. vi. p. 495.

Quinine, $C_{20}H_{24}O_2N_2$. This, the most important of the cinchona alkaloids, was isolated in an impure condition by Fourcroy in 1792 and was described by Vauquelin under the name "quina" in 1809. In the following year a Spanish physician, Dr. Gomes, obtained by the addition of caustic potash to an alcoholic extract of cinchona bark a crystalline substance which he named "*Cinchonino.*" The basic properties of this material were observed by Houtou-Labillardière in Paris, and by him communicated to Pelletier and Caventou, who, inspired by the then recent observations of Sertürner on the existence of "organic alkalis" in nature, undertook the further investigation of "*Cinchonino*" and speedily resolved it into two substances, which they named *quinine* and *cinchonine.*[1] The bases were characterised by Pelletier and Dumas,[2] and the composition of quinine was accurately determined by Liebig, Regnault, and Strecker, the two latter chemists assigning to it its present formula.

Preparation. The bark, ground to a fine powder, is mixed with slaked lime and enough water to form a stiff paste, which is then dried and extracted with hot petroleum. In the laboratory a mixture of chloroform and ether may be used in place of petroleum. The alkaloids are extracted from the organic solvent by shaking with successive quantities of dilute sulphuric acid.

The alkaloids so obtained consist of quinine, cinchonidine, cinchonine, and a little quinidine, and such a mixture, prepared by the addition of caustic soda in excess to the acid liquid, constitutes the cinchona "febrifuge" prepared in India for distribution to the natives.

The quinine may be separated by recrystallising the mixed sulphates from hot water (in which the quinine salt is least soluble) by the process described on p. 135. The salt, which first separates, is redissolved in boiling water, decolorised if necessary with animal charcoal, and recrystallised from boiling water. Hesse[3]

[1] *Ann. Chim. Phys.* 1820 [ii], **15,** 291, 1337. [2] *Ibid.* **24,** 169.
[3] *Pharm. Journ.* 1884 [iii], **15,** 869. *Cf. ibid.* 1885 [iii], **16,** 358, 818, and 1886 [iii], **17,** 585.

has stated that quinine sulphate may be freed from cinchonidine sulphate by recrystallisation twice from faintly acidulated water. Pure quinine may be prepared by precipitating the commercial sulphate as the periodide (herepathite) and regenerating the base from the latter by sulphuretted hydrogen and recrystallisation from alcohol,[1] and Tutin[2] has prepared pure specimens of the alkaloid by regeneration from the recrystallised *d*-camphorsulphonate.

Properties. Quinine is precipitated as an amorphous, colourless, pasty mass when alkalis are added to an acid solution of the alkaloid, but in presence of ammonia gradually passes into a crystalline, efflorescent hydrate, $B.3H_2O$, m.p. 57°, which becomes anhydrous at 125° and then melts at 172·8°. According to Hesse anhydrous quinine is obtained in colourless needles, m.p. 174·4° to 175·4°, when sodium carbonate is added to quinine sulphate dissolved in warm water or when the hydrate is heated during eight days in dilute alcohol at 30°.[3] Anhydrous quinine is sparingly soluble in water [1 in 1960 at 15° (Hesse), 1 in 1667 at 20° (Sestini), 1 in 1750 at 25° (U.S.P.)], but readily so in alcohol (1 in 0·6 at 25°), ether (1 in 4·5 at 25°), chloroform (1 in 1·9 at 25°), or boiling benzene. Ammonia readily forms supersaturated solutions with quinine.[4] The alkaloid is lævorotatory, $[\alpha]_D$ — 158° at 15° (Rabe), or $0{\cdot}894c$ — 169·38°, where c is the weight in grammes of anhydrous quinine dissolved in 100 c.c. of alcohol.[5] The specific rotation of the alkaloid and of its salts varies considerably with the temperature and the solvent.[6] Solutions of quinine in certain oxygenated acids, *e.g.* sulphuric, phosphoric, and tartaric, fluoresce blue, but this is not shown by solutions in haloid acids, and it disappears in presence of ferrocyanides.

In common with other alkaloids of this group, quinine has the property of forming molecular compounds with a variety of organic substances. Thus with benzene and toluene it forms compounds

[1] De Vrij and Alluard, *Jahresb.* 1864, p. 445.
[2] *Pharm. Journ.* November 13, 1909.
[3] *Annalen*, 1890, **258**, 135. *Cf.* Lenz, *Zeit. Anal. Chem.* 1888, **27**, 549.
[4] Duncan, *Pharm. Journ.* 1905, **74**, 438.
[5] Hesse, *Annalen*, 1875, **176**, 205. [6] Oudemans, *ibid.* 1876, **182**, 44.

of the formulæ $B.C_6H_6$ and $B.C_7H_8$ respectively; with phenol it gives the crystalline product, $B.C_6H_5OH$, and similar combinations with polyhydric phenols, ethers, aldehydes, and ketones are known. One of the most characteristic of these substances is cupreine-quinine, a combination of the two alkaloids, which is readily obtainable from cuprea bark and was at first regarded as a new alkaloid and named "homoquinine" (*see* p. 157).

Salts. Quinine is a strong diacidic base which forms both neutral and acid salts. The neutral salts are faintly alkaline to litmus and strongly alkaline to methyl-orange. The alkaloid and its salts are intensely bitter to the taste. Three sulphates are known. Commercial quinine sulphate, $B_2.H_2SO_4.8H_2O$ (or $7H_2O$), is the neutral sulphate and is obtained by exactly neutralising the alkaloid with dilute sulphuric acid and recrystallising from boiling water, from which it separates in bulky masses of colourless, glistening needles which effloresce and lose their lustre on exposure to dry air. Exposed over sulphuric acid, it loses $6H_2O$ and then melts at 205°; at 115° it becomes anhydrous. The salt containing $7H_2O$ is sparingly soluble in water (1 in 720 at 25°) or chloroform (1 in 400 at 25°), more soluble in alcohol (1 in 86 at 25°, 1 in 9 at 60°), readily soluble in a mixture of chloroform (2 parts) with alcohol (1 part), and very soluble in dilute acids. The solution in water is scarcely fluorescent, but is markedly so in dilute sulphuric acid. The hydrated sulphate is lævorotatory, $[\alpha]_D^{15}$ — 166·36° in alcohol, or — 233·75° in the case of the anhydrous salt, — 235° in 1 per cent. sulphuric acid (Tutin). The acid sulphate, $B.H_2SO_4.7H_2O$ (quinine disulphate), forms colourless, transparent, orthorhombic crystals, m.p. 160° (*decomp.*), $[\alpha]_D$ — 159·1° (Tutin), which effloresce in air and turn yellow on exposure to light. It is soluble in water (1 in 8·5 at 25°) or alcohol (1 in 18 at 25°), and sparingly so in ether (1 in 1770 at 25°) or chloroform (1 in 920 at 25°). The aqueous solution is acid to litmus and markedly fluorescent. The so-called tetrasulphate, $B.2H_2SO_4.7H_2O$, forms colourless prisms and is exceedingly soluble in water, much less so in alcohol.

Quinine hydrochloride, $B.HCl.2H_2O$, closely resembles the

neutral sulphate in appearance, and, like it, effloresces in dry air, m.p. begins at 156° and ends at 190°, $[\alpha]_D^{17}$ – 133·7° in water (Oudemans), — 155·8° (Tutin), soluble in water (1 in 18 at 25°), alcohol (1 in 0·6 at 25°), chloroform (1 in 0·8 at 25°), and sparingly in ether (1 in 240 at 25°). The aqueous solution is neutral and is not fluorescent except after the addition of sulphuric acid. The acid hydrochloride, B.2HCl, best obtained by treating a solution of the acid sulphate with barium chloride, crystallises in concentrically grouped needles and is very soluble in cold water (1 in 0·75). The hydrobromide, $B.HBr.H_2O$, resembles the hydrochloride, m.p. commences at 152° and ends at 200°, soluble in water (1 in 55 at 15°, Hesse), alcohol (1 in 0·67 at 25°), chloroform, or ether. The aqueous solution is neutral and fluoresces only on addition of sulphuric acid. Quinine salicylate, $2(B.C_6H_5.COOH).H_2O$, forms colourless needles, m.p. 187° (*decomp.*), which slowly become pink in air. It is soluble in water (1 in 77 at 25°), alcohol (1 in 11 at 25°), or chloroform (1 in 37 at 25°).

The foregoing are the most important quinine salts used in medicine, but a large number of other salts have been used, *e.g.* the tannate, formate, valerianate, &c.

Quinine yields a monoacetyl derivative, m.p. 116°–117°, which is tasteless.

Examination of Commercial Quinine Salts. Commercial quinine salts invariably contain small amounts of the other cinchona alkaloids, especially cinchonidine and hydroquinine, and possibly a little quinidine and cinchonine, and owing to the importance of quinine and its salts in medicine a great deal of attention has been given to devising tests which will ensure that the percentage of such impurities in the salts is small. The total substitution of one alkaloid of this group for another, say cinchonine for quinine, can be guarded against by the application of the thalleioquin (p. 145) and other tests, given under the respective alkaloids, whilst grosser impurities, such as added mineral matter and excess of water, would be detected by determination of the residue left on ignition, which should be negligible, and the loss on dehydration,

which should not be greater than the water of crystallisation (14·5 to 15·2 per cent. in the commercial sulphate). Quinine dissolves in sulphuric or nitric acids practically without development of colour, and the production of coloured solutions under these conditions would indicate the addition of organic matter.

The tests chiefly relied on for the detection of excessive amounts of other cinchona alkaloids in quinine salts are (*a*) the ether test, (*b*) the ammonia test, (*c*) certain special tests. These tests are usually described for neutral quinine sulphate, which is much the most important salt of the alkaloid, but they can be applied to the other salts if these are first converted into neutral quinine sulphate. For this purpose acid sulphate of quinine must be exactly neutralised with caustic soda; the haloid salts must be boiled with their own weight of sodium sulphate dissolved in ten times its weight of water, whilst the alkaloid must be recovered from the tannate or salicylate by adding alkali and extracting with ether and the recovered alkaloid exactly neutralised with dilute sulphuric acid.

Ammonia Test. The United States Pharmacopœia (8th Rev.) gives this in the following form: Quinine sulphate is dried at 50° for two hours, and 1·8 grm. of the dried salt is shaken with 20 c.c. of water at 65° during thirty minutes, then cooled to 15°, and set aside at this temperature with occasional agitation during two hours. It is then filtered through a filter paper 8 to 10 cm. in diameter. Five cubic centimetres of the filtrate are placed in a test tube and 7 c.c. of ammonia water (sp. gr. 0·958 at 25°) added all at once, when a clear liquid should be produced.

The ammonia test of the German Pharmacopœia (1910) is more stringent. In this case 2 grm. of quinine sulphate dried at 40° to 50° are mixed with 20 c.c. of water, kept with occasional agitation at 60° to 65° during thirty minutes, then cooled to 15° and kept at this temperature two hours with occasional agitation. It is then filtered through a 7 cm. filter paper, and 5 c.c. of the filtrate collected in a dry test tube. To this 4 c.c. of ammonia solution (sp. gr. 0·959) are added, which produces a precipitate which should dissolve completely on shaking for some time.

The same test is prescribed in other Pharmacopœias, but the amount of 10 per cent. ammonia solution specified varies between the 4 c.c. of the German Pharmacopœia and the 7 c.c. of the United States Pharmacopœia, being 5 c.c. in the French Codex and 4·5 in the Dutch Pharmacopœia.

Tutin [1] has recently critically examined the principal pharmacopœial methods for applying the ammonia test and finds that pure quinine sulphate tested by either the German or French method requires 4 c.c. of ammonia to give a clear solution, and suggests that 6 c.c. of ammonia solution would be a reasonable limit for adoption in Pharmacopœias. The same author recommends a slight modification of the French Codex process of preparing the solution, so that his method of applying the test is as follows: 0·3 grm. of quinine sulphate is dissolved by boiling with 30 c.c. of water, the solution cooled to 15° and kept at this temperature during two hours with occasional agitation. The mixture is then filtered and 5 c.c. of the filtrate collected in a test tube. With this, 6 c.c. of 10 per cent. ammonia solution should produce a clear liquid. Tutin, however, points out that commercial quinine sulphate is almost always slightly alkaline, and in such cases the amount of ammonia solution required is above the normal. Further, it is greatly affected by the presence of inorganic salts, and this renders it useless in testing acid sulphate of quinine (quinine disulphate), since in applying the test to this salt the latter is first converted into the neutral sulphate by neutralisation with an alkali, and for the same reason it is unsuitable for use with haloid salts of quinine. In view of the limited applicability of the ammonia test, therefore, Tutin suggests that the ether test of the British Pharmacopœia (*see below*) for cinchonine and cinchonidine is preferable.

Ether Test. This method of estimating the purity of commercial sulphate of quinine depends on the small solubility of cinchonidine and cinchonine in ether as compared with quinine, and the British Pharmacopœia (1898) gives it in the following form: Dissolve 4 grm. of the quinine sulphate in 120 c.c. of boiling water. Cool the

[1] *Pharm. Journ.* 1909 [iv], **29**, 600.

solution slowly to 50° with frequent stirring. Separate by filtration the purified quinine sulphate which has crystallised out. Evaporate the filtrate to 10 c.c., and when cool add 5 c.c. of solution of ammonia (sp. gr. 0·959) and 10 c.c. of ether, and shake. Set aside in a cool place for twenty-four hours. Collect the crystals, which consist of cinchonidine and cinchonine together with some quinine, on a tared filter, wash with a little dry ether, dry at 100°, and weigh. These should not amount to more than 0·12 grm.[1] Tutin [2] points out that in using this test pure ether should be employed, and that with this change as little as 3 per cent. of cinchonidine sulphate can be detected.

Special Tests. The British Pharmacopœia (1898) prescribes special tests for: (1) quinidine, (2) cupreine, (3) cinchonine and amorphous alkaloids.

(1) One gramme of quinine sulphate is dissolved in 30 c.c. of boiling water and the solution cooled and filtered. To the filtrate potassium iodide solution (10 per cent.) is added and a little alcohol. The quinidine hydriodide which separates is collected, washed with a little water, dried, and weighed. Only traces should be found.

(2) The recrystallised quinine sulphate obtained in the "ether test" (p. 142) is shaken with 6 c.c. of 10 per cent. ammonia solution and 25 c.c. of ether, and the ether separated. To it is added the ethereal liquid and washings obtained in making the original test, and the whole is shaken with 6 c.c. of a 10 per cent. solution of caustic soda. The latter is separated, shaken once with ether, heated to boiling, and then neutralised exactly with dilute sulphuric acid. Any cupreine sulphate formed will separate on cooling and may be collected and weighed. Cuprea barks rarely appear in commerce now, so that cupreine is not a usual impurity in modern quinine sulphate.

(3) One gramme of quinine sulphate is dissolved in 30 c.c. of boiling water. To this 1 grm. of sodium potassium tartrate is added and the mixture cooled and filtered. The filtrate on evaporation

[1] *Cf.* Howard, *Pharm. Journ.* 1896 [iv], **3**, 505. [2] *Loc. cit.*

to a low bulk should give little or no precipitate with ammonia solution.

The German Pharmacopœia (1910) specifies that 1 grm. of quinine hydrochloride or sulphate must be soluble in 7 c.c. of a mixture of chloroform (2 vols.) and dry alcohol (1 vol.).

Hydroquinine is commonly present in commercial quinine to the extent of from 2 to 4 per cent. It may be estimated, according to Howard,[1] by treating the ether-soluble alkaloid obtained in the pharmacopœial ether test (*see* p. 142) with excess of dilute sulphuric acid and adding drop by drop to this solution 4 per cent. potassium permanganate so long as the latter is rapidly decolorised. The manganese dioxide is then filtered out and the filtrate treated with ether and ammonia, the former separated, shaken out with dilute sulphuric acid, and the alkaloidal sulphate crystallised out by neutralisation of the acid liquid, dried, and weighed.

A considerable number of other methods of testing quinine salts have been devised, but have not been adopted generally. Among these is the chromate method, which depends on the fact that quinine chromate is less soluble in water than the chromates of the accompanying alkaloids.[2] According to Hesse[3] and Lenz[4] the chromate test gives high results for quinine owing to the inclusion of cinchonidine and hydroquinine.

In Schäfer's oxalate test the quinine is precipitated as oxalate and the accompanying alkaloids estimated by rendering the filtrate alkaline and collecting and weighing the precipitate.[5] According to Lenz[6] this gives low but uniform results for the impurities present.

Optical methods based on Oudemans' results in the investigation of the optical rotations of the cinchona alkaloids and their salts have been advocated by Hesse,[7] Byasson,[8] Koppeschaar,[9] Davies,[10]

[1] *Loc. cit.*
[2] De Vrij, *Arch. Pharm.* 1887 [iii], **24**, 1073; Schlickum, *ibid.* p. 128.
[3] *Pharm. Journ.* 1887 [iii], **17**, 585, 665; 1888 [iii], **18**, 582.
[4] *Zeit. Anal. Chem.* 1888, **27**, 575. [5] *Arch. Pharm.* 1887, **225**, 64, 1033.
[6] *Loc. cit.* [7] *Berichte*, 1871, **4**, 693. [8] *Journ. Pharm.* 1884 [v], **7**, 291.
[9] *Zeit. Anal. Chem.* 1885, **24**, 362. [10] *Pharm. Journ.* 1884–85 [iii], **16**, 358.

Léger,[1] and others, but these methods have been little used, chiefly owing to the fact that the differences in rotation caused by even considerable quantities of impurities are small.[2]

Critical *résumés* of methods of testing quinine sulphate have been published by Jungfleisch,[3] Lenz,[4] Howard,[5] and Hille.[6]

Detection of Quinine. The various properties of quinine, which are described above, may be used for its identification, especially its bitter taste, and the fluorescence of certain of its salts in acid solution.

When bromine or chlorine water is added, drop by drop, to a faintly acid solution of a quinine salt until the reagent is present in very slight excess, and then excess of ammonia is added, a characteristic deep green coloration is produced. This test, which is known as the "thalleioquin" reaction, is said to be given by 1 part of quinine in 20,000 of a solution. It is also afforded by quinidine and cupreine, but not by cinchonine or cinchonidine. For recent work on the constitution and properties of "thalleioquin," *see* papers by Führer [7] and Comanducci.[8]

Quinine is more soluble in ether and in ammonia solution than the other cinchona alkaloids, and its oxalate and chromate are less soluble in water.

It affords a series of periodides of which that known as "herepathite," $B_4.3H_2SO_4.2HI.I_4.6H_2O$, is characteristic.[9] This is prepared by dissolving neutral quinine sulphate in alcohol, adding the calculated quantity of sulphuric acid, then heating to the boiling-point and adding the requisite quantity of iodine dissolved in alcohol. The crystals which separate are washed with cold 70 per cent. alcohol and recrystallised from boiling alcohol, when they separate in tablets or leaflets which are golden green by reflected light, very pale olive-green by transmitted light, and polarise

[1] *J. Pharm. Chim.* 1904 [vi], **19**, 427.

[2] *Cf.* Paul, *Pharm. Journ.* 1885 [iii], **16**, 361; Hesse, *ibid.* 1887-88 [iii], **18**, 517; and Howard, *Watt's Dict. Chem.* vol. ii. p. 178.

[3] *Journ. Pharm.* 1887 [v], **15**, 5. [4] *Zeit. Anal. Chem.* 1888, **27**, 549.

[5] *Loc. cit.* and *Pharm. Journ.* 1896 [iv], **3**, 505.

[6] *Arch. Pharm.* 1903, **241**, 54. [7] *Ibid.* 1906, **244**, 602.

[8] *Abstr. Chem. Soc.* 1910, i, 581; 1911, i, 317.

[9] Herepath, *Annalen*, **84**, 149; **88**, 207.

light like tourmaline.[1] The formation of herepathite has been used by de Vrij[2] as a means of separating and estimating quinine.

Quinidine (*Conquinine*), $C_{20}H_{24}O_2N_2$. This isomeride of quinine is contained in small quantity in most of the ordinary cinchona barks, but especially in *Cinchona pitayensis*, *C. amygdalifolia*, and *C. Calisaya*, which sometimes contain as much as 3 per cent.[3]

It occurs in the final mother liquors from the preparation of quinine sulphate, and the mixture of alkaloids, known as "quinoidine," obtained by precipitating these liquors with caustic soda is a convenient source of the alkaloid, from which it may be obtained along with cinchonidine by extraction with ether. The cinchonidine is removed by dissolving the ethereal residue in dilute sulphuric acid, neutralising exactly with ammonia solution and precipitating with sodium potassium tartrate. From the filtrate quinidine is recovered by precipitation as the hydriodide by addition of potassium iodide solution.[4] From this it is recovered and recrystallised from boiling alcohol.

Quinidine crystallises from dry alcohol with 1 mol. of the solvent in prisms, from dry ether with $\frac{1}{3}$ mol. of ether in trimetric tablets, and from boiling water with $1\frac{1}{2}H_2O$ in leaflets. Freed from solvents of crystallisation it melts at 171·5°, and has the following solubilities: water, 1 in 2000 at 15°; ether, 1 in 35 at 10°; alcohol, 1 in 26 of 80 per cent. at 20°; and is sparingly soluble in chloroform or light petroleum. It is dextrorotatory, $[\alpha]_D + 274{\cdot}7°$ in alcohol 1 vol., chloroform 2 vols. (Lenz), + 243·5° (Rabe). The sulphate and the salts of other oxygenated acids show a blue fluorescence, especially in solution in dilute sulphuric acid. Like quinine, it crystallises with benzene.

Quinidine is alkaline in solution and behaves as a diacidic base forming two series of salts. The neutral sulphate, $B_2.H_2SO_4.2H_2O$, crystallises from hot water in colourless prisms, soluble in water

[1] Jörgensen, *Journ. prakt. Chem.* 1876 [ii], **14**, 230.
[2] *Pharm. Journ.* 1871–72 [iii], **2**, 643; 1875–76 [iii], **6**, 461.
[3] Hesse, *Annalen*, 1874, **174**, 338.
[4] Hesse, *ibid.* 1868, **146**, 358; 1873, **166**, 236.

(1 in 108 at 10°, 1 in 98–100 at 15°, or 1 in 7 at 100°), more so in alcohol or chloroform, and scarcely in ether. It is dextrorotatory, $[\alpha]_D$ + 184·17° in chloroform. The acid sulphate, $B.H_2SO_4.4H_2O$, forms hair-like, colourless needles, soluble in 8·7 parts of water at 10°. The neutral hydrochloride, $B.HCl.H_2O$, forms asbestos-like prisms, easily soluble in alcohol or hot water, less so in cold water (1 in 62·5 at 10°). The acid hydrochloride, $B.2HCl.H_2O$, forms prisms, readily soluble in alcohol, sparingly in water, chloroform, or hydrochloric acid. The neutral hydriodide, B.HI, is deposited as a crystalline powder when potassium iodide is added to a neutral aqueous solution of a quinidine salt and is the form in which the alkaloid is usually isolated and estimated, since it is less soluble in water (1 in 1250 at 15°, 1 in 1270 at 10°) than the hydriodides of the other cinchona alkaloids.

Detection and Estimation. Quinidine gives the thalleioquin reaction (p. 145), and is fluorescent in dilute sulphuric acid. Unlike quinine it is dextrorotatory, possesses a sparingly soluble hydriodide, and gives a neutral sulphate easily soluble in water or chloroform. The tartrate is soluble and the hydriodide sparingly soluble in water, and these properties are utilised in its separation from cinchonidine and quinine (p. 135).

Quinicine (*Quinotoxine*), $C_{20}H_{24}O_2N_2$. This alkaloid was isolated by Howard [1] from cinchona bark, but had been previously prepared by Pasteur [2] by heating acid quinine sulphate, and subsequently by Hesse [3] in a similar manner from quinidine. It is also formed by heating quinine in dilute acetic acid or water.[4] It is purified by conversion into the oxalate, $B_2.H_2C_2O_4.9H_2O$, small prisms, m.p. 149°, which is insoluble in water, and, unlike that of quinine, can be recrystallised from chloroform or alcohol.

The base is a bitter, alkaline, yellow oil, $[\alpha]_D$ + 38° 40′ in chloroform,[5] slightly soluble in water, easily in alcohol or ether.

[1] *Journ. Chem. Soc.* 1871, **24**, 61 ; 1872, **25**, 101.
[2] *Jahresberichte*, 1853, p. 473.
[3] *Annalen*, 1875, **178**, 245 ; 1888, **243**, 148.
[4] Biddle, *Berichte*, 1912, **45**, 526.
[5] Howard and Perry, *Journ. Soc. Chem. Ind.* 1909, **28**, 53.

It gives the thalleioquin reaction, but its salts are not fluorescent in solution.

Quinicine was long regarded as distinct from quinotoxine, but their identity was finally proved by von Miller and Rohde.[1]

In addition to quinicine the following isomerides of quinine and quinidine have been prepared and described. None of them have been found to occur naturally:

Other Isomerides of Quinine, $C_{20}H_{24}O_2N_2$

Name	Method of formation	Crystalline form	Optical rotation $[\alpha]_D$
*Pseudo*quinine (Skraup, *Monats.* 1893, **14**, 446)	These two isomerides are formed together when hydroiodoquinine dihydriodide is heated with potash in alcohol, and are separated by fractional crystallisation of their oxalates	Prisms, m.p. 190°–191°	− 164·4° in alcohol
*Iso*quinine (Lippmann and Fleissner, *Monats.* 1891, **12**, 332; 1893, **14**, 554. *Cf.* Böttcher, 1911, **32**, 793)		Minute needles, m.p. 185° (L. & F.); 189° (Böttcher)	− 186·6° in alcohol
*Iso*quinidine (Pfannl, *Monats.* 1911, **32**, 241)	By solution of quinidine sulphate in sulphuric acid	Long needles, m.p. 142°	$[\alpha]_j$ − 9°

Apoquinine, $C_{19}H_{22}O_2N_2.2H_2O$. This substance, isomeric with cupreine (p. 156), is produced from quinine together with methyl chloride by the action of strong hydrochloric acid.[2] It also results when cupreine is heated with this reagent at 140°.[3] The base crystallises in needles, m.p. 210° (*decomp.*), $[\alpha]_D$ − 178·1° in 97 per cent. alcohol. Its salts are generally amorphous.

With acetic anhydride it gives an amorphous diacetyl derivative, which resembles quinine, but not apoquinine, in giving the thalleioquin reaction and in being fluorescent in dilute sulphuric acid solution.

[1] *Berichte*, 1900, **33**, 3214.
[2] Hesse, *Annalen*, 1880, **205**, 323.
[3] Hesse, *ibid.* 1885, **230**, 65.

The base is unsaturated and readily combines with one molecule of a halogen acid.

Cinchonine, $C_{19}H_{22}ON_2$. This alkaloid occurs constantly in cinchona and cuprea barks, but the quantity is usually small and shows great variation. One of the best sources is *Cinchona micrantha* bark.

The alkaloid occurs as the sulphate in the crude mother liquors from which quinine sulphate has been crystallised. The mixed alkaloids contained in these are precipitated by the addition of caustic soda solution, and the precipitate boiled with successive small quantities of alcohol, from which cinchonine crystallises out on cooling. The crude alkaloid is exactly neutralised with dilute sulphuric acid, and the sulphate recrystallised from boiling water.

Cinchonine separates from aqueous solutions of its salts, on addition of an alkali, in an amorphous condition, but crystallises on standing. It crystallises from alcohol in rhombic prisms, m.p. 264°, $[\alpha]_D^{17} + 229°$ in dry alcohol or + 234° 33′ in alcohol 1 vol., chloroform 2 vols., is sparingly soluble in water (1 in 3810 at 10°, 1 in 3670 at 20°), more so in alcohol, sp. gr. 0·852, (1 in 140 at 10°, 1 in 125·7 at 20°) or ether, sp. gr. 0·7305, (1 in 371 at 10°). It is not fluorescent in dilute sulphuric acid.

It behaves as a diacidic base, and gives two series of salts. The neutral sulphate, $B_2.H_2SO_4.2H_2O$, forms rhombic crystals readily soluble in 80 per cent. alcohol (1 in 5·8 at 11°), moderately so in water (1 in 65·5 at 13°), $[\alpha]_D + 193·29° - 0·374c$, where $c =$ grammes of alkaloid per 100 c.c. of 97 per cent. alcohol, or + 133° in chloroform. The acid sulphate, $B.H_2SO_4.4H_2O$, colourless octahedral crystals, readily soluble in alcohol (1 in 0·9 at 14°) or water (1 in 0·46 at 14°). The neutral hydrochloride, $B.HCl.2H_2O$, forms monoclinic crystals soluble in 22 parts of cold water or 1 part of cold alcohol.

Detection. Cinchonine, unlike quinine and quinidine, does not give the thalleioquin reaction (p. 145), and is not fluorescent in dilute sulphuric acid. In these respects it resembles cinchonidine, from

which it differs in being sparingly soluble in ammonia solution or ether, and in being dextrorotatory.

Cinchonidine, $C_{19}H_{22}ON_2$. This isomeride of cinchonine occurs in most varieties of cinchona bark, but especially in those of *C. succirubra*, *C. officinalis*, *C. tucujensis*, and *C. lancifolia*. The sulphate has been largely used in medicine as a substitute for quinine.

Preparation. The mother liquors from the separation of quinine sulphate are precipitated with ammonia solution and the dry precipitate repeatedly extracted with small quantities of ether, which leaves the greater part of the cinchonine undissolved. The ethereal solution is shaken with dilute hydrochloric acid, when quinidine and cinchonidine hydrochlorides dissolve in the acid liquid, which is then separated and neutralised exactly with ammonia. To this solution sodium potassium tartrate is added, which precipitates cinchonidine tartrate. The cinchonidine is recovered from this by dissolving in dilute acid, adding ammonia solution in excess, and recrystallising the precipitate twice from alcohol. The recrystallised alkaloid is then converted into the neutral sulphate, and this recrystallised three times by dissolving it in 25 times its weight of boiling water and cooling to 35°. The crystals which separate at this temperature after the third crystallisation are generally free from impurities, and cinchonidine may be regenerated from them by solution in dilute acid, precipitation with ammonia solution, and recrystallisation from alcohol.[1]

This process may also be applied to "quinoidine" and to commercial cinchonidine sulphate, which generally contains quinine, and homocinchonidine.[2]

According to Königs and Husmann[3] cinchonine can be converted into cinchonidine by heating the former with amyl alcohol and potash. Paul and Cownley, however, state that this change does not occur under these conditions.[4]

Cinchonidine crystallises in large, trimetric prisms, m.p. 207·2°

[1] Hesse, *Annalen*, 1880, **205**, 196.
[2] Hesse, *loc. cit.*
[3] *Berichte*, 1896, **29**, 2183.
[4] *Pharm. Journ.* 1897 [iv], **4**, 141.

(Lenz), 202·4° (Hesse), $[\alpha]_D$ — 107·9° in alcohol 1 vol., chloroform 2 vols. (Lenz), — 111° in alcohol (Rabe), is very sparingly soluble in water (1 in 5263 at 11·5°, Skraup), more soluble in alcohol (1 in 303 of alcohol, sp. gr. 0·935 at 11·5°, Skraup; 1 in 16·3 of 97 per cent. alcohol at 13°, Hesse) or ether (1 in 1053 of dry ether at 11·5°, Skraup; 1 in 188 of ether, sp. gr. 0·72 at 15°, Hesse). Cinchonidine does not fluoresce in dilute sulphuric acid solution and does not give the thalleioquin reaction. It is a diacidic base, and yields two series of salts. The neutral sulphate, $B_2.H_2SO_4$, forms monoclinic prisms with $6H_2O$ from cold water, or with $3H_2O$ from hot water, and is soluble in alcohol (1 in 72 at 25°) or water (1 in 63 at 25°). The trihydrated sulphate is official in the British and United States Pharmacopœias. The acid sulphate, $B.H_2SO_4.5H_2O$, is easily soluble in water, whilst the "tetrasulphate," $B.2H_2SO_4.H_2O$, dissolves slowly in water. The neutral hydrochloride, $B.HCl.H_2O$, forms monoclinic double pyramids, or silky prisms with $2H_2O$, from its saturated aqueous solution. The dry salt is moderately soluble in water (1 in 38·5 at 10°) or ether (1 in 325 at 10°), readily in chloroform. The acid hydrochloride, $B.2HCl.H_2O$, forms large monoclinic prisms very easily soluble in water or alcohol. The tartrate, $B_2.H_2C_4H_4O_6.2H_2O$, is a crystalline precipitate, sparingly soluble in water (1 in 1265 at 10°), almost insoluble in sodium potassium tartrate solution, and is the form in which the alkaloid is usually estimated (*see* p. 135).

Detection. Cinchonidine is readily distinguished from quinine and quinidine by not being fluorescent in dilute sulphuric acid, and by not giving the thalleioquin reaction. It differs from cinchonine in being lævorotatory, in being more soluble in ether, and in the sparing solubility of its tartrate.

Homocinchonidine, $C_{19}H_{22}ON_2$, is stated by Hesse to accompany cinchonidine in many cinchona barks, but especially in *C. rosulenta*,[1] and to be produced along with apocinchonidine (*see* Table, p. 153) by the action of hydrochloric acid or diluted sulphuric

[1] *Annalen*, 1880, **205**, 203.

acid on cinchonidine at 140°.[1] It can be isolated from commercial neutral cinchonidine sulphate by dissolving this in 25 parts of hot water, cooling to 35°, filtering and cooling the filtrate, when impure homocinchonidine sulphate separates and may be purified by repeating the treatment. The base crystallises from alcohol in thick short prisms, m.p. 207·6°, 201° (Dobbie), $[\alpha]_D$ — 107·3° in 97 per cent. alcohol, soluble in chloroform or alcohol (1 in 20·5 of 97 per cent. alcohol at 13°), sparingly in ether (1 in 216 at 15°). The neutral sulphate, $B_2.H_2SO_4.6H_2O$, crystallises from hot water in thin needles, is soluble in 69 parts of water at 22°, and has $[\alpha]_D$ — 137·96° in dilute hydrochloric acid. Homocinchonidine does not give the thalleioquin reaction (p. 145), and its solutions in dilute sulphuric acid are not fluorescent. It has been suggested that homocinchonidine is merely a pure form of cinchonidine.

Homocinchonine, $C_{19}H_{22}ON_2$. This name was applied by Hesse to an alkaloid, isomeric with cinchonine, obtained from *Cinchona Palton*,[2] and which was also supposed to be formed by the action of sulphuric acid on cinchonine at 140°. Skraup, however, has shown that homocinchonine is merely impure cinchonine.[3]

Cinchotine (*Hydrocinchonine, Cinchonifine, ψ-Cinchonine*), $C_{19}H_{24}ON_2$. This alkaloid occurs in most varieties of cinchona bark and is a constant constituent of commercial cinchonine.[4] It is best prepared from the cinchonine fraction obtained from *Remijia Purdieana* bark (p. 176) by dissolving this in dilute hydrochloric acid and adding platinic chloride. The amorphous precipitate gradually deposits crystals of cinchonine platinichloride which may be separated mechanically from the cinchotine salt.[5] According to Pum[6] the separation may be effected by adding potassium iodide to a solution of the two alkaloids in strong hydrochloric acid, the cinchotine hydriodide being precipitated. According to Skraup[7]

[1] *Annalen*, 1880, **205**, 327; 1888, **243**, 148; 1890, **258**, 142.
[2] *Ibid.* 1888, **243**, 149; 1893, **276**, 103. [3] *Monats.* 1899, **20**, 579.
[4] Hesse, *Annalen*, 1873, **166**, 256; 1898, **300**, 46. *Cf.* Forst and Böhringer, *Berichte*, 1881, **14**, 436; 1882, **15**, 520.
[5] Hesse, *Annalen*, 1898, **300**, 44. [6] *Monats.* 1895, **16**, 68
[7] *Ibid.* 1899, **20**, 571.

Other Isomerides of Cinchonine, $C_{19}H_{22}ON_2$

Name	Synonym	Method of formation	Properties	References
*iso*Cinchonidine		By solution of cinchonidine sulphate in sulphuric acid	Leaflets, m.p. 235°, 252°(Paneth) $[\alpha]_D$ – 128°	Hesse, *Annalen*, 1888, **243**, 149. Paneth, *Monats.* 1911, **32**, 257
β-Cinchonidine		By the action of alcoholic potash on hydroiodocinchonidine	Tabular crystals, m.p. 244°, lævorotatory	Neumann, *Monats.* 1892, **13**, 655
γ-Cinchonidine		By heating cinchonidine trihydriodide with aqueous silver nitrate	m.p. 238°, lævorotatory	
*apo*Cinchonidine		By heating cinchonidine with hydrochloric acid at 140°–150°	Leaflets, m.p. 225° $[\alpha]_D$ – 129·2°	Hesse, *Annalen*, 1880, **205**, 327
*allo*Cinchonine	β-Cinchonine *apo*Cinchonine γ-Cinchonine *apoiso*Cinchonine *isoapo*Cinchonine	By heating hydroiodocinchonine with alcoholic potash	Needles, m.p. 214°–216°, 218°–220° (Dobbie) $[\alpha]_D$ + 164·8°	Skraup and collaborators, *Monats.* 1899, **20**, 571; 1900, **21**, 512, 535, 558; 1901, **22**, 171, 191, 253, 1083 1097, 1103; 1902, **23**, 443, 455; 1903, **24**, 311; 1904, **25**, 894.
" δ-Cinchonine " $C_{19}H_{22}ON_2$		By heating hydrobromocinchonine with alcohol	m.p. 150° $[\alpha]_D$ + 125·2°	
ε-Cinchonine		Formed with δ-cinchonine when alcoholic potash is used	m.p. 150° $[\alpha]_D$ + 58·3°	
α-*iso*Cinchonine	Cinchoniline Di*apo*cinchonine	By heating cinchonine sulphate with sulphuric acid	pseudo-rhombic prisms, m.p. 126° $[\alpha]_D$ + 49·74°	Lowenhaupt, *ibid.* 1898, **19**, 461. Kaas, *ibid.* 1904, **25**, 1145; 1905, **26**, 296. Roques, *Ann. Chim. Phys.* 1897 [vii], **10**, 234.
β-*iso*Cinchonine	Cinchonigine Di*apo*cinchonine	Formed with α-*iso*cinchonine as above	Prisms, m.p. 126°–127° $[\alpha]_D$ – 54·02°	
Cinchonicine	Cinchotoxine	By heating cinchonine or cinchonidine with acetic acid, sulphuric acid, or glycerol	Needles, m.p. 58°–59° $[\alpha]_D$ + 46·5° + 49·62° (Rabe)	
α-*iso*Cinchonicine		By heating α-*iso*cinchonine sulphate at 140°		
α-*iso*-ψ-Cinchonicine		Ditto	Amorphous m.p. 73°–74°	von Miller and Rohde, *Berichte*, 1900, **33**, 3214
β-*iso*-ψ-Cinchonicine		By heating β-*iso*cinchonine sulphate		
*tauto*Cinchonine		By action of potash on cinchonine bromide	m.p. 252·5° $[\alpha]_D$ + 209·4°	

and von Arlt [1] cinchotine is identical with "cinchonifine" [2] and pseudocinchonine [3] obtained by the action of various reagents on cinchonine and supposed to be isomerides of this base.

Cinchotine crystallises in prisms, m.p. 268°–269°, $[\alpha]_D$ + 204·5° in alcohol (Hesse), + 190° at 14° (Rabe), less soluble in chloroform or alcohol (1 in 221·5) than cinchonine. The base is diacidic and forms two series of salts; the neutral sulphate, $B_2.H_2SO_4.11H_2O$, forms fine needles, m.p. 194·8°–195° (*dry*), soluble in water (1 in 37·6 at 12°). The hydrochloride, $B.HCl.2H_2O$, m.p. 216.5°, occurs in small needles, and the platinichloride, $B_2.2HCl.PtCl_4$, in orange-red needles sparingly soluble in water.

Hydrocinchonidine (*Cinchamidine*), $C_{19}H_{24}ON_2$. This alkaloid was isolated by Forst and Böhringer [4] from the bark of *Cinchona Ledgeriana*, but has since been observed accompanying homocinchonidine (p. 151) in many varieties of cinchona, and especially *C. rosulenta* and *C. lancifolia*. It is best prepared from commercial cinchonidine sulphate by fractional precipitation with sodium tartrate, the hydrocinchonidine tartrate occurring in the last fractions; these are treated with potassium permanganate solution, which rapidly destroys cinchonidine, but only slowly attacks the hydro-base; the latter can then be regenerated by addition of excess of ammonia. The precipitated alkaloid should be crystallised from its hot alcoholic solution by gradual addition of water.

Hydrocinchonidine crystallises in six-sided leaflets, m.p. 229°, $[\alpha]_D$ — 98·4° in alcohol, is insoluble in water and only slightly soluble in other solvents. The salts exhibit no fluorescence in solution nor do they show the thalleioquin reaction (p. 145). The base is diacidic, and forms salts similar to those of quinine and cinchonine: the neutral sulphate, $B_2.H_2SO_4.7H_2O$, needles, soluble in water (1 in 57 at 10°); the acid sulphate, $B.H_2SO_4.4H_2O$, leaflets, slightly soluble in water. The hydrochloride, $B.HCl.2H_2O$, short six-sided prisms, very soluble in water or alcohol.

[1] *Monats.* 1899, **20**, 425.
[2] *Cf.* Jungfleisch and Léger, *Compt. rend.* 1901, **132**, 410.
[3] Hesse, *Annalen*, 1893, **276**, 106.
[4] *Berichte*, 1881, **14**, 1270; Hesse, *ibid.* 1683, *Annalen*, 1882, **214**, 1.

The alkaloid gives an amorphous monoacetyl derivative. The acid sulphate when melted changes into the salt of an isomeric alkaloid which has not been investigated.

Hydroquinine, $C_{20}H_{26}O_2N_2.2H_2O$. This base was isolated by Hesse [1] from the bark of *Cinchona Ledgeriana*, and is a common constituent, sometimes to the extent of 3 or 4 per cent., of commercial sulphate of quinine. It is best prepared by recrystallising the latter from hot water, and treating the mother liquor with potassium permanganate, when the remaining quinine is destroyed, leaving the hydro-base unaltered. The latter may then be obtained by the addition of sodium hydroxide solution and extraction with ether. It crystallises from ether or chloroform in needles, m.p. 172·3° (*dry*), $[\alpha]_D$ — 142·2° in alcohol, is easily soluble in ether, alcohol, chloroform, acetone, or ammonia solution. Hydroquinine gives the thalleioquin reaction (p. 145), and solutions in dilute sulphuric acid are fluorescent. It is distinguished from quinine by its resistance to permanganate.

It is a diacidic base and furnishes two series of salts resembling those of quinine. The neutral sulphate, $B_2.H_2SO_4.6H_2O$, occurs in short prisms, insoluble in ether, sparingly soluble in chloroform, and moderately so in water (1 in 348 at 15°), $[\alpha]_D^{15}$ — 220° in hydrochloric acid (4 mols.). The acid sulphate, $B.H_2SO_4.3H_2O$, forms long needles, easily soluble in water or alcohol.

The alkaloid reacts with acetic anhydride to form an amorphous acetyl derivative ; with methyl iodide it gives a methiodide, which crystallises with one molecule of methyl alcohol. It readily forms crystalline molecular compounds with quinidine and cupreine, and by heating its acid sulphate at 140° it is transformed into the isomeric hydroquinicine (hydroquinotoxine) sulphate.

Hydroquinidine (*Hydroconquinine*), $C_{20}H_{26}O_2N_2.2\frac{1}{2}H_2O$. This base occurs in the quinidine of commerce, and was isolated from this source by Forst and Böhringer [2] by the method employed for the preparation of hydroquinine from commercial sulphate of quinine,

[1] *Annalen*, 1887, **241**, 257.
[2] *Berichte*, 1881, **14**, 1954 ; 1882, **15**, 520, 1656.

but can also be obtained by repeated crystallisation of commercial quinidine sulphate or hydrochloride from water or alcohol when the hydroquinidine salt remains in the mother liquors.[1] The purified alkaloid forms thick tablets from ether or long needles from alcohol, m.p. 166°–167°, is dextrorotatory, gives the thalleioquin reaction (p. 145), and its sulphate is fluorescent in water or dilute sulphuric acid. The sulphate, $B_2.H_2SO_4.12H_2O$, forms thick bottle-shaped crystals or fine needles with $2H_2O$, soluble in 92·3 parts of water at 16°; the hydrochloride, B.HCl, prismatic plates, easily soluble in water; the platinichloride, $B.2HCl.PtCl_4$, short orange-coloured needles.

The base is transformed by hydrochloric acid at 140° into the isomeric *hydroconquinicine* corresponding to quinicine (p. 147), and is oxidised by chromic anhydride to quininic acid.

Cupreine, $C_{19}H_{22}O_2N_2.2H_2O$. Cupreine is an alkaloid contained, together with quinine, &c., in the bark (cuprea bark) of *Remijia pedunculata*, a plant closely related to, though distinct from, the cinchonas.[2]

Preparation. The total alkaloids of cuprea bark are dissolved in dilute sulphuric acid, and the solution neutralised with caustic soda, when the sulphate of a combination of cupreine and quinine, called *homoquinine* (*see* p. 157), crystallises out. This is redissolved in dilute sulphuric acid, and excess of soda added, which dissolves the cupreine and some of the quinine. The liquid is shaken with ether, which dissolves out the quinine, leaving the cupreine in the alkaline solution. The latter is neutralised with dilute sulphuric acid, when cupreine sulphate crystallises out. From this the base may be obtained by dissolving the salt in dilute sulphuric acid, adding ammonia, crystallising the precipitate from hot ether, and finally from alcohol.

Cupreine crystallises in concentrically grouped prisms, becomes anhydrous at 120°, and then melts at 198°, $[\alpha]_D^{17} - 175{\cdot}5°$ in *dry*

[1] Hesse, *Berichte*, 1882, **15**, 855, 3010.

[2] Paul and Cownley, *Pharm. Journ.* 1881, **12**, 497; 1884 [iii], **15**, 221, 401. *Cf.* Howard and Hodgkin, *ibid.* 1881 [iii], **12**, 528, and Whiffen, *ibid.* 1881, **12**, 497. *Cf.* Hesse, *Annalen*, 1885, **230**, 57.

alcohol, — 163° 45′ in aqueous alcohol. It is sparingly soluble in ether or chloroform, readily in alcohol and in solutions of caustic alkalis, but not in ammonia. It gives the thalleioquin reaction (p. 145).

Cupreine is a diacidic base and yields two series of salts : the neutral sulphate, $B_2.H_2SO_4$, colourless anhydrous needles (Howard and Chick), soluble in 813 parts of water at 17° ; the acid sulphate, $B.H_2SO_4.H_2O$, crystallises in prisms and is soluble in 73·4 parts of water at 17°.

Cupreine reacts with methyl iodide in presence of sodium methoxide to form quinine methiodide, and is, therefore, to be regarded as quinine in which a methoxyl group is replaced by hydroxyl (*see* p. 169).

Homoquinine (*Cupreine - quinine*). When cupreine and quinine in chemically equivalent quantities are dissolved in dilute sulphuric acid, the mixture precipitated with ammonia, and the precipitate dried and crystallised from ether, a molecular combination of the two alkaloids is obtained which has been called homoquinine.[1] This has the formula, $C_{19}H_{22}O_2N_2.C_{20}H_{24}O_2N_2.4H_2O$, and crystallises from ether in needles, plates, or prisms, m.p. 177° (*dry*), $[\alpha]_D$ — 235·6° in hydrochloric acid, becomes anhydrous at 125°, is easily soluble in chloroform or alcohol, less so in ether, and gives fluorescent solutions in dilute sulphuric acid. It behaves as a diacidic base and forms crystalline salts. The neutral sulphate, $B.B'.H_2SO_4.6H_2O$, forms short hexagonal prisms sparingly soluble in water, easily in boiling alcohol, insoluble in chloroform or ether. Homoquinine is resolved into its components by solution in dilute acids and addition of caustic soda solution, which dissolves the cupreine and precipitates the greater part of the quinine.

Constitution of the Chief Cinchona Alkaloids

The four best-known cinchona alkaloids, viz. quinine, quinidine, cinchonine, and cinchonidine, form two pairs of isomerides,

[1] Howard and Hodgkin, *Trans. Chem. Soc.* 1882, **41**, 61.

of which each member of the first pair differs from each member of the second by the residue of one methoxyl group, —CH_2O.

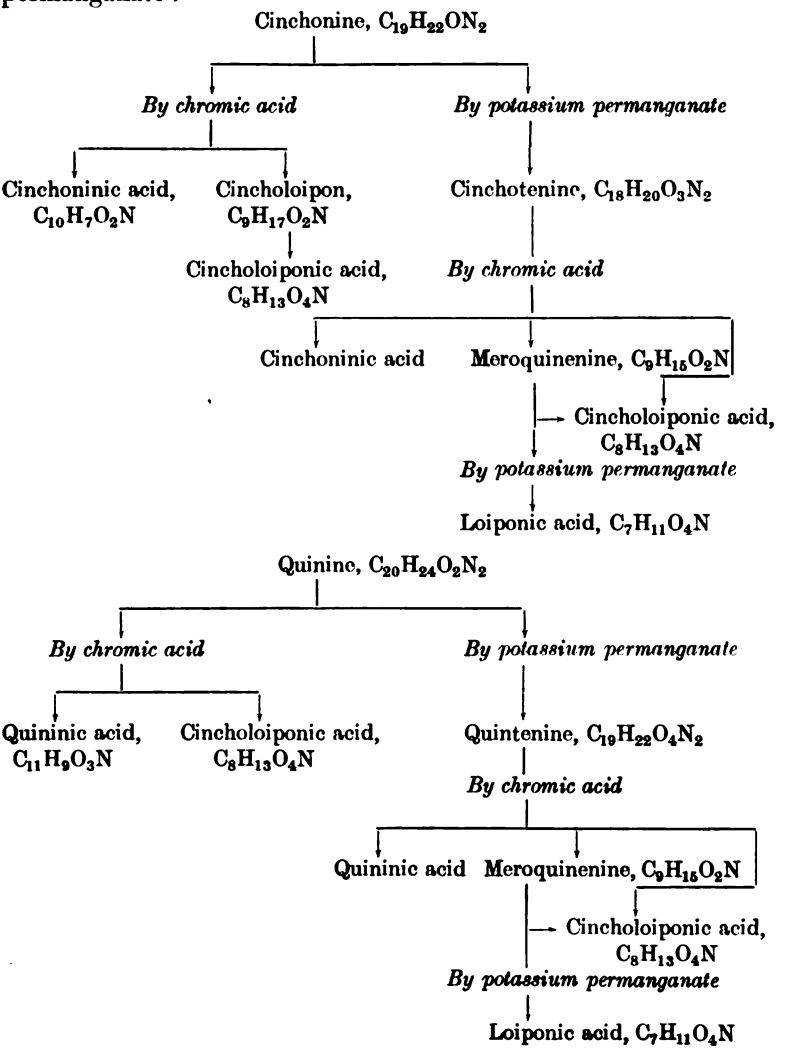
Further, the members of each pair yield for the most part the same derivatives and decomposition products under the action of various reagents, and on comparing the products yielded by the two pairs it is found that they form two parallel series differing constantly by the residue of a methoxyl group, —CH_2O. These facts, taken in conjunction with the observation that the members of each pair are of opposite optical activity, afford strong evidence for the view that the four alkaloids form two pairs of stereoisomerides, one pair, viz. quinine and quinidine, being monomethoxyl derivatives of the members of the second pair.

The relationship of cupreine to quinine is established by the fact that it differs from quinine by CH_2, contains a phenolic hydroxyl group, which is not present in quinine, and on methylation yields quinine, so that the latter is a methyl ether of cupreine. Hydrocinchonine (cinchotine) and hydrocinchonidine (cinchonamidine) have the composition of cinchonine dihydrides, and hydroquinine and hydroquinidine are similarly related to quinine, whilst quinamine and conquinamine have the composition of cupreine dihydrides. Among the other cinchona alkaloids, if regard is had merely to empirical composition, obvious relationships to the chief alkaloids of the series can also be traced, but there is at present little or no experimental evidence to justify the view that close relationship exists.

The two alkaloids which have been most completely investigated are quinine and cinchonine. The decomposition products of these two bases fall into two classes, viz. derivatives of quinoline, affording evidence of the existence in their molecules of a quinoline nucleus, and derivatives of a second heterocyclic ring system, commonly referred to as the "second half" of the molecule. The decomposition products of this "second half" are distinguished by the occurrence in their names of "loipon" (from *loipos*, a residue) or the prefix "mero" (from *meros*, a part). The two nuclear systems in each alkaloid furnish characteristic decomposition products—for example, cinchonine gives on oxidation cinchoninic

and cincholoiponic acids—and the position of any substituting group in an alkaloid of this series is ascertained by examining the oxidation products for the occurrence of substituted cinchoninic or cincholoiponic acids.

Oxidation of Cinchonine and Quinine. The following scheme exhibits the relationships of these two alkaloids to the products formed from them by oxidation with chromic acid and potassium permanganate:



CINCHOTENINE, $C_{18}H_{20}O_3N_2$, is produced when cinchonine or dehydrocinchonine is treated at ordinary temperatures with dilute permanganate.[1] It crystallises in needles or leaflets, m.p. 197°, $[\alpha]_D$ + 135·48°, and is soluble in water, dilute acids, or alkalis. The base contains two tertiary nitrogen atoms, yields a microcrystalline monoacetyl derivative, and forms salts with acids; the aurichloride, $(B.2HCl).AuCl_3$, occurs in yellow needles, and the platinichloride, $B.2HCl.PtCl_4$, in orange-coloured prisms. It is also a carboxylic acid and gives an ethyl ester crystallising in minute needles, m.p. 210·5°.

The isomeric substance, CINCHOTENIDINE,[2] similarly obtained from cinchonidine or homocinchonidine, crystallises in needles, m.p. 256°, $[\alpha]_D$ — 201·4°, and, like cinchotenine, gives by further oxidation cinchoninic and cincholoiponic acids.

QUINTENINE, $C_{19}H_{22}O_4N_2$, the corresponding quinine product,[3] forms rhombic prisms, m.p. 286°, $[\alpha]_D$ — 142·7°, slightly soluble in boiling water, insoluble in ether. It gives the thalleioquin reaction, is fluorescent in alcohol or dilute sulphuric acid, and forms salts with acids; the platinichloride, $B.2HCl.PtCl_4.3H_2O$, crystallises in yellow leaflets. With ethyl alcohol and hydrogen chloride the base gives an ethyl ester. Hydriodic acid converts quintenine into *quintenol*, $C_{18}H_{20}O_4N_2$, with the formation of methyl iodide.

The isomeride QUINTENIDINE, similarly produced by the oxidation of quinidine,[4] crystallises in prisms, m.p. 246°, and, like quintenine, gives quininic and cincholoiponic acids by further oxidation.

In the formation of these substances from the natural alkaloids a molecule of formic acid is in each case simultaneously produced, so that the oxidation probably takes place at an ethylenic linkage, the group .CH : CH_2 becoming —COOH and H.COOH.

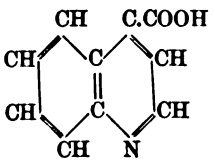
[1] Hesse, *Annalen*, 1875, **176**, 232; Skraup, *ibid.* 1879, **197**, 381.
[2] Skraup and Vortmann, *ibid.* p. 235; Hesse, *Berichte*, 1881, **14**, 1892.
[3] Kerner, *Zeit. Chem.* 1869, p. 593; Skraup, *Annalen*, 1879, **199**, 348.
[4] Forst and Böhringer, *Berichte*, 1882, **15**, 1659.

The ultimate products of the oxidation of the four alkaloids, therefore, are :

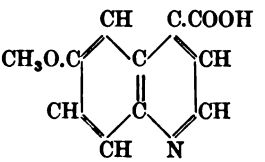
Cinchonine or *Cinchonidine* → Cinchoninic acid, $C_{10}H_7O_2N$, and loiponic acid, $C_7H_{11}O_4N$.

Quinine or *Quinidine* → Quininic acid, $C_{11}H_9O_3N$, and loiponic acid, $C_7H_{11}O_4N$.

Cinchoninic and quininic acids are related to each other as shown by the following formulæ :



Cinchoninic acid



Quininic acid

They are described in text-books of organic chemistry, and it is unnecessary to give descriptions here.

These results indicate that quinine (and quinidine) differ in structure from cinchonine (and cinchonidine) only in containing a methoxyl group in position 6 in place of a hydrogen atom in the quinoline nucleus. The identity of the second oxidation product—loiponic acid—in all four cases indicates that the " second half " of the molecule has the same structure in all four alkaloids. Further, this " second half " must be joined to the quinoline nucleus in the *para* position to the nitrogen atom.

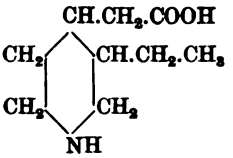
MEROQUINENINE, $C_9H_{15}O_2N$, formed by the oxidation both of quinine and cinchonine and by the hydrolysis of quinenine or cinchenine (p. 163), crystallises from methyl alcohol in needles, m.p. 223°–224° (*decomp.*), $[\alpha]_D$ + 27·5° in water. When oxidised by chromic acid it yields formic and cincholoiponic acids. It gives a nitrosoamine and a monoacetyl derivative and is, therefore, a secondary base, whilst it undergoes esterification with ethyl and methyl alcohols, forming the respective esters. On reduction with zinc dust and hydriodic acid it adds on two atoms of hydrogen, forming cincholoipon, $C_9H_{17}O_2N$, and on reduction with hydriodic acid and phosphorus gives 3-methyl-4-ethylpyridine.[1]

[1] Königs, *Berichte*, 1894, **27**, 904 ; *Annalen*, 1906, **347**, 143.

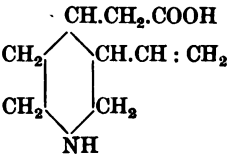
CINCHOLOIPONIC ACID, $C_8H_{13}O_4N$, results from the oxidation of cinchotenine, cinchotenidine, quintenine, quintenidine, meroquinenine, or cincholoipon (*see* p. 160), and, according to Skraup, is also formed directly by the oxidation of cinchonine, cinchonidine, or quinine. It crystallises from water in prisms with $1H_2O$, m.p. 126° or 221°–222° (*dry*), is insoluble in alcohol or ether, soluble in water, and dextrorotatory. It furnishes a nitrosoamine, a monoacetyl derivative, and a diethyl ester (long needles, m.p. 181°). When oxidised with permanganate it produces loiponic acid, $C_7H_{11}O_4N$. When heated with sulphuric acid it yields 3-methylpyridine and carbon dioxide. Racemic α- and β-cincholoiponic acids were prepared synthetically by Wohl and Losanitsch,[1] and were resolved into their components by Wohl and Maagl[2] by crystallisation of the brucine salts. Of these, β-*d*-cincholoiponic acid proved to be identical with the acid obtained from cinchonine.

LOIPONIC ACID, $C_7H_{11}O_4N$, obtained in small quantity by Skraup[3] by oxidising cincholoiponic acid with cold permanganate, forms irregular prisms, m.p. 259° (*decomp.*), from hot water. It behaves as a dibasic acid, furnishing a diethyl ester, and with acetic anhydride gives acetylloiponic anhydride, m.p. 161°. Königs[4] first pointed out the isomerism of loiponic acid with hexahydrocinchomeronic acid (piperidine-3 : 4-dicarboxylic acid) produced by reduction of methyl cinchomeronate. The latter acid was found to be a mixture of the *cis* and *trans* forms, and by treatment with potash was converted wholly into the more stable of these forms. Loiponic acid by treatment with potash is also changed into this stable form and so must be regarded as a labile modification of hexahydrocinchomeronic acid. From the facts recorded above it is clear that the four oxidation products of the "second half" of cinchonine and quinine must be represented by the following formulæ :[5]

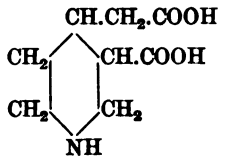
[1] *Berichte*, 1907, **40**, 4698.
[2] *Ibid.* 1909, **42**, 627.
[3] *Monats.* 1896, **17**, 377.
[4] *Berichte*, 1897, **30**, 1326.
[5] *Loc. cit.* and Königs, *Berichte*, 1902, **35**, 1357.



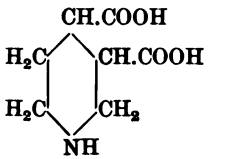
Cincholoipon



Meroquinenine



Cincholoiponic acid



Loiponic acid

Action of Phosphorus Pentachloride. The oxygen atom in cinchonine and cinchonidine and the second oxygen atom in quinine and quinidine are present as alcoholic hydroxyls, since all four alkaloids yield monoacyl derivatives with acid anhydrides or chlorides, and are not soluble in alkalis.

When acted upon by phosphorus pentachloride the alcoholic hydroxyl group is replaced by an atom of chlorine with the formation of substances which have been named cinchonine, cinchonidine, quinine, and quinidine chlorides respectively.[1]

Cinchonine chloride, $C_{19}H_{21}N_2Cl$, crystallises in needles, m.p. 72°.

Cinchonidine chloride forms crystals, m.p. 108°–109°.

Quinine chloride, $C_{20}H_{23}ON_2Cl$, minute needles, m.p. 151°, gives the thalleioquin reaction.

Quinidine chloride forms crystals, m.p. 131°-132°.

Action of Alcoholic Potash on the "Chlorides." When cinchonine or cinchonidine chloride is heated with alcoholic potash a molecule of hydrogen chloride is split off with the formation of CINCHENINE, $C_{19}H_{20}N_2$, leaflets, m.p. 123°–125°.

Similarly, quinine or quinidine chloride is converted into

[1] Comstock and Königs, *Berichte*, 1880, **13**, 286; 1884, **17**, 1986; 1885, **18**, 1229, 2379.

QUINENINE, $C_{20}H_{22}ON_2$, crystallising in trimetric prisms, m.p. 81°–82°, and giving the thalleioquin reaction.

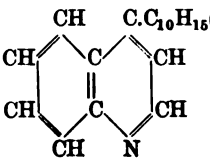
When heated with phosphoric acid at 175°, cinchenine and quinenine undergo hydrolysis according to the following equations:

$$\underset{\textit{Cinchenine}}{C_{19}H_{20}N_2} + 2H_2O = \underset{\textit{Meroquinenine}}{C_9H_{15}O_2N} + \underset{\textit{Lepidine (4-methylquinoline)}}{C_{10}H_9N}$$

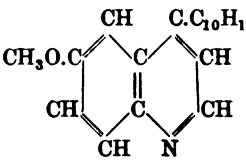
$$\underset{\textit{Quinenine}}{C_{20}H_{22}ON_2} + 2H_2O = \underset{\textit{Meroquinenine}}{C_9H_{15}O_2N} + \underset{\textit{6-Methoxylepidine}}{C_{10}H_8N(OCH_3)}$$

These hydrolyses afford further evidence of the existence in the four alkaloids of a quinoline nucleus and of a second ring system containing a nitrogen atom, whilst the production of 6-methoxylepidine from quinine and quinidine, and of lepidine from cinchonine and cinchonidine, supports the view that the two former are 6-methoxycinchonines.

The formulæ of the two alkaloids may therefore be extended thus:



Cinchonine



Quinine

the complex $C_{10}H_{15}(OH)N$, the "second half" already referred to, being the origin of meroquinenine in the hydrolyses of cinchenine and quinenine and of the loiponic acid produced by the oxidation of the parent alkaloids.

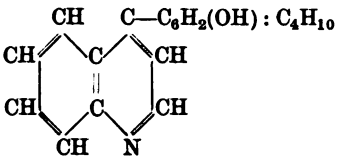
Structure of the "Second Half"

When cinchenine is heated with haloid acids at 180° it undergoes a remarkable decomposition, taking up 1 mol. H_2O and then losing 1 mol. of ammonia, producing a new base, APOCINCHENINE, $C_{19}H_{19}ON$, needles, m.p. 209°–210°.

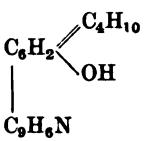
When quinenine is heated with hydrobromic acid at 190° it likewise decomposes with the production of methyl bromide, ammonia, and APOQUINENINE, $C_{19}H_{19}O_2N$. Since the latter gives

aminoapocinchenine when fused with ammonium and zinc chlorides it must be regarded as a hydroxyapocinchenine. This aminoapocinchenine, by diazotisation and treatment with alcohol and copper powder, gives apocinchenine, identical with that obtained from cinchenine.[1]

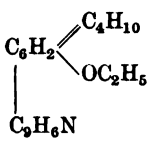
Apocinchenine still contains intact the quinoline nucleus of cinchonine, since it furnishes cinchoninic acid on oxidation with chromic acid, so that the changes involved in its formation from cinchonine and quinine must have taken place in the "second half." Comstock and Königs have also shown that it behaves like a phenol, giving ethers when treated with alkyl haloids in presence of alkali. It may, therefore, be assumed provisionally that apocinchenine contains, in addition to the quinoline complex, a benzene ring, attached to the former in the *para* position with respect to the nitrogen atom:



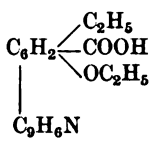
The nature of the group : C_4H_{10} was arrived at in the following manner: Apocinchenine ethyl ether, m.p. 70°, is oxidised by acid permanganate to *apocincheninic acid ethyl ether*, $C_{20}H_{19}O_3N$; the latter when heated with hydrobromic acid undergoes hydrolysis and at the same time loses carbon dioxide and forms *homoapocinchenine*, $C_{17}H_{15}ON$.[2]



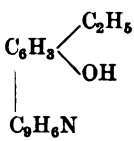
Apocinchenine



Apocinchenine ethyl ether



Apocincheninic acid ethyl ether



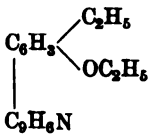
Homoapocinchenine

Homoapocinchenine by a similar series of reactions is converted into homoapocincheninic acid ethyl ether, which, when

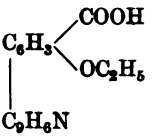
[1] Königs, *J. prakt. Chem.* 1900, ii. **61**, 41.

[2] Comstock and Königs, *Berichte*, 1885, **18**, 2384; 1887, **20**, 2683.

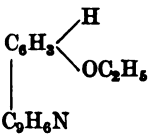
heated, in the form of its silver salt, loses carbon dioxide, giving quinolylphenetole, $C_9H_6N.C_6H_4.OC_2H_5$, and this by the action of hydrobromic acid undergoes hydrolysis, forming quinolylphenol :



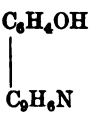
Homoapocinchenine ethyl ether



Homoapocincheninic acid ethyl ether



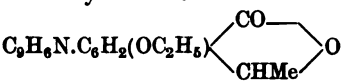
Quinolylphenetole



Quinolyl-phenol

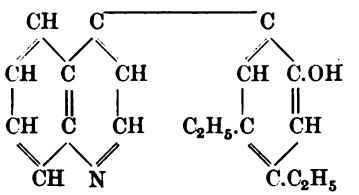
This quinolylphenol proved to be identical with *o*-hydroxy-4-phenylquinoline prepared synthetically, so that in apocinchenine the hydroxyl group must be in the *ortho* position relative to the point of attachment of the benzene ring to the quinoline nucleus.

The relative positions of the two ethyl groups are determined by the fact that apocincheninic acid ethyl ether on oxidation with manganese dioxide and sulphuric acid gives the lactone of hydroxy-apocincheninic acid ethyl ether:

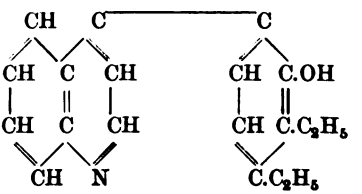


which on oxidation by sodium hypobromite yields quinolylphene-toledicarboxylic acid, $C_9H_6N.C_6H_2(OC_2H_5):(COOH)_2$. The latter must have its two carboxyl groups in the *ortho* position to each other, since it readily yields an anhydride and on fusion with resorcinol gives a fluorescein.[1]

Apocinchenine must therefore be represented by one of the three following formulæ, of which the second is the most probable since it best explains the reactions of the base, particularly the fact that it gives nitroapocinchenine when treated with nitrous acid :[2]



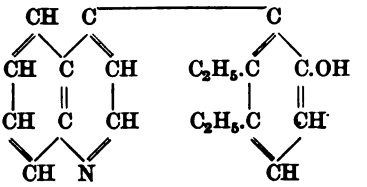
(I)



(II)

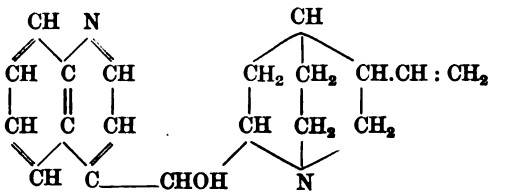
[1] Königs, *loc. cit.*

[2] Königs, *J. prakt. Chem.* 1900, **61**, 1.



(III)

The facility with which the "second half" of the molecule furnishes benzenoid derivatives recalls the similar behaviour of tropine and ecgonine, and several formulæ representing cinchonine and quinine and their isomerides as containing a quinoline ring attached to a dicyclic ring system similar to that of the tropine group have been proposed.[1] The formula now generally accepted for cinchonine is due mainly to Königs, and has received confirmation from the recent work of Rabe and his collaborators :



Cinchonine (Königs)

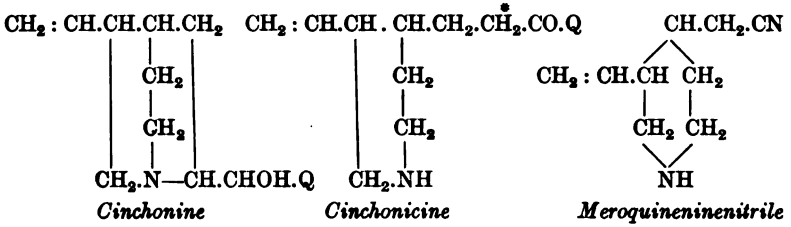
In particular this formula has now been shown to account satisfactorily for the following characteristic reactions of this group of alkaloids :

When cinchonine sulphate is heated dry, or with various reagents, or with water alone, it is converted into an isomeride, cinchonicine (cinchotoxine), already referred to (p. 153), which may also be obtained in like manner from cinchonidine. Quinine and quinidine under similar treatment give rise to quinicine (quinotoxine), which has been described already (p. 147). Cinchonicine and quinicine, unlike their generators, are keto-bases and contain one

[1] von Miller and Rohde, *Berichte*, 1894, **27**, 1280 ; 1900, **33**, 3214 ; Pictet and Wolffenstein, *Die Pflanzen Alkaloide*, p. 315 ; Königs, *Berichte*, 1899, **32**, 3599 ; 1907, **40**, 2873 ; *Annalen*, 1906, **347**, 143 ; Rohde and Antonaz, *Berichte*, 1907, **40**, 2329 ; and Rabe, *Annalen*, 1906, **350**, 180.

secondary nitrogen atom. In physiological action they differ from cinchonine and quinine in being poisonous.

When treated with amyl nitrite they form oximino compounds, which, with phosphorus pentachloride, furnish, in the case of oximinocinchonicine, cinchoninic acid and meroquineninenitrile, and in the case of oximinoquinicine, quininic acid and meroquineninenitrile.[1] Rabe has also shown that cinchonine methiodide and cinchonidine methiodide both yield the same methylcinchonicine (methylcinchotoxine) on treatment with alkali.[2] These various reactions are readily explicable from the following formulæ, in which Q represents the quinoline residue $—C_9H_6N$, and the * indicates the point at which oximino substitution takes place :[3]



Cinchonine *Cinchonicine* *Meroquineninenitrile*

The secondary alcohol corresponding to cinchonicine has not been prepared, but a number of ethers derived from it have been obtained by Comanducci.[4]

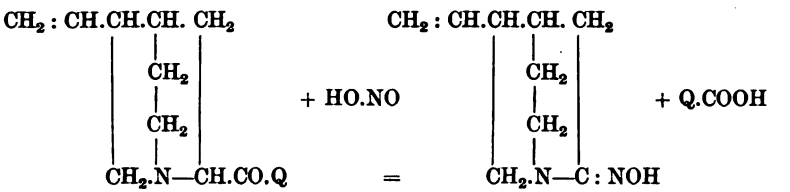
Rabe and his co-workers have also shown that when cinchonine, cinchonidine, quinine, quinidine, or hydrocinchonine (cinchotine) are oxidised they yield ketones differing by two atoms of hydrogen from the parent alkaloids. Thus :

Cinchonine and cinchonidine yield cinchoninone, $C_{19}H_{20}ON_2$.
Quinine and quinidine yield quininone, $C_{20}H_{22}O_2N_2$.
Hydrocinchonine yields hydrocinchoninone, $C_{19}H_{22}ON_2$.

These ketones react with nitrous acid, furnishing oximino deriva-

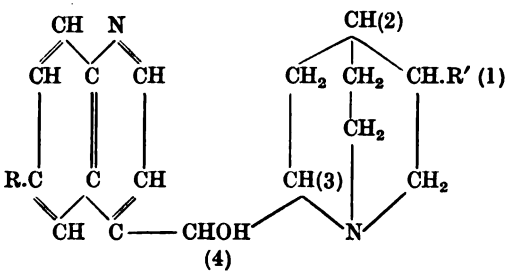
[1] Rabe and collaborators, *Annalen*, 1906, **350**, 180 ; 1911, **382**, 365.
[2] *Annalen*, 1909, **365**, 366.
[3] *Cf.* Rohde and Antonaz, *Berichte*, 1907, **40**, 2329 ; 1909, **42**, 2182.
[4] *Chem. Soc. Abstr.* 1909, i. 409 ; 1910, i. 582, 583.

tives which undergo characteristic decompositions; thus cinchoninone with nitrous acid gives cinchoninic acid and an oxime (β-vinyl-α′-quinuclidoneoxime), $C_9H_{13}N : NOH$, which on hydrolysis by acids yields meroquinenine and hydroxylamine. It must be assumed therefore that in the formation of these ketones a secondary carbinol group is converted into a —CO group, so that cinchoninone may be represented by the following formula : [1]



Cinchoninone = *β-Vinyl-α′-quinuclidoneoxime*

Cinchoninone is also formed by the action of alkali on *N*-bromocinchonicine, and since cinchoninone can be reduced to cinchonine it is possible in this way to reconvert cinchonicine into cinchonine.[2] On the basis of all these results Rabe [3] assigns the following general formula, developed from that of Königs (p. 167), to this group of alkaloids :



In cinchonine and cinchonidine R = H, R′ = .CH : CH_2.

In hydrocinchonine and hydrocinchonidine R = H, R′ = .CH_2.CH_3.

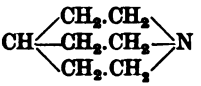
In cupreine R = .OH, R′ = .CH : CH_2.

In quinine and quinidine R = .OCH_3, R′ = .CH : CH_2.

[1] *Berichte*, 1907, **40**, 3655 ; 1908, **41**, 62 ; *Annalen*, 1909, **364**, 330.
[2] Rabe, *Berichte*, 1911, **44**, 2088.
[3] *Annalen*, 1909, **365**, 353 ; 1910, **373**, 85.

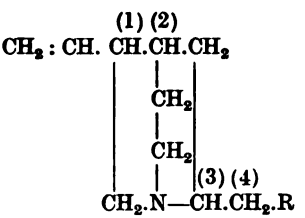
In hydroquinine and hydroquinidine $R = .OCH_3$, $R' = .CH_2.CH_3$.

To the reduced dicyclic nucleus characteristic of the cinchona alkaloids



Königs has applied the name quinuclidine, and the free base has been prepared by Löffler and Stietzel.[1]

The carbon atoms numbered (1), (2), (3), (4) in the general formula (p. 169) are asymmetric. Since cinchoninone and quininone both yield β-vinyl-α′-quinuclidineoxime of the same optical activity it follows that cinchonine, cinchonidine, quinine, and quinidine must be optically identical as regards carbon atoms (1) and (2). Further, the deoxy-bases obtained from cinchonine and cinchonidine are structurally identical, but differ in optical properties, and the same applies to the deoxy-bases from quinine and quinidine. These deoxy-bases have the following general formula :



where R is C_9H_6N for cinchonine and cinchonidine, and $C_9H_5(OMe)N$ for quinine and quinidine. It follows that optical activity in these bases, and therefore in the four alkaloids from which they are derived, depends on the arrangement of groups round carbon atom (3). In the formation of cinchonicine and quinicine the asymmetry of carbon atoms (3) and (4) disappears, and consequently in this reaction each pair of isomerides gives rise to a single substance, cinchonine and cinchonidine producing cinchonicine, and quinine and quinidine yielding quinicine. The keto-bases cinchoninone

[1] *Berichte*, 1909, **42**, 124.

and quininone are tautomeric, and consequently a single keto-base of this type is formed from each pair of isomerides.

Physiological Action of the Chief Cinchona Alkaloids

Of the various cinchona alkaloids only four have come into extensive use in medicine, viz. quinine, quinidine, cinchonine, and cinchonidine, and of these quinine far transcends the others in importance. Quinine is usually employed in the form of the neutral sulphate, but considerable quantities of the neutral hydrochloride are also used, though the acid sulphate and the acid hydrochloride have also been used to a considerable extent in recent years, the latter especially for subcutaneous injection. In addition, a number of the salts with organic acids have been employed for special purposes, *e.g.* the valerianate, formate, and tannate. The tannate is practically insoluble and therefore nearly tasteless.

Among the quinine substitutes may be mentioned "euquinine" (quinine ethyl carbonate), obtained by the action of ethyl chlorocarbonate on quinine. It forms colourless crystals sparingly soluble in water, more so in alcohol. "Aristoquinine" or quinine carbonate is a colourless, tasteless powder, m.p. 189°, which, however, has the disadvantage that it cannot be used with acids or alkalis.

Quinine is frequently called a protoplasm poison because of its action on undifferentiated protoplasm. In small amounts it stimulates movement in infusoria, but in large amounts paralyses these minute organisms immediately. Associated with this action of the alkaloid is the diminution in the number of leucocytes in the blood when quinine is administered. The alkaloid also retards the action of some unorganised ferments, especially that of the oxidases.

The first use of quinine in medicine was as a specific for malaria, and its use for this purpose has constantly increased. Its action in this disease depends on its property of poisoning minute organisms, the plasmodium which causes malaria in man being particularly

susceptible to it. The alkaloid is used not only as a remedy for malaria but as a prophylactic against this disease. Quinine causes a fall in the body temperature apparently by direct action on the tissues, and is therefore largely used as a febrifuge. It is also employed for the sake of its action on the alimentary canal, which it affects in the same way as other bitter medicines, causing especially increased secretion of gastric juice with improved appetite and digestion.

The extensive use of quinine in medicine has caused much attention to be directed to the fact that many persons are unusually susceptible to the action of the alkaloid. Quinine is apt to cause derangement of hearing and sometimes of sight. Large doses may also produce headache and depression, and in certain cases these effects are produced even by small doses. In persons suffering from old-standing malarial infection the administration of quinine may cause hæmoglobinuria. Cushny, however, states that "quinine is often credited with many disadvantages which it does not possess, and that in cases of malaria, in which it is practically without a rival or substitute, only the most pronounced idiosyncrasy can justify withholding it."

Of the other important cinchona alkaloids quinidine most closely resembles quinine in its action, but is somewhat weaker. Cinchonine and cinchonidine have the same general effects, but are stated to be much weaker and to have some tendency to produce epileptiform convulsions, whilst cinchonamine (p. 177) is stated to exhibit this peculiarity still more markedly. The isomeric substances quinicine or quinotoxine and cinchonicine or cinchotoxine, which, as already shown (pp. 147, 153), are produced by very simple operations from quinine and cinchonine or their isomerides, are highly toxic. According to Hildebrandt [1] the toxicity of these substances is associated with the presence of the piperidine group and the free imino group (p. 168).

[1] *Arch. exp. Path. Pharm.* 1908, **59**, 127.

MISCELLANEOUS CINCHONA ALKALOIDS

Quinamine, $C_{19}H_{24}O_2N_2$, an alkaloid found by Hesse in *Cinchona succirubra* and apparently existing in small quantity in many of the ordinary varieties of cinchona bark, but especially in *C. Ledgeriana*.[1] The mother liquors obtained after the isolation of cinchonidine from the total alkaloids (p. 150) are made alkaline with caustic soda solution, and the precipitate, after washing with water, is extracted with ether to dissolve the quinamine, which is purified by solution in dry ether, recrystallisation from dry alcohol, and conversion into the nitrate. The latter is finally recrystallised from water.

The alkaloid crystallises from dilute alcohol in long, silky anhydrous needles, m.p. 172°, $[\alpha]_D$ + 93·4° in chloroform, +104·5° in alcohol. It is slightly soluble in cold water (1 in 1516 at 16°), but more so in alcohol (1 in 105 of 80 per cent. at 20°), ether (1 in 32 at 20°), benzene, or light petroleum. The salts are crystalline and soluble in water. Strong aqueous hydrochloric acid in the cold converts the base into the isomeric quinamidine with some quinamicine (*see below*), while the hot acid furnishes apoquinamine, $C_{19}H_{22}ON_2$, by loss of $1H_2O$. Acetic anhydride converts quinamine into acetylapoquinamine, $C_{21}H_{24}O_2N_2$ (*see below*). The alkaloid is not attacked by oxidising agents.

Isomerides and Derivatives of Quinamine

Name and formula	Formation	Properties	Reference
Quinamidine, $C_{19}H_{24}O_2N_2$	Action of tartaric acid solution on quinamine at 130°	Crystals, m.p. 93°, $[\alpha]_D$ + 4·5° in alcohol	Hesse, *Annalen*, 1881, **207**, 299
Quinamicine, $C_{19}H_{24}O_2N_2$	By evaporating quinamine with sulphuric acid in alcohol	Crystals, m.p. 109°, $[\alpha]_D$ + 38·1°	Hesse, *ibid.* p. 305
Protoquinamicine $C_{19}H_{24}O_2N_2$	By heating quinamine sulphate at 120°	Amorphous	Hesse, *loc. cit.*
Apoquinamine, $C_{19}H_{22}ON_2$	By heating quinamine or quinamicine (*see above*) with hydrochloric acid	Crystallises in leaflets or prisms, m.p. 114°, lævorotatory	Hesse, *loc. cit.*

[1] Hesse, *Berichte*, 1877, **10**, 2157; *Annalen*, 1873, **166**, 266; 1881, **207**, 288.

Conquinamine, $C_{19}H_{24}O_2N_2$. This alkaloid is an isomeride of quinamine (p. 173), with which it occurs in several species of cinchona bark, especially *C. succirubra.*[1] It is obtained along with quinamine, and is separated from the latter by conversion into the less soluble oxalate.

Conquinamine forms triclinic crystals, m.p. 121° from alcohol, $[\alpha]_D$ + 204·6° in alcohol, is soluble in alcohol, chloroform, or ether, and slightly so in water. The salts are crystalline and soluble in water. In its reactions conquinamine closely resembles quinamine.

Paricine, $C_{16}H_{18}ON_2.\frac{1}{2}H_2O$, isolated by Hesse[2] from a *Cinchona succirubra* bark grown at Darjeeling, India. The bark was exhausted by alcohol, the crude mixture of bases dissolved in dilute sulphuric acid, and the liquid made slightly alkaline with soda, whereby paricine was precipitated. The crude alkaloid was heated with dilute sulphuric acid, forming the insoluble sulphate, from which the base was regenerated and purified by fractional precipitation of its ether solution with light petroleum. The base, m.p. 130°, and its salts are bitter, amorphous, and optically inactive.

Dicinchonine, $C_{38}H_{44}O_2N_4$, occurs, according to Hesse,[3] in the barks of *Cinchona rosulenta* and *C. succirubra.* The base and its salts are amorphous, and require further investigation.

Diconquinine, $C_{40}H_{46}O_4N_4$, according to Hesse,[4] is the chief constituent of the black extractive matter known as "quinoidine." It is amorphous and gives the thalleioquin reaction, but has not been thoroughly examined.

Javanine, an alkaloid of unknown composition obtained by Hesse[5] from the bark of *Cinchona Calisaya* var. *javanica.* It crystallises from water in rhombic plates, is very soluble in ether, and yields with dilute sulphuric acid an intense yellow colour.

[1] Hesse, *Annalen,* 1881, **209,** 62; Oudemans, *ibid.* p. 38.
[2] *Ibid.* 1873, **166,** 263.
[3] *Ibid.* 1885, **227,** 154.
[4] *Berichte,* 1877, **10,** 2155.
[5] *Ibid.* 1877, **10,** 2162.

ALKALOIDS OF CUSCO BARK

Aricine, $C_{23}H_{26}O_4N_2$ (*Quinovatine*), an alkaloid isolated in 1829 by Pelletier and Coriol[1] from Cusco bark, *Cinchona cordifolia* (*C. pubescens*), and subsequently found by Hesse in cuprea bark.[2] It is best prepared by adding aqueous sodium hydroxide to a concentrated alcoholic extract of the bark, shaking the precipitated bases with ether, and extracting the ethereal solution with acetic acid. On neutralising the solution with ammonia insoluble aricine acetate is precipitated and can be recrystallised in the same way from its solutions in dilute acetic acid. Aricine crystallises in fine prisms, m.p. 188° (*decomp.*), $[\alpha]_D$ — 58° 18′ in alcohol, $[\alpha]_D$ 0° in hydrochloric acid solution, soluble in ether (1 in 20 at 18°), more so in chloroform. The oxalate and acetate are both insoluble in water. Aricine dissolves in nitric acid, forming a green solution.

Cusconine, $C_{23}H_{26}O_4N_2.2H_2O$. This isomeride of aricine occurs with the latter in the bark of *Cinchona cordifolia*, from which it was isolated by Lever Kohn in 1829 and was subsequently examined by Hesse.[3] It occurs as the acetate in the mother liquors remaining from the preparation of aricine (*see above*) and is obtained as the acid sulphate, $B.H_2SO_4$, by the addition of ammonium sulphate.

The base forms dull leaflets, m.p. 110° (*dry*), $[\alpha]_D$ — 54·3° in alcohol, which are insoluble in water, soluble in ether (1 in 35 at 18°), more so in alcohol. The sulphate is characteristic and does not fluoresce in dilute sulphuric acid solution. Cusconine gives a green coloration with nitric acid.

Cusconidine. This remains in the mother liquors from the isolation of cusconine (*see above*) and is obtained as an amorphous substance yielding amorphous salts on adding ammonia.[3]

Cuscamine and **Cuscamidine** have been obtained by Hesse[4] from the bark of *Cinchona pubescens* by the addition of nitric acid

[1] *Journ. Pharm.* 1829 [ii], **15**, 565. *Cf.* Hesse, *Annalen*, 1873, **166**, 259; 1876, **181**, 58; 1877, **185**, 310; and Moissan and Landrin, *Bull. Soc. chim.* 1890 [iii], **4**, 258. [2] *Loc. cit.* [3] *Annalen*, 1877, **185**, 301.
[4] *Ibid.* 1880, **200**, 304.

to the mother liquors from which aricine acetate has crystallised out (p. 175). From the nitrate the alkaloids are regenerated, extracted with ether, and the ether-soluble alkaloids dissolved in boiling alcohol; on cooling, cuscamine separates in the form of flattened prisms, m.p. 218° (*decomp.*), while cuscamidine remains in solution.

ALKALOIDS OF *REMIJIA PURDIEANA*

The bark of *Remijia Purdieana*, a tree nearly related to that yielding cuprea bark (p. 156), yields cinchonine and cinchotine, already described, together with a series of other alkaloids.

These alkaloids are prepared by exhausting the finely powdered bark with hot alcohol and distilling off the solvent. The extract is made alkaline with aqueous sodium hydroxide and shaken with ether. To the ethereal extract dilute sulphuric acid is added, causing the separation of a mixture of alkaloidal sulphates comprising those of the following bases:[1] Concusconine, chairamine, conchairamine, chairamidine, conchairamidine. There remain in solution the sulphates of cinchonine and cinchonamine.

The mixed insoluble sulphates are treated with sodium hydroxide solution, the regenerated alkaloids dissolved in hot alcohol and 12·5 per cent. of their weight of sulphuric acid added; on cooling, the liquid deposits *concusconine sulphate*. The residual liquid is mixed with strong hydrochloric acid, which precipitates *chairamine hydrochloride*. To the filtrate potassium thiocyanate solution is added, which precipitates *conchairamine thiocyanate*. The alkaloids *chairamidine* and *conchairamidine* are obtained by making the mother liquor alkaline with ammonia and extracting with benzene. The recovered bases are converted into their sulphates, which are separated by fractional crystallisation from hot water.

Cinchonamine is prepared from the original mother liquor by adding ammonia solution, collecting the precipitate, dissolving in a little dilute acetic acid, and adding drop by drop dilute nitric acid.

[1] Hesse, *Annalen*, 1884, **225**, 211.

This precipitates *cinchonamine nitrate*, which can then be recrystallised from hot water.

Cinchonamine, $C_{19}H_{24}ON_2$, was first isolated by Arnaud.[1] From the nitrate obtained as already described the free base can be regenerated with ammonia and purified by recrystallisation from alcohol.

Cinchonamine crystallises in orthorhombic needles, m.p. 185°, $[\alpha]_D$ + 121·1° in alcohol, insoluble in cold water, soluble in alcohol (1 in 31·6 of 90 per cent. at 17°), easily in hot chloroform or benzene. No methoxyl is present. The crystals are triboluminescent.[2] The alkaloid forms a series of crystalline double chlorides with cadmium, zinc, or copper.[3] Cinchonamine does not give the thalleioquin reaction, nor are solutions of its sulphate fluorescent. It is diacidic and forms two series of salts ; the only important salt is the nitrate, $B.HNO_3$, crystallising in minute prisms, m.p. 196°, characteristically insoluble in water. Cinchonamine hydrochloride, B.HCl, laminæ, or $B.HCl.H_2O$, cubical crystals, has been suggested as a suitable salt for use in the estimation of nitrates.[4] The physiological action of cinchonamine is similar to that of quinine, but it is a more potent antipyretic and is also poisonous.

When warmed with strong nitric acid the alkaloid furnishes dinitrocinchonamine. It gives an amorphous monoacetyl derivative and combines with methyl iodide to form a methiodide crystallising in prisms, m.p. 208°, which with silver oxide gives methylcinchonamine, an amorphous powder, from which no well-defined derivatives have so far been obtained.

Concusconine, $C_{23}H_{26}O_4N_2$, is prepared as already described, the base being regenerated with caustic soda and recrystallised from hot alcohol. It forms monoclinic needles, $[\alpha]_D^{15}$ + 40·8° (Léger) in alcohol, $[\alpha]_D$ + 19° 34′ (Howard and Chick[5]), melts at 144° and remelts at

[1] *Compt. rend.* 1881, **93**, 593 ; 1883, **97**, 174 ; Hesse, *Annalen*, 1884, **225**, 218
[2] Tschugaeff, *Berichte*, 1901, **34**, 1824.
[3] Boutrioux and Genvresse, *Compt. rend.* 1897, **125**, 467.
[4] Howard and collaborators, *J. Soc. Chem. Ind.* 1905, **24**, 1281 ; 1909, **28**, 53.
[5] *Ibid.* 1909, **28**, 53.

206°–208°, is insoluble in water, very sparingly in cold alcohol, easily soluble in ether or chloroform. It dissolves in concentrated sulphuric acid with a bluish-green colour, becoming olive-green on warming. Concusconine contains two methoxyl groups.[1] The salts are amorphous.

The base reacts with methyl iodide, forming α- and β-methiodides, which in turn furnish α- and β-methylhydroxides, the former crystalline, the latter amorphous.

The chief characters of the remaining bases from this bark are stated in the following table :

Name and formula	Crystalline form	Optical rotation $[\alpha]_D$	Colour reactions
Chairamine, $C_{22}H_{26}O_4N_2.H_2O$	Needles or prisms, m.p. 233° (*dry*)	Dextrorotatory	A solution in acetic acid gives a dark green colour with nitric acid
Conchairamine, $C_{22}H_{26}O_4N_2.H_2O$	Prisms, m.p. 120° (*dry*)	+ 68·4° at 15° in alcohol	As above; also sulphuric acid gives a brown colour, becoming green
Chairamidine, $C_{22}H_{26}O_4N_2.H_2O$	Amorphous	+ 7·3° at 15° in alcohol	Sulphuric acid gives a green colour. Nitric acid colours a hydrochloric acid solution green
Conchairamidine, $C_{22}H_{26}O_4N_2.H_2O$	Crystalline, m.p. 114° (*dry*)	− 60° at 15° in alcohol	Sulphuric acid gives a deep green colour

ALKALOIDS OF *STRYCHNOS* SPECIES

These alkaloids include strychnine, brucine, and strychnicine. Strychnine, the most important of them, occurs in several species of *Strychnos*, usually together with brucine. So far only two materails have been found sufficiently rich in the alkaloid to be

[1] Howard and Chick, *loc. cit.*

used as sources of it, namely, nux-vomica seeds and Ignatius beans. The former are derived from *Strychnos Nux-vomica*, found in the East Indies, and the latter from *S. Ignatii* and possibly a second species, both found in the Philippine Islands. According to Dunstan and Short,[1] Indian nux-vomica seeds contain from 2·74 to 3·90 per cent. of total alkaloids, whilst Ceylon seeds contain 4·47 to 5·31, of which one-third is strychnine and the rest brucine. As a rule commercial nux-vomica seeds contain from 2·5 to 3·0 per cent. of total alkaloids, of which rather less than half is strychnine. *Strychnos Ignatii* seeds contain 2·5 to 3·0 per cent. of total alkaloids, of which two-thirds is stated to be strychnine and the rest brucine. Strychnine and brucine also occur in other parts of *Strychnos Nux-vomica*, especially in the leaves, bark, wood, fruit pulp, and root. According to van Boorsma the leaves of this plant contain a third alkaloid, strychnicine, which is not present in the seeds. The seeds of *S. Tieuté*, found in Java, contain 1·47 per cent. of strychnine, with traces of brucine. The dry wood and dry bark of *S. ligustrina* contain respectively 2·26 and 7·38 per cent. of brucine, but are free from strychnine.[2] The seeds of *S. Rheedei*, an Indian species, contain brucine only, and this is also the case with *S. aculeata* of West Africa. Among species free from poisonous alkaloids are *S. potatorum*, the seeds of which are highly mucilaginous and are used for clearing drinking water in India.

The *Strychnos* species referred to in the foregoing paragraphs are inhabitants of the East Indies. The South American species, such as *S. toxifera* and *S. Castelnaei*, yield the highly toxic product "Curare" or "Woorari" (*see* p. 196).

Estimation of Total Alkaloids

For the estimation of total alkaloids in nux-vomica, Ignatius beans, &c., the following process has been devised by Dunstan and Short:[3] Five grammes of the finely ground seeds of *S. Nux-*

[1] *Pharm. Journ.* 1882–83 [iii], **13**, 665, 1053; 1884–85 [iii.], **15**, 1.
[2] Greenish, *ibid.* 1879 [iii], **9**, 1013. [3] *Loc. cit.*

vomica or *S. Ignatii* previously dried at 100° are exhausted by repercolation in an extraction apparatus with chloroform containing 25 per cent. by volume of alcohol. The solution is shaken out twice, using each time about half its volume of 5 per cent. sulphuric acid. The combined solutions of the acid sulphates of strychnine and brucine are made alkaline with ammonia, and the alkaloids extracted with chloroform. The residue left by the evaporation of the chloroform is dried at 100° and weighed.

The German Pharmacopœia (1910) gives a process for the estimation of the total alkaloids, based on the same principle as that used in the first part of the United States process (*see below*), but using different reagents. The alkaloidal residue is titrated finally, using iodeosin as indicator.

Estimation of Strychnine. The foregoing processes yield alkaloidal residues consisting of strychnine and brucine, and as the former is the valuable medicinal constituent it is desirable that it should be estimated. The chief processes available for this purpose depend on the isolation of a clean mixture of the two alkaloids, and precipitation of the strychnine as ferrocyanide [1] or removal of the brucine by oxidation with nitric acid.[2] The following are examples of these processes:

For the seeds the United States Pharmacopœia (8th Rev.) gives the following process: Twenty grammes of nux-vomica in No. 60 powder are mixed with 200 c.c. of a mixture of ether 137·5 c.c., chloroform 44 c.c., alcohol 13·5 c.c., and ammonia water (sp. gr. 0·958 at 25°) 5 c.c., shaken frequently during one hour and then allowed to stand twelve hours. One hundred cubic centimetres of the liquid (= 10 grm. of seed) are placed in a separator and shaken out four times, using 15, 5, 3, and 5 c.c. of *N*-sulphuric acid respectively (the fourth extraction may be omitted if a drop of the third acid extract gives no precipitate with Mayer's reagent). The combined acid liquids are made alkaline with ammonia water and shaken out three times with chloroform, using 25, 15, and 15 c.c. The

[1] Dunstan and Short, *Pharm. Journ.* 1883 [iii], **14**, 292.
[2] Keller, *Zeit. Oesterr. Apoth. Ver.* 1903, p. 587.

residue left on distilling off the chloroform is dissolved in 15 c.c. of 3 per cent. sulphuric acid, by warming at 100° if necessary. When cold, 3 c.c. of a cold mixture of equal volumes of nitric acid (sp. gr. 1·42) and water are added, the whole mixed and set aside for ten minutes, shaking three times in this interval. The liquid is then transferred to a separator containing 25 c.c. (or 27 c.c. if necessary to produce turbidity) of soda solution (1 in 10), using a little water to wash out the beaker. The alkaline solution is now shaken out successively with 20, 10, and 10 c.c. of chloroform, and the latter filtered into a flask, using 5 c.c. of chloroform to wash the filter. The solvent is evaporated, the residue dissolved in 6 c.c. of $N/10$ sulphuric acid, 80 c.c. of distilled water, and 20 c.c. of ether. The excess of acid is titrated with x c.c. of $N/50$ potassium hydroxide solution, using iodeosin as an indicator. The percentage of strychnine is given by the formula $(6 - x/5)\,0{\cdot}332$. The seeds should contain not less than 1·25 per cent. of strychnine.

For the *extract*, *fluid extract*, and *tincture* of nux-vomica the same Pharmacopœia proceeds as follows:

Two grammes of extract are dissolved in 25 c.c. of a mixture of ether 16 c.c., chloroform 5 c.c., and ammonia water 4 c.c., transferred to a separator, using a little chloroform for washing, and well shaken for a few minutes. The chloroform layer is run off and the extraction repeated twice, using 15 and 10 c.c. of chloroform, or until the liquid no longer gives a precipitate with Mayer's reagent. The combined chloroform solution is shaken out three times with 3 per cent. sulphuric acid,* using 15, 10, and 10 c.c. The combined acid solutions are made alkaline, and shaken out three times with chloroform, using 15, 10, and 10 c.c.† The chloroform is evaporated and the strychnine in the residue estimated as described under the United States Pharmacopœia method for seeds (*see above*), except that for the final titration the residue is dissolved in 10 c.c. $N/10$ sulphuric acid, 90 c.c. of distilled water,§ and 20 c.c. of ether. The percentage of strychnine is given by the formula $(10 - x/5)\,0{\cdot}332 \times 5$, and should be equal to 5.

For the fluid extract 10 c.c. are evaporated to dryness at 100°

and dissolved in a mixture of ether 16 c.c., chloroform 5 c.c., ammonia water 4 c.c., and the rest of the process carried out as described above for the extract except that *N*-sulphuric acid is used for extracting the alkaloids from the chloroform solution (*see* * in preceding paragraph), 25, 10, and 10 c.c. of chloroform are used for extracting the alkaloids from solution in dilute sulphuric acid after this has been made alkaline (*see* † in preceding paragraph), and 80 c.c. of distilled water are added after finally dissolving in *N*/10 sulphuric acid instead of 90 c.c. (*see* § in preceding paragraph). The fluid extract should contain 1 per cent. of strychnine.

The assay of the tincture is carried out by the same process as that described for the extract, 100 c.c. of the tincture being evaporated to dryness at 100° and the residue treated as described on p. 181, under extract of nux-vomica. The percentage of strychnine in this case is given by the formula $(6 - x/5)0{\cdot}0332$.

For tincture and liquid extract of nux-vomica the British Pharmacopœia (1898) prescribes the following process: Ten cubic centimetres of the liquid extract, or 100 c.c. of the tincture, are evaporated at 100° to a syrup, the residue dissolved in 20 c.c. of water and placed in a separator with 5 grm. of sodium carbonate dissolved in 25 c.c. of water. This mixture is shaken out three times in succession, using 10 c.c. of chloroform each time. The combined chloroform solutions are then shaken out three times, using each time one-third of a mixture of 6 c.c. of dilute sulphuric acid (sp. gr. 1·094) with 25 c.c. of water. The combined acid liquids are diluted with water to 175 c.c., and 25 c.c. of potassium ferrocyanide solution (10 grm. in 200 c.c.) added, the mixture frequently shaken during thirty minutes and then set aside six hours. The precipitate is filtered off, using water containing 0·025 of its volume of dilute sulphuric acid for rinsing, and washed until the washings are no longer bitter. The precipitate is rinsed into a separator, 5 c.c. of ammonia solution (sp. gr. 0·959) and 15 c.c. of chloroform added in two portions, the mixture being well shaken after each addition. The chloroform solutions are drawn off in turn into a tared dish,

the solvent allowed to evaporate, and the residue dried and weighed. The liquid extract should yield 1·5 grm. of strychnine per 100 c.c., and the tincture 0·24 to 0·25 grm. of strychnine per 100 c.c., as determined by this method.

For observations on the accuracy and applicability of the ferrocyanide method of separation, *see* Beckurts and Holst,[1] Schweissinger,[2] Stoeder,[3] Farr and Wright.[4]

Keller's nitric acid method has been examined and modifications of it suggested by Stoeder,[5] Gordin,[6] Howard,[7] Smith,[8] Reynolds and Sutcliffe,[9] and Webster and Pursel.[10] Gerock[11] has suggested a quantitative method of separation based on the difference in the behaviour of strychnine and brucine picrates towards nitric acid.

Strychnine, $C_{21}H_{22}O_2N_2$. This alkaloid was discovered by Pelletier and Caventou in 1817. It was investigated by Regnault,[12] who assigned to it the formula given above. Its composition, however, remained in doubt until 1849, when Nicholson and Abel[13] established the formula used by Regnault.

For the extraction of strychnine and brucine from the seeds of *Strychnos Nux-vomica* or *Strychnos Ignatii*, the finely ground seeds are mixed with 25 per cent. of their weight of slaked lime and made into a stiff paste with water. This is then dried at 100°, powdered, and exhausted with chloroform by hot repercolation. From this the alkaloids are removed by repeated agitation with dilute sulphuric acid. From the latter they are regenerated by ammonia and the precipitate extracted with 25 per cent. alcohol, which dissolves the brucine and leaves most of the strychnine undissolved. The latter is purified by recrystallisation from alcohol, in which brucine is more soluble (*see also under* Brucine).

[1] *Arch. Pharm.* 1887 [iii], **25**, 313.
[2] *Pharm. Journ.* 1885 [iii], **16**, 447.
[3] *Ned. Tydschr. Pharm.* 1889, **11**, 1.
[4] *Pharm. Journ.* 1900 [iv], **11**, 82.
[5] *Loc. cit.*
[6] *Arch. Pharm.* 1902, **240**, 641.
[7] *Analyst*, 1905, **30**, 261.
[8] *Amer. J. Pharm.* 1903, **75**, 253.
[9] *Journ. Soc. Chem. Ind.* 1906, **25**, 512.
[10] *Amer. J. Pharm.* 1907, **79**, 1.
[11] *Arch. Pharm.* 1889 [iii], **27**, 158.
[12] *Annalen*, 1838, **26**, 17.
[13] *Journ. Chem. Soc.* 1850, **2**, 241.

Strychnine crystallises in colourless rhombs, m.p. 268°, $[\alpha]_D$ — 132·07° in alcohol. According to Loebisch and Schoop it distils unchanged at 270° under 5 mm. pressure.[1] The base is slightly soluble in water (1 in 6400 at 25°, 1 in 3000 at 80°) or ether (1 in 5500 at 25°), more so in alcohol (1 in 110 at 25° or 1 in 28 at 60°) or benzene (1 in 150 at 25°), readily so in chloroform (1 in 6 at 25°). The aqueous solution is alkaline and has a persistent bitter taste, even in a solution containing 1 part in 700,000 of water. The salts crystallise well. Three of them are used in medicine, viz. the nitrate, sulphate, and hydrochloride. Strychnine nitrate forms colourless shining needles, soluble in water (1 in 42 at 25°), alcohol (1 in 120 at 25°), or chloroform (1 in 156 at 25°); lævorotatory. The sulphate, $B_2.H_2SO_4.5H_2O$, forms colourless prismatic crystals, m.p. 200° (*dry*), and is soluble in water (1 in 31 at 25°) or alcohol (1 in 65 at 25°), less so in chloroform (1 in 325 at 25°). The hydrochloride, $B.HCl.1\frac{1}{2}H_2O$, forms colourless, efflorescent, trimetric prisms, soluble in cold water (1 in 35) or alcohol (1 in 60). The aurichloride, $B.HAuCl_4$, crystallises from alcohol in orange-yellow needles. The hydriodide, $B.HI.H_2O$, is sparingly soluble in water, as is also the periodide, $B.HI.I_2$; the latter crystallises from alcohol in reddish-brown prisms. The dichromate is very slightly soluble in water (1 in 1815 at 18°).

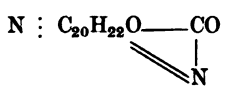
Strychnine is not coloured by sulphuric acid, even on warming. With nitric acid it gives a yellowish coloration, and the residue left on evaporating the liquid at 100° gives a reddish-purple colour with ammonia. A fragment of the alkaloid in a drop of sulphuric acid gives, with a crystal of potassium dichromate, manganese dioxide, ceric oxide, or potassium permanganate stirred in it, a series of colours, beiginning with blue, which gradually passes through violet and red to yellow.[2] The only other alkaloids which closely resemble strychnine in this respect are curarine and gelsemine. Certain other alkaloids give a somewhat similar colour reaction, but most of these are also coloured by sulphuric acid alone. Brucine gives a deep red colour when oxidised, and this is apt to obscure the

[1] *Monatshefte*, 1885, **6**, 858. [2] Marchand, *Journ. Pharm.* [iii], **4**, 200.

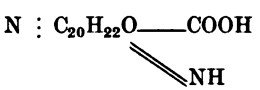
colour change produced by strychnine, so that if brucine is present it should first be eliminated by treatment with potassium ferrocyanide or nitric acid as described on p. 181. Organic matter also masks the reaction and may be got rid of by warming with sulphuric acid and recovering the strychnine by adding water and ammonia and shaking out with chloroform. Sulphuric acid containing vanadic acid gives with strychnine a deep bluish-violet colour, changing to purple and finally to red.

Constitution of Strychnine

Strychnine, although containing two atoms of nitrogen, behaves as a monoacidic base. When warmed with a solution of sodium ethoxide a molecule of water is taken up with the formation of strychnine monohydrate, $C_{21}H_{24}O_3N_2$, which was named strychnol by Loebisch and Schoop,[1] who first prepared it, and more recently strychninic acid by Tafel,[2] who has investigated its behaviour with various reagents. It crystallises in minute needles, m.p. 215°, is soluble in water, insoluble in ether or dry alcohol, but readily soluble in aqueous solutions of ammonium salts. The substance forms salts with mineral acids, but when warmed with excess of the latter strychnine is re-formed. It reacts with sodium nitrite and hydrochloric acid to form a nitrosoamine of the formula $C_{21}H_{23}(NO)O_3N_2$. It dissolves in alkaline solutions to form unstable salts, undergoes indirect esterification, and with methyl iodide yields methylstrychninic acid methiodide.[3] These reactions are best accounted for by regarding strychninic acid as an iminocarboxylic acid produced by the hydration of a betaine group in strychnine :



Strychnine



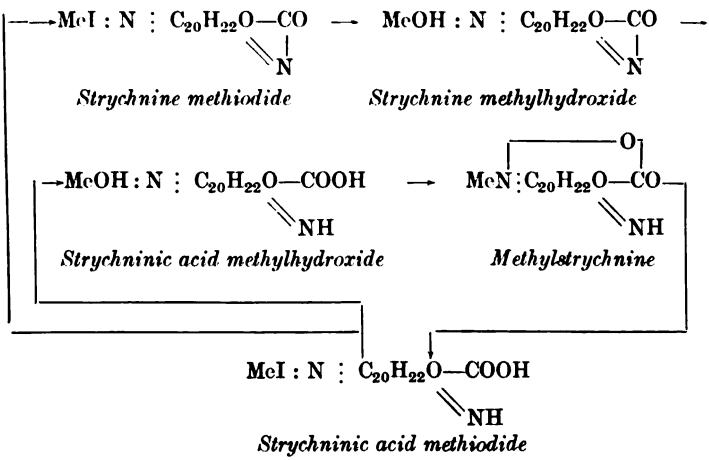
Strychninic acid

The nitrogen atom included in the betaine group is non-basic and accounts for the monoacidic character of strychnine. When strych-

[1] *Monatshefte*, 1886, **7**, 83. [2] *Annalen*, 1891, **264**, 50.
[3] Tafel, *loc. cit.*

nine is warmed with a saturated aqueous solution of barium hydroxide at 140° it is converted into *iso*strychninic acid,[1] which has been isolated as the hydriodide (microscopic needles). It is readily distinguished from its isomeride by not giving strychnine, when warmed with dilute acids. It furnishes a nitrosoamine which is readily converted into a nitroso compound by the action of an alcoholic solution of hydrogen chloride.[2] According to Bacovescu and Pictet[3] *iso*strychnine (needles, m.p. 214°–215°) is formed when strychnine is heated in water at 160°–180°, and this with sodium ethoxide in alcohol yields *iso*strychninic acid.

Strychnine readily combines with methyl iodide, forming a methiodide, which is converted by silver oxide or baryta into the corresponding strychninic acid methylhydroxide. The latter by the loss of a molecule of water gives methylstrychnine.[4] This base is also formed when strychninic acid methiodide is treated with silver oxide.[5] Further, when methylstrychnine reacts with aqueous hydriodic acid it forms strychninic acid methiodide, and the latter on warming furnishes strychninemethiodide. This series of changes may be represented in the following way :



Methylstrychnine crystallises in long prisms, is soluble in water,

[1] Tafel, *Annalen*, 1891, **264**, 69. [2] *Loc. cit.* [3] *Berichte*, 1905, **38**, 2787.
[4] Tafel, *ibid.* 1890, **23**, 2732. [5] Tafel, *Annalen*, 1891, **264**, 62.

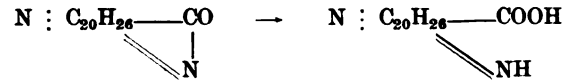
gives the characteristic colour reactions of strychnine but is not bitter, and although still poisonous exerts a physiological action distinct from that of strychnine. It behaves as a secondary amine, and with methyl iodide gives a methiodide which on heating with silver sulphate and barium hydroxide yields dimethylstrychnine.[1] This base is also produced from strychninic acid by conversion of the latter into the corresponding methiodide, which in presence of caustic soda and methyl iodide furnishes *N*-methylstrychninic acid methiodide : the latter readily loses a molecule of hydrogen iodide when warmed with silver oxide, forming the corresponding betaine, dimethylstrychnine.[2]

Dimethylstrychnine with nitrous acid yields nitrosodimethylstrychnine. This compound exhibits the same peculiarities as nitrosodimethylaniline,[3] giving colouring matters by condensation with benzaldehyde, &c. Such behaviour is also characteristic of *N*-methyltetrahydroquinoline, and it has been suggested by Tafel that this base is the nucleus of the strychnine molecule.

In a manner strictly analogous with that by which methylstrychnine and dimethylstrychnine are obtained from strychninic acid, *iso*strychninic acid furnishes methyl*iso*strychnine (needles from water) and dimethyl*iso*strychnine (microscopic needles from water). Similarly this acid reacts with methyl iodide to form a *N*-methyl*iso*strychninic acid.

When strychnine is reduced with hydriodic acid and phosphorus, a crystalline product, desoxystrychnine, $C_{21}H_{26}ON_2$, is formed. This substance gives the characteristic colour reactions of strychnine and contains unchanged the betaine group of the latter, since it reacts with sodium ethoxide, forming desoxystrychninic acid. It also forms a methiodide, so that in the formation of desoxystrychnine no change has occurred in connection with the second nitrogen atom of strychnine. Desoxystrychnine must, therefore, be represented by the formula :

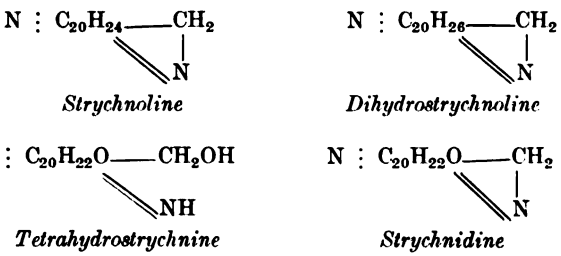
[1] Tafel, *Berichte*, 1890, **23**, 2731.
[2] Tafel, *Annalen*, 1891, **264**, 66. [3] Tafel, *loc. cit.*



Desoxystrychnine *Desoxystrychninic acid*

When solutions of desoxystrychnine sulphate are reduced electrolytically a dihydrostrychnoline, $C_{21}H_{28}N_2$, is formed, whilst the less reduced substance, strychnoline, $C_{21}H_{26}N_2$, is obtained when desoxystrychnine dissolved in boiling amyl alcohol is treated with sodium. These reduction products show a gradual weakening of the specific physiological action of the parent alkaloid, dihydrostrychnoline being non-poisonous. A similar behaviour is exhibited by α-piperidone and its reduction product, piperidine; the former exerts a strong tetanising action, whilst the latter is physiologically inactive.[1]

Strychnine, when reduced electrolytically[2] or by hydrogen in presence of palladium chloride,[3] furnishes a tetrahydro-derivative, $C_{21}H_{26}O_2N_2$, together with strychnidine, $C_{21}H_{24}ON_2$, the latter being also formed by loss of $1H_2O$ when tetrahydrostrychnine is warmed with mineral acids. Strychnidine closely resembles dihydrostrychnoline in properties, but still possesses the characteristic physiological action of strychnine. These reduction products may be represented thus:



Strychnoline *Dihydrostrychnoline*

Tetrahydrostrychnine *Strychnidine*

When strychnine is oxidised with chromic acid it furnishes an acid, $C_{15}H_{17}O_2N_2.COOH$;[4] the latter on distillation with zinc dust

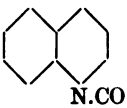
[1] Schotten, *Berichte*, 1888, **21**, 2244; and Tafel, *Annalen*, 1892, **68**, 234; 1898, **301**, 285. [2] Tafel and Naumann, *Berichte*, 1901, **34**, 3291.

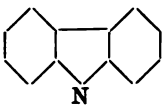
[3] Skita and Franck, *ibid.* 1911, **44**, 2862.

[4] Hanssen, *ibid.* 1884, **17**, 2849; 1885, **18**, 777, 1917; 1887, **20**, 451.

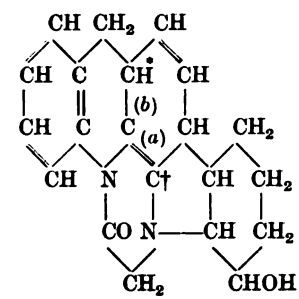
yields carbazole (diphenylimide), which Loebisch and Malfatti also obtained by distilling strychnine with soda-lime.[1] Perkin and Robinson[2] first called attention to the important bearing which this formation of carbazole and carbazole derivatives has on the constitution of strychnine.

The work summarised thus far shows that strychnine must contain both quinoline and carbazole nuclei:

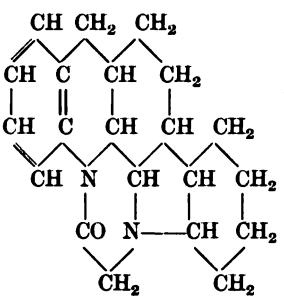




Since strychnine can be sulphonated[3] and nitrated[4] the quinoline nucleus probably contains a benzene ring, and to account for the reduced character of strychnine it must be assumed that the pyridine ring of the quinoline nucleus, and probably also the carbazole nucleus, are almost completely reduced. Further, as the N atom in the quinoline nucleus is in a betaine group, it follows that the N atom in the carbazole nucleus must be that which is basic and tertiary. Of the possible ways of combining these two nuclei to give the molecule, $C_{21}H_{22}O_2N_2$, Perkin and Robinson[5] regard the following as the most probable:



Strychnine (Perkin and Robinson)

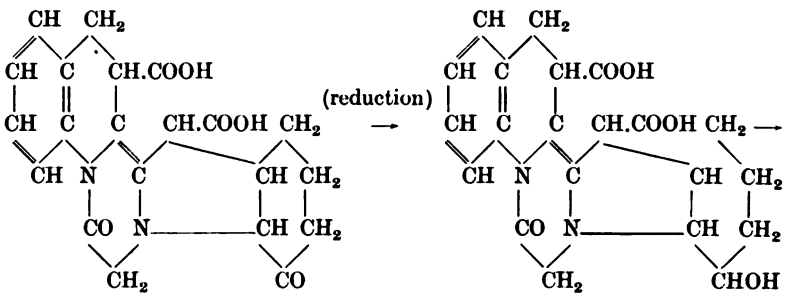


Desoxystrychnine

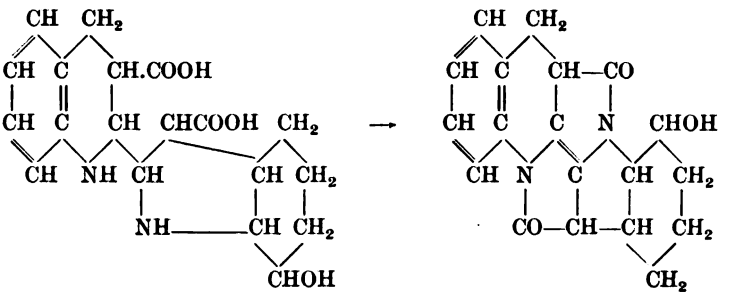
This formula affords an explanation of the results obtained by

[1] *Monatshefte*, 1888, **9**, 629. [2] *Trans. Chem. Soc.* 1910, **97**, 309.
[3] Stöhr, *Berichte*, 1885, **18**, 3430; Leuchs and Schneider, *ibid.* 1908, **41**, 4393; 1909, **42**, 2681. [4] Tafel, *Annalen*, 1898, **301**, 299. [5] *Loc. cit.*

Leuchs and collaborators,[1] who found that when strychnine dissolved in acetone is oxidised with permanganate it yields strychninonic acid, $N : C_{17}H_{18}(:N.CO)(CO)(COOH)_2$, which on reduction with sodium amalgam gives the corresponding hydroxydicarboxylic acid, strychninolic acid, $N : C_{17}H_{18}(:N.CO)(CHOH)(COOH)_2$, and this on treatment with dilute potash yields glycollic acid and strychninolone, $C_{19}H_{18}O_3N_2$, which is neutral. The formation of these substances is explained by Perkin and Robinson's formula thus :



Strychninonic acid *Strychninolic acid*



Intermediate product *Strychninolone*

Perkin and Robinson regard *iso*strychnine and *iso*strychninic acid as structural isomerides of strychnine and strychninic acid respectively, the isomerism being due to change of the double bond marked *a* to the position marked *b* in the formula for strychnine (p. 189), and migration of an H atom from the position marked * to that marked †.

[1] *Berichte*, 1908, **41**, 1711 ; 1909, **42**, 2494 ; 1910, **43**, 2417 ; 1912, **45**, 201.

Brucine, $C_{23}H_{26}O_4N_2$. Brucine occurs with strychnine in *S. Nux-vomica* and in other species of *Strychnos*. It was first obtained in 1819 by Pelletier and Caventou from the bark of the former plant, which was at that time supposed to be derived from *Brucea ferruginea*. Its composition was determined by Regnault, and his formula has been confirmed by subsequent investigators.

Preparation. The total alkaloids having been extracted from the seeds as already described (p. 183), the mixture is repeatedly washed with 25 per cent. alcohol, in which brucine is much more soluble than strychnine. The alkaloid thus dissolved is recrystallised from the same solvent until pure. Flückiger has stated that if the mixture of the two alkaloids is converted into the acetates and the solution evaporated to dryness, the strychnine salt dissociates into the alkaloid and acetic acid, whilst brucine acetate remains unchanged and may be dissolved from the residue by cold water.

A method of separation depending on the greater solubility in water of strychnine hydriodide was successfully employed by Shenstone,[1] whilst others have made use of the sparing solubility of strychnine chromate for the removal of small quantities of this alkaloid from brucine.

The estimation of brucine (by difference) in presence of strychnine has been described already (p. 180).

Brucine crystallises from water or aqueous alcohol in monoclinic prisms containing $4H_2O$, m.p. 105° or 178° (*dry*), $[\alpha]_D$ — 119° to — 127° in chloroform. The alkaloid is slightly soluble in cold water (1 in 320), more so in boiling water (1 in 150), very soluble in alcohol, chloroform, or amyl alcohol, almost insoluble in ether.

Brucine is a monoacidic base ; the salts crystallise well and are readily soluble in water. The hydrochloride, B.HCl, forms small groups of needles, and the hydriodide, B.HI, leaflets sparingly soluble in water. The sulphate, $B_2.H_2SO_4.7H_2O$, forms long needles.

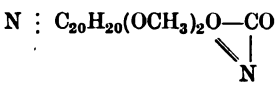
Brucine is easily distinguished from strychnine by not giving the characteristic play of colours when oxidised with chromic acid, and by affording an intense red colour with nitric acid. This red

[1] *Journ. Chem. Soc.* 1881, **39**, 456.

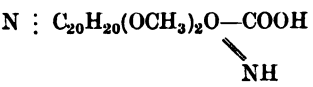
coloration may be distinguished from that given by morphine by cautiously adding stannous chloride, when in the case of brucine the red colour changes to violet.

Constitution. It has long been surmised that brucine is related to strychnine as a dimethoxy derivative, and all the work done on it shows that it yields a series of derivatives, which are completely parallel with those obtained in like manner from strychnine, the two series differing by $2CH_2O$, *i.e.* by the replacement of two hydrogen atoms by two methoxyl groups. The most important reactions bearing on the constitution of brucine are summarised in the following paragraphs.

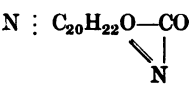
Brucine contains two methoxyl groups. When warmed with sodium in alcohol at 80° it takes up a molecule of water, forming brucinic acid, $C_{23}H_{28}O_5N_2$, which crystallises in microscopic needles, m.p. 245°. The acid is very unstable, and on heating is reconverted into brucine; it reacts with nitrous acid to form a nitrosoamine and is an iminocarboxylic acid, of which brucine is the corresponding betaine, just as strychnine is the betaine of strychninic acid (p. 185).



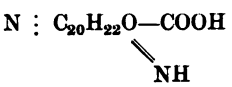
Brucine



Brucinic acid

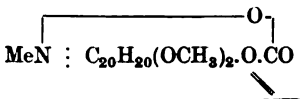


Strychnine



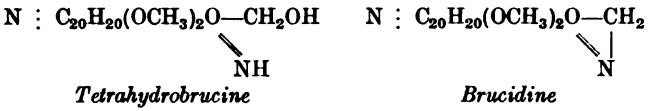
Strychninic acid

Brucine forms a methiodide, which crystallises in needles, m.p. 270° (*decomp.*). Brucinic acid methiodide forms small needles, m.p. 218°, which readily lose water, passing into brucinemethiodide; the latter on digestion with silver oxide gives methylbrucine.



Methylbrucine

When reduced electrolytically brucine is converted into tetrahydrobrucine, $C_{23}H_{30}O_4N_2$, and brucidine, $C_{23}H_{28}O_3N_2$, analogous with tetrahydrostrychnine and strychnidine.[1]



Tetrahydrobrucine *Brucidine*

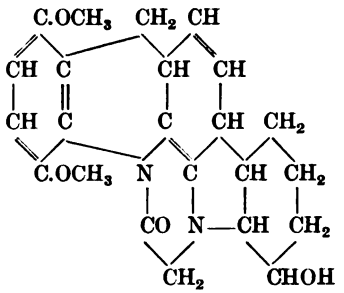
On oxidation with permanganate in acetone solution brucine furnishes brucinonic acid, $N : C_{17}H_{16}(OCH_3)_2(:N.CO)(CO)(COOH)_2$, and this on reduction yields the corresponding hydroxydicarboxylic acid, brucinolic acid, $N : C_{17}H_{16}(OCH_3)_2(:N.CO)(CHOH)(COOH)_2$, which by hydrolysis with dilute potash furnishes brucinolone, $C_{21}H_{22}O_5N_2$. These three substances are completely analogous with the strychninonic acid, strychninolic acid, and strychninolone obtained from strychnine (*see* p. 190), and have been fully investigated by Leuchs and collaborators, and shown to contain still the two methoxyl groups of the parent base.[2]

On oxidation with chromic acid brucine yields Hanssen's acid, $C_{15}H_{17}O_2N_2.COOH$, identical with that furnished by strychnine (*see* p. 188), so that in the oxidation the ring containing the two methoxyl groups of brucine must have disappeared. Perkin and Robinson,[3] after elaborating their formula for strychnine, pointed out that the positions of the two methoxyl groups in brucine are fairly clearly fixed by this fact and by the observation of Leuchs and Weber[4] that brucinolone on treatment with dilute nitric acid yields a quinone, $C_{19}H_{16}O_5N_2$, crystallising in red needles, m.p. 295°, and which is reduced by sulphurous acid to the corresponding quinol bisdesmethylbrucinolone, $C_{19}H_{18}O_5N_2$. A similar quinone is formed when brucine is treated with nitric acid and is the cause of the well-known brucine reaction with nitric acid.[5]

These quinones have all the properties of *p*-quinones, and

[1] Tafel and Naumann, *Berichte*, 1901, **34**, 3291.
[2] *Berichte*, 1908, **41**, 1711 ; 1909, **42**, 770.
[3] *Trans. Chem. Soc.* 1910, **97**, 309. [4] *Berichte*, 1909, **42**, 3709.
[5] Leuchs and Anderson, *ibid.* 1911, **44**, 2136, 3040.

consequently Perkin and Robinson suggest that brucine may be represented as a dimethoxystrychnine of the following formula:



Brucine (Perkin and Robinson)

Strychnicine. This alkaloid, the composition of which is still unknown, was isolated by van Boorsma from the leaves of *Strychnos Nux-vomica*, grown in Java. It forms colourless needles, which begin to decompose at 240°. Strychnicine is characterised chiefly by the fact that when a solution of sodium hydroxide is added drop by drop to a solution of a salt of the alkaloid in water, a precipitate is formed which with more alkali redissolves, forming an orange-tinted liquid, which develops a deep violet colour on further addition of hydrochloric acid. Strychnicine is scarcely poisonous, though it causes slight tetanus in frogs.[1]

Physiological Action of Strychnos Alkaloids

Brucine closely resembles strychnine in physiological action (*see below*), but is much less toxic, the relative toxicities of the two alkaloids being as 4 : 33. It also differs from strychnine in its more powerful curare-like action on the nerve terminations in voluntary muscle.

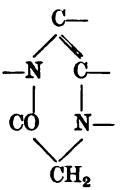
Strychnine is highly toxic; in poisonous doses it acts principally on the spinal cord, causing excessive reflex irritability, which results in convulsions (tetanus) in which all the muscles of the body are involved. The respiratory muscles are affected in the paroxysm, and, as a general rule, after two or three convulsions respiration

[1] *Bull. Inst. bot. Buitenzorg*, 1902, No. XIV, p. 3.

fails to return. With very large doses death may occur almost immediately from asphyxia resulting from paralysis of the central nervous system. The terminations of the motor nerves are paralysed by large doses of strychnine in the same way as by curare, but this effect is only well seen in certain kinds of frogs where this action occurs before that on the central nervous system. In small quantities strychnine slows the heart and raises the blood-pressure, and with poisonous doses the blood-pressure is very high, due to the increased activity of the vaso-motor centre.

In medicine strychnine is chiefly used as a " tonic " for the sake of its local action on the digestive organs.

It is also employed in various forms of paralysis owing to its stimulant action on the central nervous system. It has also been used as a remedy in chronic alcoholism. Its principal use is probably as a vermin killer.

Among the other tetanising alkaloids are " calabarine " and " gelsemine," neither of which is well defined. Thebaine, belonging to the opium group, is more active than brucine, but much less so than strychnine in producing tetanus. It has been supposed that the tetanising action of strychnine is correlated with the existence of the keto-di-nitrogen group  since desoxystrychnine is active, whilst dihydrostrychnoline and strychnoline, in which the : CO group has become : CH_2, are not. But against this view is the fact that strychnidine, which contains : CH_2 in place of : CO, lies between desoxystrychnine and strychnine as a tetanising poison, whilst strychninonic acid (p. 190), which contains the keto-di-nitrogen ring intact, is non-poisonous.[1]

Strychnine oxide, $C_{21}H_{22}O_3N_2.3H_2O$, obtained by Pictet and Mattisson[2] by the action of hydrogen peroxide on strychnine,

[1] *Cf.* Loeb and Oldenburg, *Abstr. Chem. Soc.* 1912, ii, 373.
[2] *Berichte*, 1905, **38**, 2782. *Cf.* Mossler, *Monats.* 1910, **31**, 329.

is said to be about as toxic as strychnine itself, whilst *iso*strychnine (*see* p. 186) is about as toxic as brucine.

ALKALOIDS OF CURARE

Curare consists of a dried aqueous extract of various species of Strychnos indigenous to South America, where it is prepared by Indians for use as an arrow poison. It was first examined by Roulin and Boussingault in 1829, who isolated from it a crystalline alkaloid, curarine ; some years later a similar alkaloid was obtained by Buchner, and in 1865 Preyer announced that he had obtained curarine and its salts in a well-crystallised condition, and by analysis of the platinichloride ascertained its composition to be $C_{10}H_{35}N$. In 1878 curare was reinvestigated by Sachs,[1] who was only able to obtain an amorphous alkaloid, to which he assigned the empirical formula, $C_{18}H_{35}N$. The more recent work of Boehm [2] to a certain extent explains these discrepant results, since he shows that the curare of commerce varies in composition.

According to this author the extract is of three kinds, distinguished by the packing in which they are sent into commerce :

(*a*) *Para curare*, in bamboo tubes.

(*b*) *Calabash curare*, in gourds.

(*c*) *Pot curare*, in unburnt earthenware pots.

The drug contains alkaloids of two kinds, typified by the curine and curarine of Para curare, the former being physiologically inactive, the latter exhibiting the nerve-paralysing action peculiar to curare.

Para Curare. This is the variety now found in commerce. It consists of a dark brown extract containing much quercitol. The toxic dose for rabbits is 0·005 to 0·01 grm. per kilogramme of body weight. It contains the alkaloid, CURINE, $C_{18}H_{19}O_3N$, to the extent of 12 to 15 per cent. This is isolated by extracting with water, precipitating with ammonia solution, and recrystallising the precipitated alkaloid from benzene, when it forms four-sided

[1] *Annal.* 178, **191**, 354. [2] *Arch. Pharm.* 1897, **235**, 660.

prisms, m.p. 161°, containing 1 mol. of benzene. It is soluble in aqueous alcohol or dilute acids, but insoluble in water. It is precipitated by *meta*phosphoric acid, and with sulphovanadic acid gives a black solution, which becomes dark blue and eventually bright red. The platinichloride is an amorphous yellow powder: the methiodide forms yellow needles, m.p. 252°, and the methyl chloride, rhombic plates. The alkaloid contains a methoxyl, but no hydroxyl group. Since on distillation with zinc dust it gives a substance having the properties of *para*quinoneanisole, Boehm considers that curine contains a methylquinoline nucleus. In addition to this physiologically inactive crystalline alkaloid Boehm obtained from the mother liquor an amorphous, bitter, highly toxic base, soluble in water or alcohol and having the characteristic physiological action of curare. This was named PARACURARINE or TUBOCURARINE, $C_{19}H_{21}O_4N$.[1]

Calabash Curare. This extract was formerly well known in commerce, and was probably prepared from *Strychnos toxifera*. The toxic constituent is apparently an amorphous CURARINE, $C_{19}H_{26}ON_2$, yielding a crystalline hydrochloride.

Pot Curare is a dark brown, comparatively dry extract obtained principally from *Strychnos Castelnaei*. It contains PROTOCURINE, $C_{20}H_{23}O_3N$, which crystallises from methyl alcohol in colourless needles, m.p. 306° (*decomp.*). Its salts crystallise well and are bitter to the taste. This base is slightly toxic. A similar base, PROTOCURIDINE, $C_{19}H_{21}O_3N$, crystallises from boiling chloroform in prisms, m.p. 274°–276°, and is not toxic. The poisonous constituent is PROTOCURARINE, $C_{19}H_{23}O_2N$, an amorphous red powder easily soluble in water, and giving characteristic colour reactions with sulphuric and nitric acids. It is intensely poisonous, the toxic dose for rabbits being 0·00024 grm. per kilogramme of body weight.

[1] *Cf.* Buraczewski and Zjibewski, *Bull. Acad. Sci. Crac.* 1910, p. 352.

Physiological Action of Curare

Curare, unlike strychnine and brucine, the characteristic alkaloids of *Strychnos Nux-vomica*, exerts a strong paralysing action on the motor nerve endings without affecting the excitability of muscle. This action appears to be due to soluble, amorphous substances (*curarines*) which have probably not yet been obtained in a pure state.[1]

Strychnos Vacacoua

Bakankosine, $C_{16}H_{23}O_8N.H_2O$, was isolated by Bourquelot and Hérissey[2] from the seeds of *Strychnos Vacacoua*, Baill., and is described as a nitrogenous glucoside. It forms large colourless crystals from alcohol, melts at 157°, remelts at 200°, and has $[\alpha]_D$ — 205·2°. It is hydrolysed by boiling dilute acids and by emulsin, yielding dextrose and a product, $C_{10}H_{13}O_3N$. Neither bakankosine nor its hydrolytic product is toxic.

[1] *Cf.* Edmund and Roth, *Amer. J. Physiol.* 1908, **23**, 28, 46.
[2] *Compt. rend.* 1907, **144**, 575 ; 1908, **147**, 750.

V. *ISO*QUINOLINE GROUP

ALKALOIDS OF OPIUM

OPIUM is the sun-dried latex of the unripe fruit of the opium poppy, *Papaver somniferum*, which has been cultivated from very early times for the sake of this drug. At the present time opium is produced in many tropical and sub-tropical countries, but only on a large scale in India, China, Persia, and Asia Minor. The opium used in medicine in Europe and America is almost wholly the Asia Minor variety (Smyrna opium), but a good deal of Persian opium is imported for the manufacture of opium alkaloids. Indian opium is largely exported to China for use by the Chinese in opium smoking, and a small amount is sent to other countries for use by Chinese and Hindoos living abroad, but the production of opium in India and its export are declining.

The large scale on which the two principal alkaloids of opium, morphine and codeine, are manufactured has made it possible to conduct investigations on practically unlimited supplies of this drug, with the result that a very large number of alkaloids have been isolated from it. At present twenty-five opium bases are known; their names and the approximate extent to which they generally occur in Smyrna opium are given in the following table :

Morphine Group

Name	Composition	Percentage	Name	Composition	Per-centage
Morphine	$C_{17}H_{19}O_3N$	9·00–10·00	Pseudo-morphine	$(C_{17}H_{18}O_3N)_2$	0·02
Codeine	$C_{18}H_{21}O_3N$	0·30–0·4	Thebaine	$C_{19}H_{21}O_3N$	0·40
Hydroxy-codeine	$C_{18}H_{21}O_4N$	—			

Narcotine—Papaverine Group

Name	Composition	Per-centage	Name	Composition	Per-centage
Narcotine	$C_{22}H_{23}O_7N$	5·00	Proto-papaverine	$C_{19}H_{19}O_4N$	—
Gnoscopine (*dl*-narcotine)	$C_{22}H_{23}O_7N$	—	Meconidine	$C_{21}H_{23}O_4N$	—
Oxynarcotine	$C_{22}H_{23}O_8N$	—	Lanthopine	$C_{23}H_{25}O_4N$	0·006
Narceine	$C_{23}H_{27}O_8N$	0·20	Protopine	$C_{20}H_{19}O_5N$	0·003
Papaverine	$C_{20}H_{21}O_4N$	0·80	Cryptopine	$C_{21}H_{23}O_5N$	0·08
Laudanosine	$C_{21}H_{27}O_4N$	0·0008	Tritopine	$(C_{21}H_{27}O_3N)_2O$	0·0015
Laudanine	$C_{20}H_{25}O_4N$	0·01	Rheadine	$C_{21}H_{21}O_6N$	—
Laudanidine	$C_{20}H_{25}O_4N$	—	Hydrocotar-nine [1]	$C_{12}H_{15}O_3N$	
Codamine	$C_{20}H_{25}O_4N$	0·002			
Pseudo-papaverine	$C_{21}H_{21}O_4N$	—	Xanthaline (Papaveral-dine)[1]	$C_{20}H_{19}O_5N$	
Papaveramine	$C_{21}H_{25}O_6N$	—			

A very large number of analyses of opium from different sources have been recorded, and, as a considerable amount of attention has been directed by pharmacists and others to the estimation of morphine, widely different methods have been employed, so that it is difficult to collect analytical results which are strictly comparable; but as far as possible this has been done in compiling the tabular statement on page 201 showing the morphine and narcotine values of different kinds of opium.[2]

Estimation of the Chief Alkaloids of Opium

Morphine. The poisonous character of this base, the most important constituent of opium, lends particular interest to the problem of accurately determining the amount of it contained in the crude drug and its medicinal preparations, and many processes have been devised for this purpose.

The British Pharmacopœia (1898) adopts the following method: Fourteen grammes of opium dried at 100° and in No. 50 powder are mixed with 6 grm. of slaked lime, and stirred in a mortar with 40 c.c. of water. The mixture is then diluted with 100 c.c. of

[1] These are possibly decomposition products of narcotine and papaverine respectively.

[2] Flückiger, *Pharm. Journ.* 1875 [iii], **5**, 845; and Dott, *Yearbook of Pharmacy*, 1876, 498.

water and occasionally stirred during half an hour. The liquid is filtered through a plaited filter, 10 cm. in diameter, into a wide-mouthed bottle, until a volume of 104 c.c., representing 10 grm. of opium, has been obtained. To this filtrate 10 c.c. of alcohol (90 per cent.) and 50 c.c. of ether are added and the mixture well shaken. In order to precipitate the morphine from its solution in

Percentages of Morphine and Narcotine in Opium

Source of opium	Morphine (average)	Narcotine (average)	Author
Indian—			
Patna	8·6 [1]	4·0	Flückiger
Malwa	6·50	—	Dott
	6·1 [1]	4·7	Flückiger
Jeypore	4·6 to 7·75 [1]	4·5 to 7·1	Dunstan and Brown
Sind.	3·8 [1]	3·1	Flückiger
Hyderabad	3·2 [1]	5·4	Flückiger
Smyrna	10·0 [2]	—	Dott
Egyptian	7·0	—	Dott
	5·8 [1]	8·7	Flückiger
Persian	7·1 [1]	6·4	Flückiger
	7·2 [3]	—	Dott
Chinese	4·3 to 11·2	1·9 to 6·6	F. Browne

the lime-water, 4 grm. of ammonium chloride are added, and the mixture well shaken during thirty minutes and then set aside for twelve hours. After this time the morphine will have crystallised out. The ethereal layer is then collected in a pipette and filtered through two small counterbalanced filter papers placed one within the other and previously wetted with ether; 20 c.c. of ether are added to the contents of the bottle, the mixture shaken, and the ether again transferred by a pipette, the filter papers being washed with small portions of ether, using 10 c.c. of ether in all, and dried. The crystals which remain in the bottle are filtered off

[1] These figures represent pure morphine, determined by Flückiger's method, and are probably below the truth.

[2] Average of twelve samples ranging from 6·9 to 12·3 per cent. of hydrated morphine.

[3] Average of two samples containing 6·00 and 8·50 per cent. of hydrated morphine.

through the two filter papers and washed, using a saturated solution of morphine in chloroform water. The crystals of morphine are dried first at 55°–60°, and finally at 110° for two hours, and weighed, using the second filter to counterbalance the first.

The purity of the morphine is checked by titrating 0·5 grm. of the dry crystals with $N/10$ sulphuric acid until the liquid, after boiling, slightly reddens litmus paper. One cubic centimetre of the acid is equal to 0·0283 grm. of morphine. The weight of pure morphine indicated by the titration as present in the crystals, plus 0·104 grm., representing the average loss by this method of estimation, should amount to not less than 0·95 and not more than 1·05 grm., corresponding to about 10 per cent. of morphine in the dry powdered opium.

The same Pharmacopœia prescribes the following process for tincture of opium :

Eighty cubic centimetres of the liquid are evaporated on a water-bath to 30 c.c., the residue mixed with 3 grm. of slaked lime and diluted with water to 85 c.c., and occasionally stirred during thirty minutes. Fifty cubic centimetres of the liquid (50 c.c. of the tincture) are filtered through a plaited filter, 10 cm. in diameter, into a wide-mouthed stoppered bottle ; to this 5 c.c. of alcohol (90 per cent.) and 30 c.c. of ether are added and the mixture shaken. Two grammes of ammonium chloride are next added, the mixture shaken well and frequently during thirty minutes, and then set aside during twelve hours. At the end of this time the crystals of morphine that have separated are filtered off with the precautions described above, 15 c.c. of ether being used to rinse out the bottle and 10 c.c. of ether in all to wash the crystals. For titration 0·3 grm. of the crystals is used. To the weight of pure morphine in the crystals as determined by titration, 0·05 grm. is added (or 0·1 grm. per 100 c.c. of filtrate originally used). The tincture should yield not less than 0·7 nor more than 0·8 grm. of pure anhydrous morphine per 100 c.c. by this process.

For liquid extract of opium the same process is used. This preparation also should yield not less than 0·7 nor more than 0·8 grm. of morphine per 100 c.c.

For the manufacture of these two preparations the Pharmacopœia permits the use of crude opium containing not less than 7·5 per cent. of dry morphine, but for other galenical preparations opium yielding, after being dried at 100° and powdered, not less than 9·5 nor more than 10·5 per cent. of dry morphine is prescribed.

Slight modifications of these processes have been suggested by Farr and Wright,[1] Dott,[2] Dowzard,[3] and Lenton.[4]

The United States Pharmacopœia (8th Rev.) prescribes the following process for opium: Ten grammes of opium, in small pieces if moist, or in fine powder if dry, are mixed with 100 c.c. of water in a 300 c.c. flask and shaken at least every ten minutes during three hours, and the mixture then poured on a moistened 12 cm. filter. The residue on the filter is washed with enough water to increase the filtrate to 150 c.c., then replaced in the flask and shaken with 50 c.c. of water during fifteen minutes. It is again transferred to the filter and washed to produce a second filtrate measuring 150 c.c. Finally it is further washed to produce a third filtrate measuring 20 c.c. The second filtrate is evaporated to a low bulk in a tared dish, the first filtrate is then added to this, the third filtrate being employed to wash out the vessels used, after which it is also added to the concentrated extract in the dish. Evaporation is then continued till the concentrated extract weighs 14 grm. This is next transferred to a tared 100 c.c. flask, using enough water for washing out the dish to make the weight of extract 20 grm. To this 10 grm. (12·2 c.c.) of alcohol (sp. gr. 0·816 at 15·6°) are added, then 25 c.c. of ether, followed by 3·5 c.c. of ammonia water (sp. gr. 0·958 at 25°), the flask being well shaken after each addition and finally set aside in a cool place during sixteen hours. The ethereal layer is then carefully and completely decanted through two 7 cm. folded filters, placed one within the other and previously wetted with ether. Ten cubic centimetres of ether are now added to the flask, the latter shaken, and the ethereal layer decanted as before, and this operation is repeated, using again 10 c.c. of ether. The

[1] *Pharm. Journ.* 1907 [iv], **24**, 164.
[2] *Ibid.* pp. 78, 356.
[3] *Ibid.* 1903 [iv], **17**, 909; 1904, **18**, 397.
[4] *Ibid.* 1905 [iv], **20**, 652.

contents of the flask are then poured into the filter and the flask washed out with water, using not more than 15 c.c. in all. Finally the drained crystals are washed, using (1) water drop by drop until all adhering mother liquor has been removed; (2) a saturated solution of morphine in alcohol drop by drop; and (3) not more than 10 c.c. of ether to displace the alcohol. The filter and its contents are next dried at a temperature not exceeding 60°, and the crystals of morphine placed in a watch-glass and weighed. They are next transferred to a flask, mixed with 10 c.c. of lime-water for each 0·1 grm. of morphine, and shaken during thirty minutes. The liquid is then passed through two counterpoised filter papers placed one within the other. The flask and the filter papers are washed with lime-water till the washings no longer give a precipitate with potassium mercuric iodide solution (p. 8). The filter papers are then dried and the increase in weight of the inner one determined and deducted from the weight of crude morphine found. The difference multiplied by 10 gives the percentage of morphine in the opium. This should be 9 for crude opium and 12 to 12·5 for powdered opium, deodorised opium, or granulated opium as prescribed in the United States Pharmacopœia.

The same process is recommended by the United States Pharmacopœia for extract of opium, but the quantity of extract used is 4 grm. The extract is dissolved in 30 c.c. of water, filtered, the residue washed, the washings collected separately and evaporated at 100° to a low bulk. To this the filtrate is added, and the whole evaporated to 10 grm. The rest of the process is carried out as described under opium, dilution to 15 grm. being allowed in the transfer to the flask. The quantity of alcohol used is 8·5 c.c., of ether 20 c.c., and ammonia water 2·2 c.c. The mixture is set aside six hours. For washing the crystals by decantation, two portions of ether, each 15 c.c., are to be used, followed by not more than 10 c.c. of water when the crystals are on the filter paper, and, last of all, not more than 10 c.c. of ether to displace the saturated solution of morphine in alcohol. The purification with lime-water is carried out as described above. The weight of morphine found, multiplied

by 25, gives the percentage of morphine in the extract, which should be 20.

For "tincture of opium" and "tincture of deodorised opium" the same Pharmacopœia gives the following process: One hundred cubic centimetres of the tincture are evaporated at 100° to 20 c.c., diluted with 40 c.c. of water and set aside during one hour, stirring occasionally. The mixture is then filtered, the filtrate and washings being collected separately. The washings are evaporated to a low bulk, the filtrate added, and the evaporation continued till the weight is 14 grm. The rest of the process is carried out as described above for opium; the weight of morphine obtained is the weight of morphine in 100 c.c. of the tincture and should be from 1·2 to 1·25 grm.

Modified forms of these processes have been described by Dohme and Lamar.[1]

Other methods differing in principle from the foregoing have been described by Schidrowitz,[2] Prescott and Gordin,[3] Asher,[4] Léger,[5] van der Wielen,[6] and Thorburn.[7]

For the estimation of morphine in solutions or preparations containing this alkaloid alone, warm amyl alcohol is a useful extracting medium or a mixture of cresol, 2 parts, with amyl alcohol, 1 part.[8]

Other Opium Alkaloids. It is not often necessary to estimate other alkaloidal constituents of opium than morphine, but occasionally determinations of narcotine or codeine are required. Narcotine is usually estimated by extracting the dried opium with dry ether or benzene, and shaking the solution with ammonia, which removes narceine. The narcotine left on distilling off the ether or benzene is dried and weighed.

For codeine, methods have been given by van der Wielen[9] and

[1] *Bull. No.* 99, *Bur. Chem., U.S. Dept. Agric.*
[2] *Analyst*, 1904, **29**, 144.
[3] *J. Am. Chem. Soc.* 1898, **20**, 724.
[4] *Amer. J. Pharm.* 1906, **78**, 262.
[5] *J. Pharm. Chim.* 1903 [ii], **17**, 553.
[6] *Bull. Sci. Pharm.* 1910, **17**, 59.
[7] *J. Ind. Eng. Chem.*, 1911, **3**, 754.
[8] Tickle, *Pharm. Journ.* 1907 [iv], **24**, 162.
[9] *Pharm. Zeit.* 1903, **48**, 267.

Caspari.[1] The following process devised by Andrews[2] gives good results :

Twelve grammes of dry opium are extracted with small quantities of cold water to make in all 100 c.c. of filtrate, to which 20 c.c. of lead acetate solution (20 per cent.) are added. After standing over-night the liquid is filtered and 100 c.c. of the filtrate (10 grm. of opium) are treated with sulphuretted hydrogen, the lead sulphide filtered off, the filtrate being collected in a 200 c.c. flask and the sulphuretted hydrogen removed by a current of air. The precipitate is washed with water, the washings collected apart, concentrated, and added to the main liquid so that the total filtrate does not exceed 130 c.c. Twenty cubic centimetres of sodium salicylate solution (20 per cent.) are now added, the flask corked, and the contents shaken. The resinous precipitate formed quickly aggregates, and the liquid is passed through a small fluted filter paper into a beaker containing a few crystals of thebaine salicylate. The liquid is well stirred and the sides of the beaker occasionally scratched with a glass rod to promote the separation of thebaine salicylate. After standing over-night the liquid is passed through the same filter, and the above treatment is repeated until no more solid matter forms. The liquid is now filtered through the same filter paper, which is then washed with a little water. The total filtrate is concentrated at 100° to about 10 to 15 c.c., and whilst still warm transferred to a glass separator, using a little water to rinse out the dish, the final rinsings being transferred to a second separator. The main liquid in the separator is now freed from ether-soluble substances by shaking well with ether, which is then transferred to the second separator and shaken with the aqueous rinsings contained in it. This washing of the aqueous liquid and the rinsings, with ether is repeated at least three times. The aqueous portion in the second separator is now added to the main liquid in the other separator and 10 c.c. of a 20 per cent. solution of caustic soda added ; the strongly alkaline liquid is extracted with ether at least four times, using each time a volume of solvent

[1] *Apoth. Zeit.* 1904, **19**, 874. [2] *Analyst*, 1911, **36**, 489.

rather more than that of the alkaline liquid. Each portion of ether is in turn passed into a second separator and washed with 20 to 30 c.c. of water, then transferred to a dry flask and dried by the use of a little anhydrous sodium sulphate before being distilled. The total ether used for the extraction of the codeine is distilled in a flask down to a few cubic centimetres, which are then allowed to evaporate spontaneously, when, as a rule, the codeine separates in well-defined crystals.

The alkaloid is dried in a desiccator under reduced pressure and weighed, the weight being checked by dissolving in excess of $N/10$ acid and titrating the excess with $N/10$ caustic soda solution, using litmus or methyl orange as indicator.

General methods for the separation and estimation of the chief opium alkaloids have been described by Plugge [1] and by Dott.[2]

Isolation of Opium Alkaloids

Hesse has given the following scheme for the separation of the rarer opium bases contained in the mother liquors (*see* p. 209) produced in the manufacture of morphine and codeine : [3]

The opium is extracted with water, and to the aqueous extract calcium chloride is added, precipitating *calcium meconate.*

The filtrate on gradual concentration deposits *morphine hydrochloride*, *pseudomorphine hydrochloride*, and *codeine hydrochloride* in this order.

The mother liquor is mixed with an equal bulk of water and excess of ammonia ; the precipitate thus obtained is dissolved in acetic acid, filtered, purified by shaking with ether, and then made alkaline with caustic soda, which

(1) Precipitates papaverine, narcotine, thebaine, some cryptopine, protopine, laudanosine, and hydrocotarnine.

(2) Dissolves lanthopine, laudanine, codamine, some cryptopine, and meconidine, if the latter is present.

[1] *Rec. Trav. chim.* 1887, **6**, 157.
[2] *Allen's Organic Analysis*, 4th ed. vol. vi, p. 372.
[3] *Cf.* Knuder, *Arch. Pharm.* 1890, **228**, 419.

The precipitated alkaloids are dissolved in dilute alcohol as far as possible, the liquid slightly acidified with acetic acid and three times its volume of boiling water added, which precipitates *papaverine* and *narcotine*.

The filtrate from these is evaporated to remove alcohol, and tartaric acid added, precipitating *thebaine hydrogen tartrate*.

The mother liquor is neutralised with ammonia, mixed with 3 per cent. by weight of sodium bicarbonate, and set aside for a week, filtered, and ammonia added. The precipitate thus obtained is extracted with boiling benzene, which removes laudanosine and hydrocotarnine. By shaking the benzene solution with aqueous sodium bicarbonate, *laudanosine* is precipitated, and by passing through it hydrogen chloride, *hydrocotarnine chloride* is obtained.

The bases insoluble in benzene are protopine and cryptopine, which may be separated by conversion into the hydrochlorides, and washing with a very little water, the *cryptopine* salt being very soluble, and the *protopine* salt only slightly so, in water.

The alkaloids which remained dissolved in the caustic soda solution are obtained by neutralising with dilute hydrochloric acid, adding ammonia, extracting with ether, and shaking out the ethereal solution with acetic acid; *lanthopine* separates in the course of twenty-four hours, when the acid liquid is neutralised with ammonia.

On adding excess of ammonia to the filtrate, laudanine, codamine, and cryptopine are precipitated. This precipitate is dissolved in a little boiling dilute alcohol, which on cooling deposits *laudanine* and *cryptopine*, and from the mother liquor *codamine* may be obtained by evaporation and addition of ether. Hesse's scheme does not provide for the separation of narceine and meconidine, and he assumes that the second of these two alkaloids is decomposed during extraction by this method.

Morphine Sub-Group

Morphine, $C_{17}H_{19}O_3N$. Already in the seventeenth and eighteenth centuries attempts had been made to prepare from opium the principle or principles to which it owes its physiological

activity, and the extracts obtained in the course of these experiments were employed in medicine under the name of *Magisterium Opii*. Early in the nineteenth century Bucholz endeavoured to crystallise from aqueous extracts of the drug a "salt" which could be used in place of opium; and about the same time Derosne, an apothecary practising in Paris, observed the separation of a crystalline substance, when an aqueous syrup-like extract of opium was diluted with water. This crystalline material was probably narcotine, or a mixture of that alkaloid with morphine. Séguin in 1804 read to the Institute of France a paper entitled "*Sur l'opium*," in which he described the isolation of morphine, although he did not recognise its basic character. This paper was not published till 1814, and in the meantime Sertürner had obtained both morphine and meconic acid from opium and pointed out that the former was the first member of a new class of substances, "the vegetable alkalis." [1]

The composition of the alkaloid was first determined by Liebig in 1831, who represented it by the formula $C_{34}H_{36}O_6N_2$, which was reduced by Laurent in 1847 to the simpler formula, $C_{17}H_{19}O_3N$, now in use.

Preparation. The opium is extracted with warm water, the extract mixed with chalk, and evaporated to a small volume. Calcium chloride is then added and the liquid diluted with water. The precipitate of resin, calcium meconate, &c., is filtered off, and the filtrate evaporated to a low bulk, when a mixture of morphine and codeine hydrochlorides crystallises out. This mixture is pressed, redissolved in water, and excess of ammonia added, which precipitates the morphine and a little codeine. The morphine may be freed from traces of codeine [2] by washing with ether or benzene, or it may be purified by recrystallising the hydrochloride from hot water and then regenerating the alkaloid and recrystallising from hot alcohol. The codeine may be recovered from the mother liquor referred to above by adding potash solution, or the mother liquor may be evaporated to a low bulk, when codeine crystallises

[1] *Gilbert's Annalen*, 1817, **55**, 61. [2] Andrews, *Analyst*, 1911, **36**, 489.

out, and may be purified by decolorisation of its aqueous solution in water and concentration of this.[1]

Properties. Morphine crystallises from alcohol in colourless, trimetric prisms containing $1H_2O$, becomes anhydrous at 100° and then melts with decomposition at 254°. It is bitter to the taste and sparingly soluble in most solvents. The solubilities given by different observers vary greatly, and Prescott has pointed out that the physical condition of the alkaloid used affects the solubility to a considerable extent: thus he states that morphine in powder is nearly three times as soluble in ether as the crystalline alkaloid.[2] Some of the most recent determinations are those of Seidell given in the United States Pharmacopœia as follows: water (1 in 3330 at 25° or 1 in 1040 at 80°), dry alcohol (1 in 30 at b.p. or 1 in 50 cold), 95 per cent. alcohol (1 in 168 at 25° or 1 in 76 at 60°), ether (1 in 4464 at 25°). Müller [3] gives the following figures: water (1 in 3533), ether (1 in 7632), benzene (1 in 1599), chloroform (1 in 1525), ethyl acetate (1 in 537). According to Florio the solubility in amyl alcohol is about 1 in 50 at 78°. Müller's figure for solubility in benzene is unusually high, and though Prescott [4] states that "nascent" or freshly precipitated morphine dissolves in 1997 parts of benzene whilst the crystallised alkaloid dissolves in 8930 parts, the alkaloid is generally stated to be insoluble in benzene. Morphine is readily soluble in lime-water (1 in 100 at 25°) or in alkali hydroxide solutions, but less so in ammonia solution (1 in 117, sp. gr. 0·97, Duplos). Morphine is lævorotatory, $[\alpha]_D^{23}$ — 130·9° in methyl alcohol, — 128° in neutral salts, — 70° in excess of alkali. It behaves as a monoacidic base, and its salts are neutral to litmus and methyl orange. The salts are usually well crystallised. Those chiefly used in medicine are the sulphate, hydrochloride, and acetate, though the tartrate and bimeconate have also been employed.

The sulphate, $B_2.H_2SO_4.5H_2O$, forms small silky crystals or cubical masses from water, is soluble in water (1 in 15·3 at

[1] Gregory, *Annalen*, **7**, 263.
[2] *Journ. Amer. Chem. Soc.* 1907, **29**, 405.
[3] *Apoth. Zeit.* 1903, **18**, 257.
[4] *Loc. cit.*

25°, or 1 in 0·6 at 80°) or alcohol (1 in 465 at 25°, or 1 in 187 at 60°). It chars at 250°, but does not melt. It is lævorotatory, $[\alpha]_D^{15}$ — 100·47° + 0·96*c*. in water. The hydrochloride, $B.HCl.3H_2O$, forms colourless silky needles from water, $[\alpha]_D^{15}$ — 100·67° + 1·14*c*. in water (Hesse), or — 111·5° at 25° in dry alcohol (Schryver and Lees), is soluble in water (1 in 17·2 at 25° or 1 in 0·5 at 80°) or alcohol (1 in 42 at 25° or 1 in 35·5 at 60°). The hydrobromide, $B.HBr.2H_2O$, and the hydriodide, $B.HI.2H_2O$, form long needles. The acetate, $B.CH_3COOH.3H_2O$, forms a crystalline, colourless powder, m.p. 200° (*decomp.*), $[\alpha]_D$ — 77° in water, — 100·4° in dry alcohol. It is very soluble in water (1 in 2·25 at 25°), less so in alcohol (1 in 21·6 at 25°), and sparingly so in chloroform (1 in 480 at 25°).

Detection. Morphine is at most coloured faintly pink by cold sulphuric acid, but becomes dirty green and then brown on warming. With nitric acid it gives an orange-red coloration. With sulphuric acid and potassium iodate it yields a brown coloration, and with sulphuric acid containing potassium dichromate, a green tint after a time, and with sulphuric acid containing selenious acid, blue changing to green and then brown. Morphine salts in solution, on warming with potassium ferricyanide solution containing a little neutral ferric chloride, give after a time a blue precipitate. A few drops of neutral ferric chloride solution added to a solution of a morphine salt produce a blue coloration which disappears on warming or on addition of an acid or alcohol.

Isomerides of Morphine. When morphine is heated with phosphorous chloride the alcoholic hydroxyl group of the alkaloid (*see below*) is replaced by an atom of chlorine, forming *chloromorphide*, $C_{17}H_{18}O_2NCl$, and phosphorous bromide under like conditions yields *bromomorphide*. Both these substances when boiled with water yield a mixture of two isomerides of morphine, thus :

Bromomorphide → *iso*Morphine, colourless needles, m.p. 246–248°, $[\alpha]_D^{25}$ – 164·3° in methyl alcohol

Chloromorphide → β-*iso*Morphine, rhombic pyramids, m.p. 182°, $[\alpha]_D^{17}$ – 216·2° in methyl alcohol

→ neo*iso*Morphine, prismatic needles, m.p. 278°, for B.HCl $[\alpha]_D$ – 79·1° ; in water $[\alpha]_D$ – 94° (Knorr

These isomerides, according to Schryver and Lees,[1] differ from morphine in not being narcotic.

Knorr and Hörlein[2] have named these substances α-, β-, and γ-*iso*morphines in the order given above. Each of them yields a corresponding *iso*codeine (*see* p. 215).

Derivatives of Morphine

Apomorphine, $C_{17}H_{17}O_2N$. When morphine or its hydrochloride is heated in sealed tubes with strong hydrochloric acid at 140°, apomorphine hydrochloride is formed by the loss of a molecule of water from the parent alkaloid.[3] This change has also been asserted to occur spontaneously in certain salts of morphine after exposure to light for considerable periods and in solutions of morphine hydrochloride, but no conclusive evidence on this point has been adduced. Apomorphine is separated from any unchanged morphine by adding excess of sodium bicarbonate to the mixture and extracting with ether or chloroform. From the latter it may be crystallised in the absence of oxygen or it may be isolated as the hydrochloride by shaking with a little hydrochloric acid.

Apomorphine forms colourless prisms from ether with 1 mol. of solvent, but is usually seen as an amorphous white substance which becomes green on exposure to air, a change which occurs even more readily in solution, especially in presence of potassium hydrogen carbonate. Unlike morphine it is readily soluble in chloroform or ether, and the alkaloid which has become green by exposure to air forms a bluish-red solution in ether and gives a violet solution in chloroform. The alkaloid is not coloured by sulphuric acid, gives a crimson tint with nitric acid and a rose-red changing to violet and black with ferric chloride. These reactions serve to distinguish it from morphine. The hydrochloride, B.HCl, is the salt generally used in medicine ; it forms minute crystals, which become greenish

[1] *Trans. Chem. Soc.* 1900, **77**, 1024 ; 1901, **79**, 563 ; Lees, 1907, **91**, 1408.
[2] *Berichte*, 1907, **40**, 4889.
[3] Matthiessen and Wright, *Annalen*, 1870, *Suppl.* **7**, 170, 177.

in light and air. It is soluble in water (1 in 39·5 at 25°) or alcohol (1 in 38·2 at 25°), less so in ether (1 in 1864 at 25°), and is neutral to litmus. The taste is slightly bitter. When a solution of 1 part of the hydrochloride in 10,000 of water is shaken with chloroform and then sodium hydroxide, the chloroform is coloured blue and the aqueous layer reddish violet. When 0·05 grm. of the hydrochloride is shaken with 0·5 per cent. ferrous sulphate solution, the latter becomes blue and then black, the blue colour being restored by alcohol. According to Pschorr, Jaeckel, and Fecht,[1] apomorphine contains two hydroxyl groups and the nitrogen is tertiary (for constitution, *see* pp. 223, 226). On methylation apomorphine yields apo-ψ-codeine (*see* p. 216).

Apomorphine in physiological action differs markedly from morphine, being a powerful emetic in doses of 0·001 to 0·01 grm.

Pseudomorphine (*Oxydimorphine, dehydromorphine*), $C_{34}H_{36}O_6N_2.3H_2O$. This alkaloid was isolated from opium by Pelletier in 1835 and was subsequently obtained pure by Hesse.[2] The formation of a similar substance by the action of various mild oxidising agents on morphine was observed by Schützenberger and by Polstorff [3] among others. It occurs with morphine and codeine hydrochlorides separated from opium as described above (p. 207), and is isolated by precipitation of the morphine with ammonia in alcoholic solution; on distilling the alcohol from the filtrate and replacing it by water, the addition of ammonia causes the separation of pseudomorphine, which is purified by crystallisation from hot ammonia solution. It forms crusts or silky needles, is insoluble in water or organic solvents, but dissolves in warm aqueous or alcoholic ammonia or in aqueous alkali hydroxide solutions. The hydrochloride has the composition $B.2HCl.2H_2O$, or $4H_2O$ or $6H_2O$, $[\alpha]_D$ — 103·13° (anhydrous salt). Pseudomorphine mixed with sucrose dissolves in sulphuric acid, forming a dark green solution changing to brown. The alkaloid is tasteless and physiologically inactive.

[1] *Berichte*, 1902, **35**, 4377.
[2] *Annalen*, 1867, **141**, 87; 1884, **222**, 234.
[3] *Berichte*, 1880, **13**, 86.

Codeine, $C_{18}H_{21}O_3N$. This alkaloid was isolated from opium by Robiquet in 1832.[1] It occurs in opium to the extent of 0·1 to 3 per cent., and may be prepared therefrom by the process already described (p. 209). It is a methyl ether of morphine, and may be obtained from the latter by methylation—for example, by the action of potassium methyl sulphate on morphine dissolved in methyl alcohol in presence of potassium hydroxide,[2] or by the action of dimethyl sulphate on alkali or alkaline earth derivatives of morphine. The solvent is distilled from the reaction mixture, water added, any unchanged morphine precipitated with ammonia and the codeine extracted with benzene. Its estimation in opium is described on p. 206.

Properties. Codeine crystallises with $1H_2O$ from water in large translucent orthorhombic prisms, m.p. 155° (*dry*), $[\alpha]_D$ — 137·7° in alcohol or — 111·5° in chloroform, and is generally seen in this form, but it separates from dry ether in small anhydrous crystals. Its taste is slightly bitter. Codeine is moderately soluble in water (1 in 120 at 25°, 1 in 59 at 80°), more so in ether (1 in 12·5 at 25°), and readily so in alcohol (1 in 1·6 at 25°, 1 in 0·92 at 60°) or chloroform (1 in 0·66 at 25°); it is moderately soluble in ammonia solution (1 in 68 at 15·5°). It differs from morphine in being fairly soluble in anisole (1 in 6·5 at 16°) or cold benzene (1 in 10·4), and in being sparingly soluble in aqueous solutions of alkali hydroxides.

Codeine is a strong monoacidic base forming salts, which are neutral to litmus or methyl orange. The free base and also the sulphate and phosphate are used in medicine. The hydrochloride, $B.HCl.2H_2O$, forms short needles soluble in water (1 in 26 at 15°), $[\alpha]_D^{22·5}$ — 108·2° in water: the salt effloresces in air and loses its water completely and readily at 120°. The sulphate, $B_2.H_2SO_4.5H_2O$, forms rhombic prisms, m.p. 278° (*decomp.*), $[\alpha]_D^{15}$ — 101·2° in water, which readily lose $2H_2O$ on exposure to air, and are completely dehydrated at 100°. It is soluble in water (1 in 30 at 25°), sparingly so in alcohol (1 in 1035 at 25°), insoluble in ether. The phosphate, $B.H_3PO_4$, 1, $1\frac{1}{2}$, or $2H_2O$, forms needle-

[1] *Annalen*, 1832, **5**, 106. [2] Knoll, *D.R.P.* 39,887.

shaped crystals, m.p. 235° (*decomp.*), and is soluble in water (1 in 2·25 at 25°), less so in alcohol (1 in 261 at 25°).

Detection. Codeine is distinguished from morphine by the differences in solubility recorded above and by the facts that it gives no coloration with ferric chloride solution, a yellow, not a reddish, solution with nitric acid, and a blue, not a brown, tint when warmed with sulphuric acid. Sulphuric acid containing a trace of selenious acid gives a green coloration, changing to blue and back again to green.

Isomerides of Codeine. Codeine yields three isomerides, *iso*codeine, β-*iso*codeine (*allo*-ψ-codeine of Knorr and Hörlein), and neo*iso*codeine (ψ-codeine of Knorr and Hörlein), which are formed from chlorocodeide or bromocodeide in a manner strictly analogous with the corresponding isomerides of morphine, from which they are also formed by methylation. The relationship between these six substances is shown by the following scheme :

β-*iso*Morphine	←	Bromomorphide	→	*iso*Morphine
↓		↓		↓
β-*iso*Codeine	←	Bromocodeide	→	*iso*Codeine
β-*iso*Morphine	←	Chloromorphide	→	neo*iso*Morphine
↓		↓		↓
β-*iso*Codeine	←	Chlorocodeide	→	neo*iso*Codeine

The horizontal arrows point to products of hydrolysis, and the vertical arrows to products of methylation. The chief papers relating to this subject are by Vongerichten,[1] Schryver and Lees,[2] Lees,[3] Knorr and Hörlein,[4] Oppe,[5] and Pschorr and Dickhäuser.[6] An isomeride of codeine was first obtained by Merck,[7] and named pseudocodeine. This is the base now known as neo*iso*codeine.

[1] *Annalen*, 1881, **210**, 107 ; *Berichte*, 1903, **36**, 159.
[2] *Trans. Chem. Soc.* 1900, **77**, 1024 ; 1901, **79**, 563.
[3] *Ibid.* 1907, **91**, 1408.
[4] *Berichte*, 1906, **39**, 4409 ; 1907, **40**, 376, 2032, 3844, 4883, 4889 1908, **41**, 969 ; *Annalen*, 1909, **368**, 305.
[5] *Berichte*, 1908, **41**, 975. [6] *Ibid.* 1912, **45**, 1567, 1570.
[7] *Arch. Pharm.* 1891, **229**, 161.

Derivatives of Codeine

Apocodeine, $C_{18}H_{19}O_2N$. This substance was obtained by Matthiessen and Burnside [1] as a gummy mass, by the action of zinc chloride solution on codeine hydrochloride, and was subsequently prepared by Merck [2] and by Göhlich.[3] According to Dott [4] it is a mixture of chlorocodeide, apomorphine, amorphous bases, and codeine.[5]

Apo-ψ-codeine, $C_{18}H_{19}O_2N$, was obtained by Knorr and Hörlein by heating codeine or ψ-codeine with oxalic acid.[6] It crystallises from alcohol in brilliant plates with 1 mol. of alcohol, m.p. 100°–110° (*decomp.*), $[\alpha]_D^{15}$ — 90° in alcohol. It may also be prepared by methylating apomorphine and stands in the same relation to this substance as codeine does to morphine.[7]

Hydroxycodeine, $C_{18}H_{21}O_4N$ (*Neopine*). This alkaloid was discovered by T. and H. Smith in the final mother liquors obtained in the extraction of opium alkaloids, and has been examined by Dobbie and Lauder.[8] It is amorphous and readily soluble in water, alcohol, ether, chloroform, or benzene. The salts crystallise well, the hydrobromide being sparingly soluble in water, from which it separates in hard prismatic crystals, $[\alpha]_D^{20}$ + 17·2° in water. The alkaloid contains one methoxyl group and behaves as a tertiary base with methyl iodide. It gives colour reactions and an absorption spectrum similar to those of codeine, so that it is probably closely related in constitution to that alkaloid. It is not identical with Ach and Knorr's hydroxycodeine (*see* p. 224).

Constitution of Morphine and Codeine

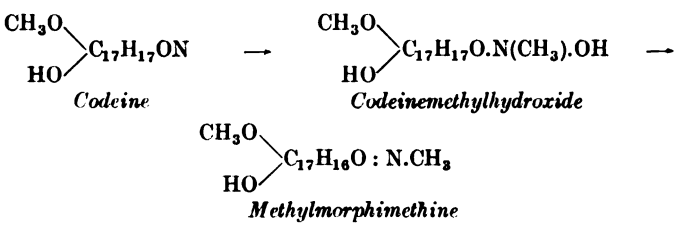
Of the three oxygen atoms in morphine, two are present as hydroxyl groups, since the alkaloid readily furnishes a crystalline

[1] *Annalen*, 1871, **158**, 131. [2] *Arch. Pharm.* 1891, **229**, 161.
[3] *Ibid.* 1893, **231**, 235.
[4] *Pharm. Journ.* 1891 [iii], **21**, 878, 916, 955, 996.
[5] *Cf.* Knorr and Hörlein, *Berichte*, 1907, **40**, 3356. [6] *Loc. cit.*
[7] Knorr and Raabe, *ibid.* 1908, **41**, 3050.
[8] *Trans. Chem. Soc.* 1911, **99**, 34.

diacetyl derivative, m.p. 169°, which has been introduced into medicine as a hypnotic under the name HEROINE. One of these hydroxyl groups is phenolic, since morphine readily yields metallic derivatives with the alkali metals, and is soluble in aqueous solutions of alkali-hydroxides.

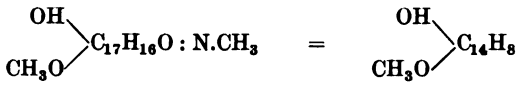
The relationship of morphine to codeine is established by the facts that morphine on methylation (*see* p. 214) yields codeine, and that the latter is insoluble in aqueous alkali hydroxide solutions. Codeine must therefore be formed by the conversion of the phenolic hydroxyl group of morphine into a methoxyl group, so that it is a methyl ether of morphine. A number of homologous morphine ethers have been prepared, and of these *ethylmorphine*, m.p. 123°–125°, has been introduced into medicine under the name DIONINE. The third oxygen atom in morphine and codeine is probably present as a constituent of a heterocyclic nucleus.

Action of Methyl Iodide. Codeine with methyl iodide yields codeinemethiodide, and this when warmed with alkalis furnishes codeinemethylhydroxide, which, under the conditions of the experiment, immediately decomposes, forming a tertiary base formerly named methocodeine, but now known as α-methylmorphimethine, $C_{19}H_{23}O_3N$. The reactions of this substance and of its isomerides [1] have thrown considerable light on the constitution of the parent alkaloids. It crystallises from alcohol or ether in prisms, m.p. 118·5°, $[\alpha]_D$ — 208·6° in alcohol, and dissolves in strong sulphuric acid with a characteristic violet colour, which on warming changes to blue. With acetic anhydride it gives a monoacetyl derivative. The formation of methylmorphimethine from codeine may be represented as follows :



[1] *Berichte*, 1906, **39**, 19, 4412 ; *Trans. Chem. Soc.* 1901, **79**, 577.

When *α*-methylmorphimethine is warmed with hydrochloric acid or acetic anhydride it is partially converted into its isomeride, *β*-methylmorphimethine, an oily, dextrorotatory substance. In addition to producing this isomeric change these reagents decompose a portion of the base into two new substances, one basic, the other neutral : [1]



Methylmorphimethine *Methylmorphol*

$$+ C_4H_{11}ON \quad [= CH_2OH.CH_2.N(CH_3)_2]$$

Hydroxyethyldimethylamine

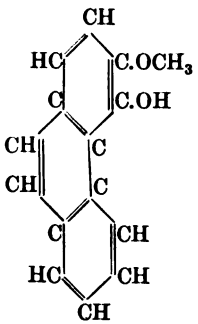
When acetic anhydride is used the methylmorphol is converted by the further action of the reagent into acetylmethylmorphol, whilst when hydrochloric acid is employed methylmorphol, $C_{14}H_8(OCH_3)OH$, or morphol, $C_{14}H_8(OH)_2$, is produced depending on the temperature of the reaction. Morphol on distillation with zinc dust is converted into phenanthrene, whilst on oxidation with chromic acid it furnishes morpholquinone, which, according to Vongerichten,[2] is 3 : 4-dihydroxyphenanthraquinone.

The positions of the hydroxyl groups in morphol are determined from the observation that by the further oxidation of morpholquinone only phthalic acid is produced, showing that the two hydroxyl groups are attached to the same benzene nucleus. Further, since morpholquinone is a mordant dyestuff it is probable that the two hydroxyl groups are in the *ortho* position to each other in this substance and, therefore, also in morphol, whilst Barth and Wiedel's observation that protocatechuic acid is formed by the action of fused potash on morphine also supports this view. From these and other considerations Vongerichten was led to assign the following formulæ to morphol and its allies : [3]

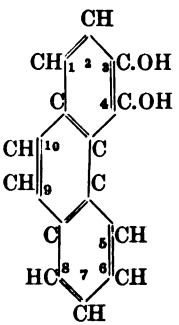
[1] Fischer and Vongerichten, *Berichte*, 1886, **19**, 792 ; Knorr, *ibid.* 1889, **22**, 185, 1113 ; 1894, **27**, 1148 ; 1904, **37**, 3494.

[2] *Ibid.* 1898, **31**, 2924 ; 1899, **32**, 1521.

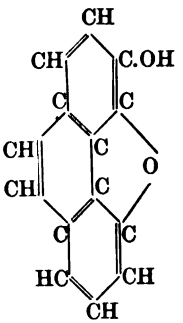
[3] *Ibid.* 1897, **30**, 2439 ; 1898, **31**, 3198 ; 1899, **32**, 1521 ; 1900, **33**, 352.



Methylmorphol

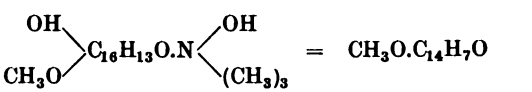


Morphol



Morphenol

The validity of these formulæ has been confirmed by Pschorr and Sumuleana by the synthesis of 3 : 4-dimethoxyphenanthrene,[1] which Vongerichten[2] has shown to be identical with dimethylmorphol prepared from acetylmethylmorphol by the action of sodium methoxide followed by that of methyl iodide. When either *α*-methylmorphimethine methylhydroxide or its *β*-isomeride, obtained by the action of alkalis on the respective methiodides, is heated, a somewhat different decomposition ensues, which may be represented by the following equation :[3]



Methylmorphimethine methylhydroxide *Methylmorphenol*

$$+ N(CH_3)_3 \quad + \quad C_2H_4 \quad + \quad 2H_2O$$

Trimethylamine *Ethylene* *Water*

Methylmorphol yields a bromo derivative, which on treatment with hydriodic acid gives methyl iodide, the bromine atom being at the same time eliminated with the formation of morphenol, thus :

$$C_{14}H_8BrO.OCH_3 \quad \longrightarrow \quad C_{14}H_7O.OH$$

Bromomethylmorphol *Morphenol*

[1] *Berichte*, 1900, **33**, 1810. [2] *Ibid.* p. 1824.

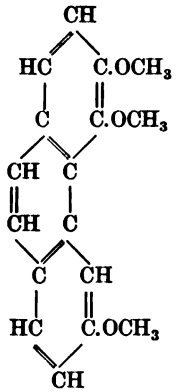
[3] Vongerichten, *ibid.* 1896, **29**, 67.

Morphenol may also be obtained directly from β-methylmorphimethine by the action of alcoholic potash at 160°.[1] Morphenol is reduced by heating with zinc dust to phenanthrene, and by sodium amalgam to morphol by the addition of two atoms of hydrogen. In view of these facts morphenol must be represented by the formula already given, p. 219.[2]

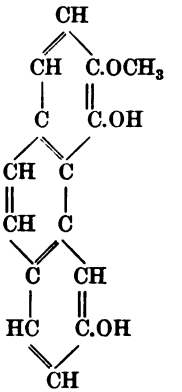
In methylmorphenol and methylmorphol, the methyl ethers of morphenol and morphol respectively, the methoxy group occupies the same position as in codeine and, therefore, the same position as the phenolic hydroxyl in morphine. This position is fixed by Pschorr and Vogtherr's synthesis of 3-methoxy-4-acetoxyphenanthraquinone,[3] which proved to be identical with the acetylmethylmorpholquinone that Vongerichten obtained by the oxidation of acetylmethylmorphol.[4] The methoxy group in codeine and the phenolic hydroxyl group in morphine, therefore, occupy position 3 in the phenanthrene nucleus as shown in the formula for methylmorphol (p. 219). The position of the alcoholic hydroxyl group of morphine and codeine was determined in the following way:

When codeine is oxidised by permanganate in acetone solution, or with chromic and sulphuric acids, codeinone, $C_{18}H_{19}O_3N$, m.p. 185°–186°, $[\alpha]_D^{15} - 205°$ in alcohol, is formed.[5] This, on treatment with acetic anhydride, yields a diacetoxymethoxyphenanthrene, which on replacement of the two acetyl groups by methyl groups gives methylthebaol,[6] a substance already synthesised by Pschorr, Seydel, and Stöhrer,[7] and shown to have formula I, whence formula II must represent the dihydroxymethoxyphenanthrene (hydroxymethylmorphol) first formed from codeinone in this reaction.

[1] Vongerichten, *Berichte*, 1896, **29**, 67; 1897, **30**, 2441; 1901, **34**, 2722.
[2] Vongerichten, *ibid.* 1900, **33**, 352.
[3] *Ibid.* 1902, **35**, 4412. [4] *Ibid.* 1898, **31**, 52.
[5] Ach and Knorr, *ibid.* 1903, **36**, 3067.
[6] Knorr, *ibid.* 1903, **36**, 3074.
[7] *Ibid.* 1902, **35**, 4400.



(I.) *Methylthebaol* (Pschorr and co-workers)



(II.) *Hydroxymethylmorphol* (from codeinone)

It follows from these results that morphine and codeine are derivatives of 3 : 4 : 6-trihydroxyphenanthrene and that the oxygen atoms in 3 and 6 form the phenolic and alcoholic hydroxyl groups respectively of morphine, whilst that in 4 must be the " indifferent " oxygen of the alkaloid. All the evidence points to this indifferent oxygen being present in morphine as a " bridge " oxygen, forming a furane ring, as shown in the formula for morphenol (p. 219).

The Nitrogen Complex of Morphine and Codeine. The decomposition of methylmorphimethine was reinvestigated by Knorr [1] with a view to the determination of the exact nature of the basic decomposition product, with the results shown in the following equations :

(1) $HO(CH_3O)C_{16}H_{13}O.N(CH_3)_2$ (*Methylmorphimethine*) $+ HCl =$ $HO(CH_3O)C_{14}H_8$ (*Methylmorphol*) $+ C_2H_4Cl.N(CH_3)_2$ (*Chloroethyldimethylamine*) $+ H_2O$

(2) $HO(CH_3O)C_{16}H_{13}O.N(CH_3)_2$ (*Methylmorphimethine*) $+ C_2H_5ONa =$ $HO(CH_3O)C_{14}H_8$ (*Methylmorphol*) $+ C_2H_5O.CH_2.CH_2.N(CH_3)_2$ (*Dimethylaminoethyl ether*) $+ NaOH$

[1] *Berichte*, 1904, **37**, 3494.

The chloroethyldimethylamine produced by the action of hydrogen chloride on the methine base is not actually obtained in the reaction, but, instead, a mixture of tetramethylethylenediamine, $(CH_3)_2N.CH_2.CH_2.N(CH_3)_2$, and hydroxyethyldimethylamine, $HO.CH_2.CH_2.N(CH_3)_2$, is formed, identical with that produced by the action of caustic soda on chloroethyldimethylamine itself.[1]

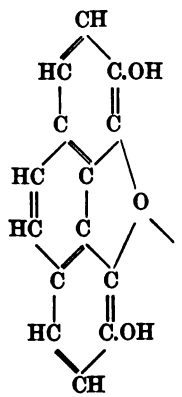
The dimethylaminoethyl ether formed by the action of sodium ethoxide on methylmorphimethine was synthesised by the action of dimethylamine on iodoethyl ether, so that its constitution is also certain.

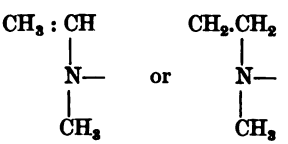
Similarly when codeinonemethiodide is heated with alcohol at 160°–165°, it yields the 3-methoxy-4 : 6-dihydroxyphenanthrene already mentioned (p. 221) and dimethylaminoethyl ether.

Knorr explains the formation of these substances by assuming the existence in the methine base and in codeinonemethiodide of a vinyldimethylamine complex, $CH_2 : CH.N(CH_3)_2$, which may combine with hydrogen chloride to give chloroethyldimethylamine, and with alcohol to form dimethylaminoethyl ether, thus :

$$CH_2 : CH.N(CH_3)_2 \begin{cases} + HCl = CH_2Cl.CH_2.N(CH_3)_2 \\ + C_2H_5OH = C_2H_5O.CH_2.CH_2.N(CH_3)_2 \end{cases}$$

It follows from the evidence thus obtained as to the nature of the basic and neutral decomposition products of methylmorphimethine that the morphine molecule must be built up from the following two complexes :[2]

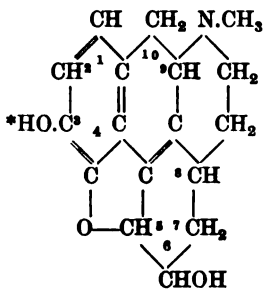




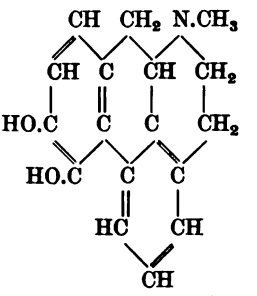
[1] *Berichte*, 1904, **37**, 3507. [2] Knorr and Pschorr, *Berichte*, 1905, **38**, 3176.

Knorr's first hypothesis that the basic portion is bound up to the phenanthrene nucleus by means of the "indifferent" oxygen proved untenable, especially in view of the observation of Knorr and Pschorr [1] that thebainone (*see* p. 231), which does not contain "indifferent" oxygen, under exhaustive methylation and treatment with acetic anhydride yields methylmorphol and hydroxyethyldimethylamine.

Pschorr's Formula. This was advanced by Pschorr, Jaeckel, and Fecht,[2] mainly as the result of an investigation of apomorphine, and received support from the further work of Pschorr and collaborators on this alkaloid.[3] They have shown especially that apomorphine contains two hydroxyl groups and a tertiary nitrogen atom, that on treatment with benzoyl chloride in the cold the hydroxyl groups are benzoylated, and that on warming with this reagent the nitrogen ring is opened and a benzoyl group is attached to the nitrogen. This tribenzoylapomorphine on oxidation yields tribenzoylapomorphinequinone, which contains all the original constituents, so that the nitrogen ring cannot be attached to the carbon atoms 9 and 10 in the phenanthrene nucleus. Further, exhaustive methylation of apomorphine gave eventually 3 : 4-dimethoxyvinylphenanthrene, which was converted into the corresponding 3 : 4 : 8-trimethoxyphenanthrene, indicating that the carbon end of the nitrogen chain is attached at position 8.



Morphine (Pschorr)



Apomorphine (Pschorr)

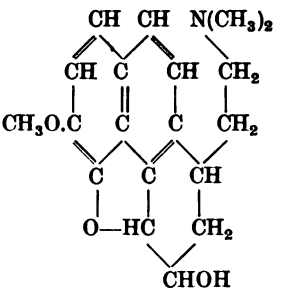
* This H is replaced by CH_3 in codeine.

[1] *Berichte*, 1905, **38**, 3173. *Cf.* Knorr, *ibid.* 1904, **37**, 3499.

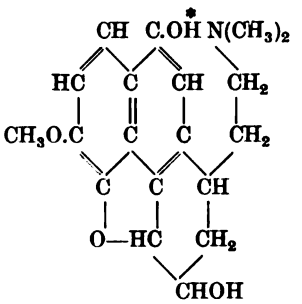
[2] *Ibid.* 1902, **35**, 4377.

[3] *Ibid.* 1906, **39**, 3124; 1907, **40**, 1984, 1995, 1998, 2004. *Cf.* however, *ibid.* 1912, **45**, 2212.

This formula necessitates the following expressions for methylmorphimethine (p. 217) and for hydroxymethylmorphimethine (ketodihydromethylmorphimethine) obtained by the action of alkali on the methiodides of morphine (or codeine) and hydroxycodeine [1] respectively :



Methylmorphimethine



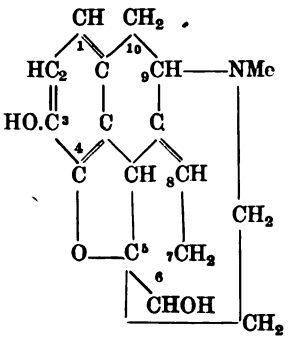
Hydroxymethylmorphimethine

Knorr and collaborators had shown [2] that in hydroxymethylmorphimethine the hydroxyl group marked * must be in position 9 or 10, and be present as an alcoholic hydroxyl, and the formula given above represents Pschorr and Einbeck's explanation of the fact that this substance may behave as a dihydroxy body or as a ketone by tautomeric change of the group —C.OH : CH— into —CO—CH_2—.[3]

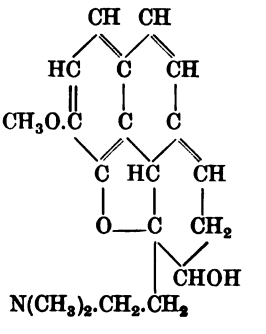
Knorr's Formula II. It will be seen that Pschorr's formula, discussed above, is based mainly on a consideration of the degradation products of apomorphine, and there is as yet no definite evidence that the change from morphine to apomorphine takes place in the simple manner which Pschorr assumed. Knorr's second formula was introduced by Knorr and Hörlein [4] to explain the fact that whilst codeinone (p. 220) under exhaustive methylation yields 3 : 4 : 6-trimethoxyphenanthrene, *pseudo*codeinone, obtained by the oxidation of *pseudo*codeine (neo*iso*codeine, p. 215), yields 3 : 4 : 8-trimethoxyphenanthrene. Both ketones, however, yield

[1] Ach and Knorr, *Berichte*, 1903, **36**, 3067.
[2] *Ibid.* 1906, **39**, 1414, 3252.
[3] *Ibid.* 1907, **40**, 1982. *Cf.* Knorr and Hörlein, *ibid.* p. 2042.
[4] *Ibid.* 1907, **40**, 3341.

the same desoxycodeine, $C_{18}H_{21}O_2N$,[1] so that they contain the same nuclear system and the change from codeine to *pseudo*codeine consists merely in the migration of the alcoholic hydroxyl in position 6 to position 8. This implies that in codeine and, therefore, in morphine position 8 is not occupied by a substituent group, thereby rendering Pschorr's morphine formula untenable. Of the remaining positions in the phenanthrene nucleus at which the nitrogen chain could be attached, 7 is unavailable, because the behaviour of codeinone indicates that the carbon atom at 7 is fully hydrogenised. This leaves only position 5 for its attachment, and accordingly Knorr has modified Pschorr's formula in the following way :



Morphine (Knorr)

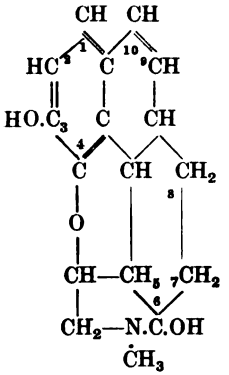


Methylmorphimethine (Knorr)

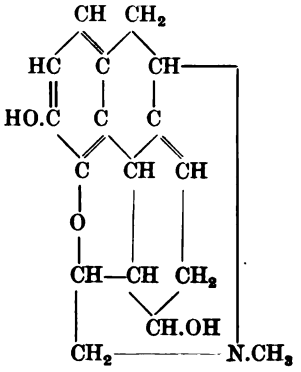
Other Formulæ. Of the other formulæ for morphine and codeine, Freund's, which differs from Knorr's only in having the nitrogen chain linked to atoms 5 and 8 instead of 5 and 9 in the phenanthrene nucleus, is negatived by evidence brought forward by Knorr and Hörlein in introducing their formula discussed above.

Bucherer[2] has suggested a formula which Knorr[3] thinks might be accepted with certain modifications (p. 226). In this the hydroxyl group at 3 becomes methoxyl in codeine ; and in thebaine methoxyls replace the hydroxyls at 3 and 6, and an ethylenic linking is formed between 8 and the contiguous bridge atom.

[1] *Berichte*, 1907, **40**, 376, 3860. [2] *J. prakt. Chem.* 1907 [ii], **76**, 428.
[3] *Berichte*, 1907, **40**, 4891.

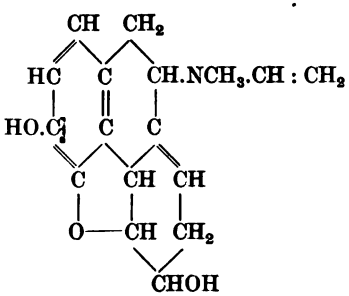


Morphine (Bucherer)



Morphine (Bucherer-Knorr)

Wieland and Kappelmeier[1] have also suggested a formula, which has much in its favour :



Morphine (Wieland and Kappelmeier)

In the formation of apomorphine these authors assume that ring formation takes place by the aid of the vinyl group.

Thebaine, $C_{19}H_{21}O_3N$. This base was first obtained by Thiboumery,[2] who regarded it as isomeric with morphine and named it "paramorphine," and was subsequently examined by Kane,[3] who first called it thebaine, and by Anderson,[4] who assigned to it the formula given above. It occurs in opium to the extent of 0·1 to 1 per cent.

The alkaloid remains in the mother liquor left after the removal

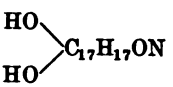
[1] *Annalen*, 1911, **382**, 306.
[2] *Ibid.* 1835, **16**, 38.
[3] *Ibid.* 1836, **19**, 9.
[4] *Ibid.* 1853, **86**, 184.

of the hydrochlorides of morphine and codeine in Gregory's process, and Hesse's method of preparing it from this source has been described already (p. 208). The acid tartrate thus obtained is crystallised from hot water, and the alkaloid regenerated from it is recrystallised from dilute alcohol.

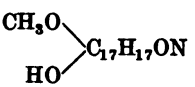
Thebaine crystallises in leaflets from dilute alcohol or in prisms from dry alcohol, m.p. 193°, $[\alpha]_D^{15} - 218{\cdot}6°$ in alcohol. It is readily soluble in alcohol, chloroform, or benzene, less so in ether, and almost insoluble in cold water, but sparingly so in ammonia or milk of lime. Thebaine behaves as a monoacidic base. The hydrochloride, $B.HCl.H_2O$, forms large rhombic prisms, $[\alpha]_j - (168{\cdot}32° - 2{\cdot}33\,c.)$, soluble in 15·8 parts of water at 10°. The salicylate is sparingly soluble in water, and is made use of for the separation of thebaine from other opium alkaloids in Plugge's process.[1]

Thebaine gives a blood-red coloration with sulphuric acid, which turns orange-yellow and eventually olive-green on warming.[2]

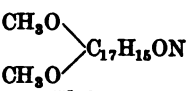
Constitution. The first investigation into the constitution of thebaine was made by Roser and Howard,[3] who showed that it behaved as a tertiary base, contained two methoxyl groups, and was probably related to morphine and codeine as shown by the following slightly extended formulæ:



Morphine



Codeine



Thebaine

and in accordance with this view it has been found that the principal decompositions of thebaine are similar to those that take place with morphine and codeine.

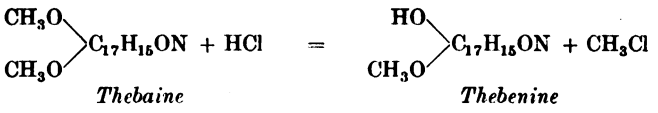
When thebaine is warmed with dilute hydrochloric acid it is hydrolysed into thebenine, $C_{18}H_{19}O_3N$, and methyl chloride.[4]

[1] *Rec. trav. chim.* 1887, **6**, 157.

[2] For other colour reactions of thebaine, *see* Reichard, *Pharm. Centr.-Halle*, 1906, **47**, 623; *Abstr. Chem. Soc.* 1906, ii, 909.

[3] *Berichte*, 1886, **19**, 1596.

[4] Freund, *ibid.* 1897, **30**, 1375. *Cf.* Pschorr and Massaciu, *ibid.* 1904, **37**, 2780.

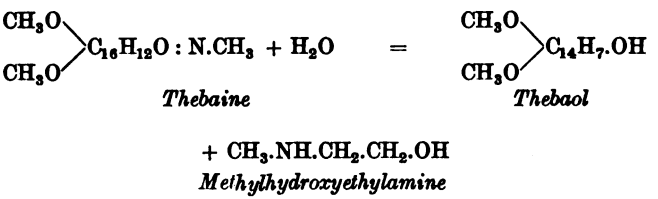


Thebaine *Thebenine*

The latter with methyl iodide forms thebeninemethinemethiodide, $C_{17}H_{15}O_3N(CH_3)_3I$, and is, therefore, a secondary base. When thebaine is warmed with concentrated hydrochloric acid, morphothebaine, an isomeride of thebenine is formed, also by the loss of methyl chloride.[1]

When hydrochloric acid reacts with thebaine in methyl alcohol the alkaloid is converted into an isomeride, methebenine. The latter differs from thebaine in reacting with alkyl iodides as a secondary base; thus with methyl iodide it furnishes methebeninemethinemethiodide, $(CH_3O)_2C_{16}H_{11}O.N(CH_3)_3I$. By the action of hydrochloric acid on thebaine dissolved in ethyl or propyl alcohol, ethebenine and prothebenine have also been prepared.[2]

When thebaine is warmed with acetic anhydride a decomposition similar to that occurring with methylmorphimethine takes place (p. 218), the products of the reaction being the acetyl derivative of a phenol, thebaol, and the diacetyl derivative of methylhydroxyethylamine.[3] The reaction may be represented by the following equation:



Thebaine *Thebaol*

Methylhydroxyethylamine

When distilled with zinc dust thebaol furnishes phenanthrene. It contains two methoxyl groups, and acetylthebaol is oxidised by chromic acid to the acetyl derivative of thebaolquinone, $(CH_3O)_2.C_{14}H_{15}O_2.OH$, and the latter in turn is oxidised by potassium permanganate to *o*-methoxyphthalic acid, indicating that the two

[1] Freund, *Berichte*, 1899, **32**, 168. [2] *Loc. cit.*

[3] Freund, *ibid.* 1897, **30**, 1364. *Cf.* Knorr, *ibid.* 1904, **37**, 3499, and Pschorr and Haas, *ibid.* 1906, **39**, 16.

methoxyl groups of thebaol, and, therefore, those of thebaine, are not attached to the same ring of the phenanthrene nucleus.

Further evidence of the close connection of thebaine to morphine and codeine was afforded by Knorr's observation that codeinone (p. 220) behaves like thebaine with hydrochloric acid, yielding thebenine when heated with the dilute acid and morphothebaine when warmed with the concentrated acid at 100°. Further, when codeinone is boiled with acetic anhydride it yields (1) methylhydroxyethylamine, identical with that given by thebaine, and (2) a diacetoxymethoxyphenanthrene, which on replacement of its two acetyl groups by methyl groups gives methylthebaol (*see* p. 220). The close relationship thus established between thebaine and codeinone [1] may be seen from the following scheme :

Action of Hot Dilute Hydrochloric Acid

Codeinone, $C_{18}H_{19}O_3N$ → Thebenine, $C_{18}H_{19}O_3N$

Thebaine, $C_{19}H_{21}O_3N$ → Thebenine, $C_{18}H_{19}O_3N$, and methyl chloride

Action of Fuming Hydrochloric Acid at 100°

Codeinone, $C_{18}H_{19}O_3N$ → Morphothebaine, $C_{18}H_{19}O_3N$

Thebaine, $C_{19}H_{21}O_3N$ → Morphothebaine, $C_{18}H_{19}O_3N$, and methyl chloride

Action of Acetic Anhydride

$$\underset{\textit{Codeinone}}{C_{18}H_{19}O_3N} + H_2O = CH_3O.C_{14}H_7(OH)_2 + CH_3.NH.CH_2.CH_2.OH$$

$$\underset{\textit{Thebaine}}{C_{19}H_{21}O_3N} + H_2O = \underset{\textit{Thebaol}}{(CH_3O)_2.C_{14}H_7.OH} + \underset{\textit{Methylhydroxyethylamine}}{CH_3.NH.CH_2.CH_2.OH}$$

As already stated, thebaol has been synthesised by Pschorr, Seydel, and Stöhrer,[2] and shown to be 3 : 6-dimethoxy-4-hydroxyphenanthrene.

Knorr has pointed out [3] that thebaine must be the methyl ether of the enolic form of codeinone, and has shown that thebaine

[1] *Cf.* Freund, *Berichte*, 1906, **39**, 844.
[2] *Ibid.* 1902, **35**, 4400. [3] *Ibid.* 1903, **36**, 3074.

when hydrolysed by boiling for a few minutes with *N*-sulphuric acid yields codeinone.[1] The formula to be assigned to thebaine depends, therefore, on that adopted for codeinone and consequently on that adopted for morphine.

In view of this close relationship of thebaine to morphine and codeine it is possible to deduce a formula for thebaine from each of the expressions that have been put forward to represent morphine (*see* p. 223).

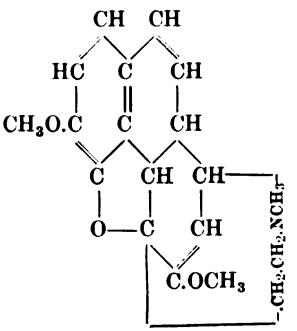
Freund's thebaine formula was advanced mainly to explain the behaviour of this alkaloid with the Grignard reagent, and to account for the production of pyrene when thebenine is distilled with zinc dust.[2]

It has been criticised by Knorr,[3] on the ground that the carbon atoms at positions 9 and 10 should be fully hydrogenised to account for the introduction of an —OH group at one of these points in the formation of hydroxycodeine from codeine.

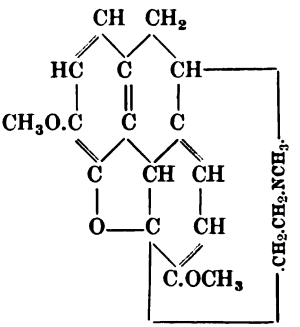
Pschorr's formula for thebaine [4] is derived from his morphine formula and gives a satisfactory explanation of the formation of a ketone, thebainone, from thebaine by reduction and also makes morphothebaine strictly analogous with apomorphine in structure.[5]

Knorr's objection to Pschorr's morphine formula (p. 224) applies equally to this author's formula for thebaine.

These various formulæ are as follows :

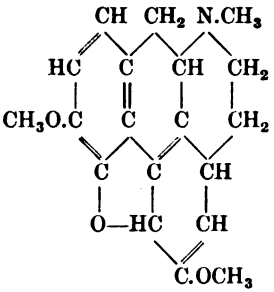


Thebaine (Freund)

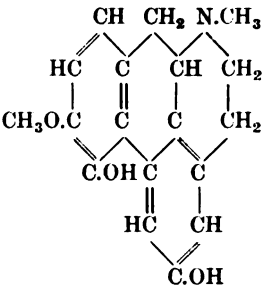


Thebaine (Knorr)

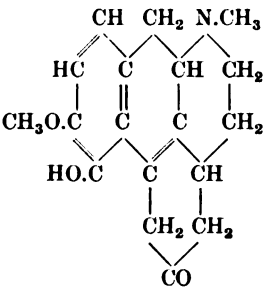
[1] *Berichte*, 1906, **39**, 1409. [2] *Ibid.* 1905, **38**, 3238 ; 1910, **43**, 2128.
[3] *Ibid.* 1906, **39**, 3252. [4] *Ibid.* 1905, **38**, 3153, 3160.
[5] *Ibid.* 1907, **40**, 2004 ; *Annalen*, 1910, **373**, 51.



Thebaine (Pschorr)



Morphothebaine (Pschorr)



Thebainone (Pschorr)

Pschorr has confirmed the constitution he assigned to morphothebaine by preparing from the alkaloid a tetramethyoxyphenanthrene by a process analogous with that described on p. 223, which proves to be identical with 3 : 4 : 6 : 8-tetramethoxyphenanthrene.[1]

A thebaine formula has also been put forward by Bucherer (p. 225).

Narcotine—Papaverine Group

Narcotine, $C_{22}H_{23}O_7N$. This alkaloid was obtained in an impure state by Derosne in 1803, but was first definitely isolated by Robiquet in 1817, who assigned to it the formula $C_{23}H_{25}O_7N$, which was changed by Matthiessen and Foster[2] to that now in use.

When opium is extracted with water to obtain morphine, &c., most of the narcotine remains in the insoluble residue, from which it may be obtained by extraction with dilute hydrochloric acid.

[1] Pschorr and Knöffler, *Annalen*, 1911, **382**, 50.

[2] *Ibid.* 1862, *Suppl.* **1**, 330 ; 1863, **2**, 377.

From the solution of narcotine hydrochloride so obtained, the alkaloid may be precipitated by sodium bicarbonate and recrystallised from boiling alcohol; narcotine may also be extracted from opium by boiling it with ether. For another method of obtaining it, *see* p. 207. The quantity present in opium varies from 1 to 9 per cent., being largest in Indian and Persian opiums.

Narcotine crystallises from alcohol in long colourless needles, m.p. 176°, $[\alpha]j$ — 207·35° in chloroform, + 47° in dilute hydrochloric acid; it is nearly insoluble in water, sparingly so in cold 85 per cent. alcohol (1 in 100) or ether (1 in 166 at 16°), readily in benzene; insoluble in cold alkalis or ammonia, but soluble in hot alkalis or "milk of lime." With acids it forms unstable salts that are dissociated by water, so that the alkaloid can often be extracted by indifferent solvents from its solutions in dilute acids. The salts are dextrorotatory, whilst narcotine itself is lævorotatory.

The alkaloid dissolves in sulphuric acid with a greenish colour, changing to red and reddish violet on warming. With sulphuric acid containing a trace of nitric acid a deep red colour is produced. According to Labat [1] a solution of narcotine in sulphuric acid gives, on warming with gallic acid, a deep blue coloration. This colour is due to the liberation of opianic acid and is also given by hydrastine.

Constitution. Narcotine is a weak, monoacidic, tertiary base. It reacts with methyl iodide, furnishing an oily methiodide, which is converted by silver chloride and caustic soda into narceine (*see* p. 241).[2]

Narcotine contains three methoxyl groups, and when heated in closed tubes with dilute hydrochloric acid furnishes the following series of demethylated derivatives: [3]

Dimethylnornarcotine, $C_{19}H_{14}O_4N.OH(OCH_3)_2$.
Methylnornarcotine, $C_{19}H_{14}O_4N(OH)_2.OCH_3$.
Nornarcotine, $C_{19}H_{14}O_4N(OH)_3$.

[1] *Bull. Soc. chim.* 1909 [iv], **5**, 742, 743.
[2] Freund and Frankforter, *Annalen*, 1893, **277**, 35, 48. *Cf.* Roser, *ibid.* 1888, **247**, 167.
[3] Matthiessen and Wright, *loc. cit.*

Hydrolysis of Narcotine. When the alkaloid is heated with water at 150° or boiled with dilute acids, it undergoes simple hydrolysis into a basic substance, *hydrocotarnine*, which also occurs free in opium, and *opianic acid*. Similar decompositions are induced by either acid oxidation or acid reduction, thus :

(1) Water and dilute acids furnish *opianic acid*, $C_{10}H_{10}O_5$, and hydrocotarnine, $C_{12}H_{15}O_3N$.

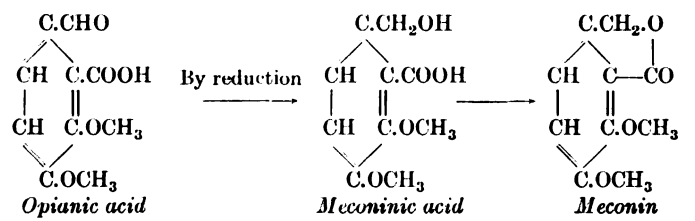
(2) Dilute nitric acid furnishes *opianic acid*, $C_{10}H_{10}O_5$, and *cotarnine*, $C_{12}H_{15}O_4N$.

(3) Nascent hydrogen gives *meconin*, $C_{10}H_{10}O_4$, and *hydrocotarnine*, $C_{12}H_{15}O_3N$.

The non-nitrogenous decomposition products, meconin and opianic acid, are closely related to each other.

Meconin, $C_{10}H_{10}O_4$, is a constant constituent of opium and was isolated therefrom in 1832 by Dublanc and has also been found in the root of *Hydrastis canadensis*. It crystallises from water in prisms, m.p. 102°, is soluble in most organic solvents, and dissolves in alkaline solutions, forming unstable salts of meconinic acid, $C_{10}H_{12}O_5$, of which it is the lactone and from which meconin is regenerated on addition of dilute mineral acids. It contains two methoxyl groups. The synthesis of meconin has been effected by Fritsch [1] from guaiacol as a starting-point.

Opianic acid, $C_{10}H_{10}O_5$, crystallises in prisms, m.p. 150°. Its constitution is clearly shown by the formation from it of protocatechuicaldehyde, carbon dioxide, and two molecular proportions of methyl chloride, when it is heated with hydriodic acid, and by its conversion into hemipinic acid on oxidation and into meconinic acid by reduction :



Opianic acid — *Meconinic acid* — *Meconin*

[1] *Annalen*, 1898, **301**, 351.

Hydrocotarnine, $C_{12}H_{15}O_3N.\frac{1}{2}H_2O$, the basic hydrolytic product of narcotine, also occurs in opium.[1] It crystallises from alcohol in monoclinic prisms, m.p. 55°–56°, and yields well-crystallised salts, of which the hydrobromide, $B.HBr.1\frac{1}{2}H_2O$, m.p. 236°–237°, is sparingly soluble in water. On oxidation hydrocotarnine is converted into cotarnine, and on reduction by sodium in alcohol it yields hydrohydrastinine (p. 280).

Cotarnine, $C_{12}H_{15}O_4N$. This base was first obtained by Wöhler[2] by the oxidation of narcotine with manganese dioxide in presence of sulphuric acid, but is more conveniently prepared by the action of dilute nitric acid on narcotine.[3] It crystallises from benzene in small needles, m.p. 132° (*decomp.*), is easily soluble in alcohol or ether, sparingly in cold water, and forms salts with mineral acids, losing at the same time a molecule of water; thus the hydrochloride has the composition $C_{12}H_{13}O_3N.HCl.2H_2O$, m.p. 197° (*decomp.*), and crystallises in pale yellow silky needles. This salt of cotarnine, under the name "stypticin," has come into use in medicine as an internal styptic. The phthalate is similarly used under the name "styptol." Cotarnine aurichloride forms golden-yellow plates, m.p. 136°–137°; the picrate crystallises in yellow needles, m.p. 143°.

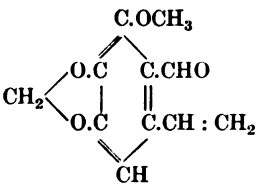
Cotarnine behaves as a secondary base and reacts with methyl iodide to form cotarnine hydriodide and cotarninemethinemethiodide, $C_{11}H_{11}O_4.N(CH_3)_3.I$. The latter when warmed with alkalis furnishes trimethylamine and *cotarnone*, $C_{11}H_{10}O_4$. This crystallises from alcohol in leaflets, m.p. 78°, and with hydroxylamine gives cotarnonoxime, m.p. 130°–132°. When cotarnone is oxidised with potassium permanganate a mixture of cotarnic acid, $C_{10}H_8O_7$, and cotarnlactone, $C_{11}H_{10}O_6$, is produced. The former crystallises in needles, melting and passing into the anhydride at 178°, and when heated with concentrated hydrochloric acid loses a molecule of carbon dioxide, forming the methylmethylene ether of gallic acid.

Cotarnlactone, $C_{11}H_{10}O_6$, brilliant leaflets, m.p. 154°, dissolves in

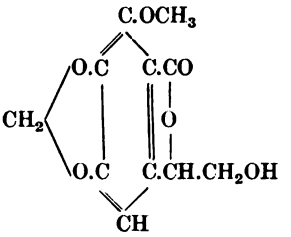
[1] Hesse, *Annalen*, 1871, *Suppl.* **8**, p. 326.
[2] *Annalen*, 1844, **50**, 19. [3] Anderson, *ibid.* 1853, **86**, 187.

alkaline liquids, forming salts of an unstable lactonic acid from which the lactone is readily regenerated. It furnishes cotarnic acid on further oxidation.

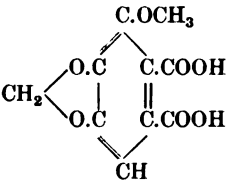
On the basis of these results Roser assigned the following formulæ to these non-nitrogenous products of the exhaustive methylation of cotarnine : [1]



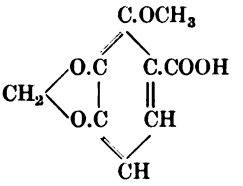
Cotarnone



Cotarnlactone

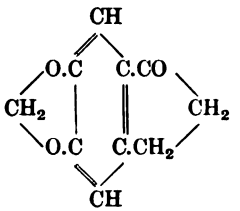


Cotarnic acid

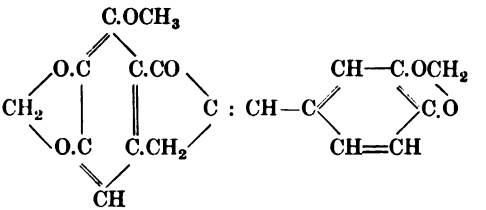


Methylmethylene ether of gallic acid

The formula for cotarnic acid has been confirmed by Perkin Robinson, and Thomas' synthesis of this acid [2] from 5 : 6-methylenedioxy-1-hydrindone (I) as a starting-point. This was nitrated, the nitro group reduced, replaced by hydroxyl, and the latter methylated. The 7-methoxy-5 : 6-methylenedioxy-1-hydrindone so produced was condensed with piperonal, and the product (II) obtained, oxidised with permanganate when it yielded cotarnic acid (III).



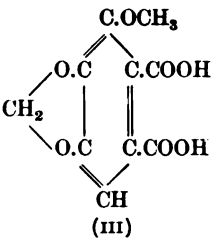
(I)



(II)

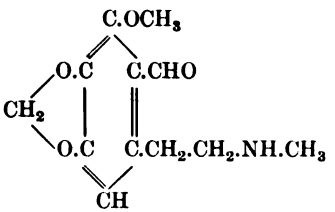
[1] *Annalen*, 1888, **249**, 141 : 1889, **254**, 341.

[2] *Trans. Chem. Soc.* 1909, **95**, 1977.

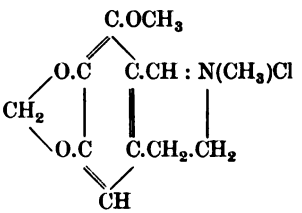


(III)

The formation of cotarnone from cotarninemethinemethiodide by the action of potash led Roser to the representation of cotarnine and its salts by the following formulæ,[1] the loss of a molecule of water in the formation of cotarnine salts being explained by the production of a reduced pyridine ring :



Cotarnine

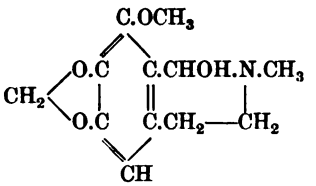


Cotarnine hydrochloride

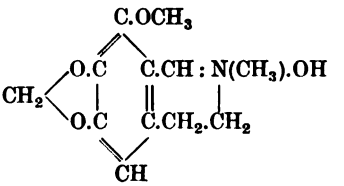
The positions of the methoxyl and dioxymethylene groups left unsettled by Roser were determined by Freund and Becker,[2] and their results were confirmed by the synthesis of cotarnic acid described above. Decker pointed out [3] that it was improbable that a secondary amine group and the aldehyde group —CHO could co-exist in the same molecule, and suggested that the reactions of cotarnine could be better accounted for by a dicyclic formula (p. 237). Hantzsch and Kalb,[4] in investigating the electrical conductivities of solutions of cotarnine, obtained results which indicated the existence in such solutions of an equilibrium mixture of two, or possibly three, substances,[5] one having Roser's formula, another Decker's formula, and a third having the formula of the ammonium

[1] *Annalen*, 1889, **254**, 334, 359 ; 1893, **272**, 221.
[2] *Berichte*, 1903, **36**, 1521. [3] *Journ. prakt. Chem.* 1893 [ii], **47**, 222.
[4] *Berichte*, 1899, **32**, 3109.
[5] *Cf.* Freund and Bamberg, *Berichte*, 1902, **35**, 1739.

base (*see below*) corresponding to that used by Roser for cotarnine salts. Dobbie, Lauder, and Tinkler[1] have shown by comparison of the ultra-violet absorption spectra of solutions of cotarnine that the solid alkaloid probably possesses the constitution assigned to it by Decker, whilst in solution in dissociating solvents such as water or alcohol it possesses, at least in part, the constitution assigned by Roser[2] to the salts.

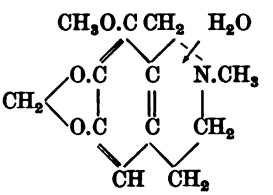


Cotarnine (Decker)
ψ-Cotarnine (Hantzsch and Kalb)

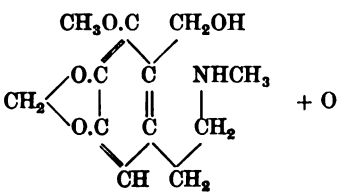


Cotarnine in dissociating solvents

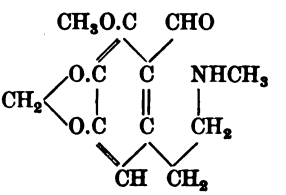
In assigning a formula to hydrocotarnine the chief point to be accounted for is the ready oxidation of this tertiary base to the secondary amine cotarnine. Roser assumed that in this reaction a partially reduced pyridine ring is opened, giving rise to the side-chain of cotarnine, thus :



Hydrocotarnine (Roser)



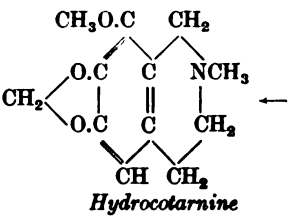
Intermediate product



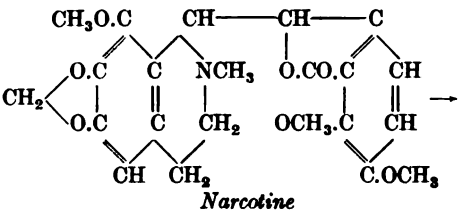
Cotarnine (Roser)

[1] *Journ. Chem. Soc.* 1903, **83**, 598. [2] *Loc. cit.*

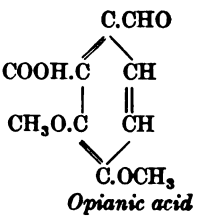
Utilising the formulæ assigned to the two products of hydrolysis of narcotine, viz. hydrocotarnine and opianic acid, Roser constructed the following formula for narcotine : [1]



Hydrocotarnine



Narcotine



Opianic acid

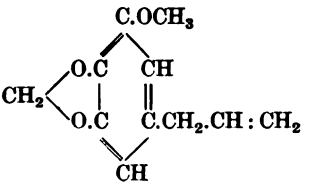
Roser's formula has been confirmed by Perkin and Robinson's synthesis of narcotine from meconin and cotarnine.[2]

A synthesis of narcotine was attempted by Liebermann,[3] who by condensing opianic acid and hydrocotarnine obtained *iso*-narcotine, distinguished from narcotine by its melting-point, 194° instead of 176°, and by the fact that it gives a red instead of a green coloration with sulphuric acid.

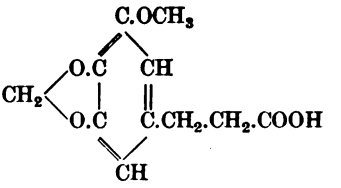
The synthesis of meconin by Fritsch has been referred to already. Cotarnine has been synthesised by Salway [4] from myristicin (i) as a starting-point. This was converted into β-3-methoxy-4:5-methylenedioxyphenylpropionic acid (ii), which was transformed into the amide, and the latter converted by means of Hofmann's reaction into β-3-methoxy-4 : 5-methylenedioxyphenylethylamine, and the phenylacetyl derivative (iii) of this was then condensed by heating it with phosphoric oxide in xylene solution. This gave rise to the two possible dihydro*iso*quinoline derivatives (iv) and (v).

[1] *Annalen*, 1888, **249**, 156 ; 1889, **254**, 334, 351 ; 1893, **272**. 221.
[2] *Trans. Chem. Soc.* 1911, **99**, 775. [3] *Berichte*, 1896, **29**, 180 ; 1904, **37**, 211.
[4] *Trans. Chem. Soc.* 1910, **97**, 1208.

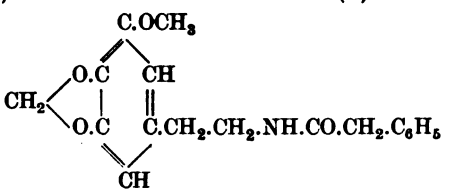
The first of these substances, 8-methoxy-6 : 7-methylenedioxy-1-benzyl-3 : 4-dihydro*iso*quinoline, on conversion into the methochloride and reduction with tin and hydrochloric acid gave 1-benzylhydrocotarnine, and this on oxidation with manganese dioxide and sulphuric acid yielded cotarnine (vi). The isomeride (v) on like treatment furnished an isomeride of cotarnine which was named *neo*cotarnine (vii).



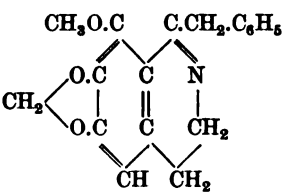
(i)



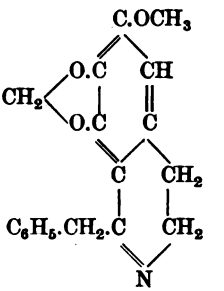
(ii)



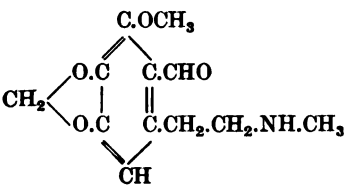
(iii)



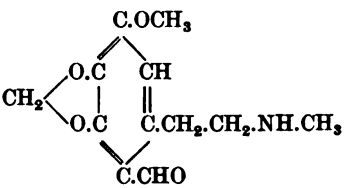
(iv)



(v)



(vi)
Cotarnine



(vii)
neo*Cotarnine*

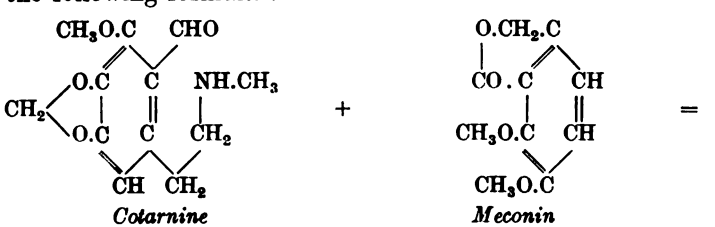
The syntheses of meconin and cotarnine having been effected, Perkin and Robinson completed this work by condensing these two substances in presence of potassium carbonate or by simply boiling them together in alcoholic solution.[1]

The product obtained proved to be the alkaloid GNOSCOPINE, an inactive isomeride of narcotine obtained from opium by T. and H. Smith,[2] who also showed that this substance is formed when narcotine is boiled in acetic acid solution, and that it gives the same colour reactions as narcotine, and like this alkaloid is oxidised to opianic acid and cotarnine. These observations on gnoscopine were extended by Rabe and MacMillan,[3] who found that on boiling narcotine in dilute acetic acid the alkaloid is racemised to gnoscopine, and the latter partly decomposed into *nor*narceine (*see* p. 244), cotarnine, and meconin. Perkin and Robinson deracemised their synthetic gnoscopine and also natural gnoscopine by crystallisation of the *d*- and *l*-bromocamphorsulphonates. The three isomerides thus obtained had the following characters: dl-*Narcotine* (*gnoscopine*), colourless needles, m.p. 229°; picrate, yellow prisms, m.p. 188°–189°; methiodide, $B.CH_3I.2H_2O$, magnificent prisms, m.p. 210°–212° (*dry*).

d-*Narcotine*. Colourless needles, m.p. 175°, $[\alpha]_D$ + 199·92° in chloroform.

l-*Narcotine* (natural narcotine). Colourless needles, m.p. 175°, $[\alpha]_D$ — 199·85° in chloroform.

The relationship of narcotine to *iso*narcotine (*see* p. 238) is shown by the following formulæ:[4]

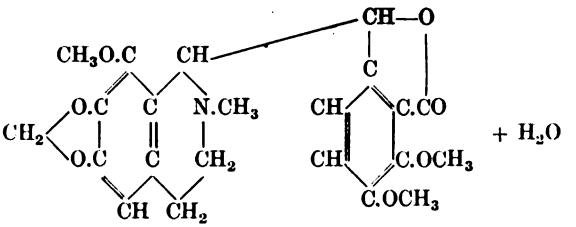


Cotarnine *Meconin*

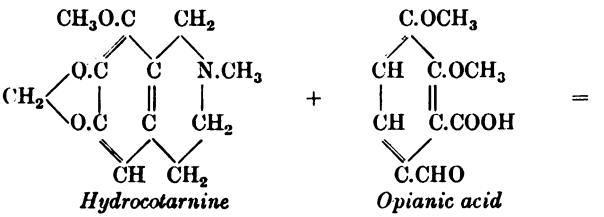
[1] *Loc. cit.* [2] *Pharm. Journ.* 1878 [iii], **9**, 82; 1893 [iii], **23**, 794.

[3] *Berichte*, 1907, **40**, 3280; *Annalen*, 1910, **377**, 223.

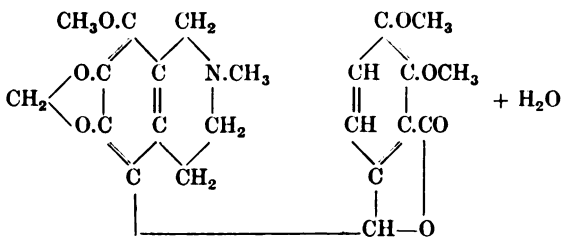
[4] Perkin and Robinson, *loc. cit.*, and Jones, Perkin, and Robinson, *Trans. Chem. Soc.* 1912, **101**, 258.



Narcotine



Hydrocotarnine *Opianic acid*



iso*Narcotine*

Narceine, $C_{23}H_{27}O_8N.H_2O$. This alkaloid was obtained by Pelletier in 1832, and was subsequently characterised by Courbe and by Anderson.[1] The latter assigned to it the formula $C_{23}H_{29}O_9N$, which was also found by Beckett and Wright and by Claus and Meixner. Freund,[2] however, observed that the base crystallised from water with three molecules of water, of which only two are lost at 100°; consequently the composition of the base examined by former workers was $C_{23}H_{27}O_8N.H_2O$.

Narceine remains dissolved in opium extract after the removal of morphine and codeine (p. 207), and the precipitation of narcotine, thebaine, and papaverine from the mother liquor by dilution and addition of ammonia: it is isolated by decolorising this brown liquid by lead acetate and removing the excess of lead by

[1] *Annalen*, 1853, **86**, 182. [2] *Ibid.* 1893, 277, 20.

sulphuretted hydrogen. The filtrate is made alkaline with ammonia and exposed in a warm place, when narceine gradually crystallises out and may be recrystallised from alcohol by addition of water. It forms slender needles or prisms, m.p. 170° or 140°–145° (*dry*), $[\alpha]_D$ 0°, slightly soluble in cold 80 per cent. alcohol (1 in 945 at 13°) or water (1 in 1285 at 13°), but much more soluble when warmed. It dissolves in alkaline liquids, including ammonia, forming metallic derivatives which crystallise from alcohol on addition of ether with 1 mol. of the solvent, the general formula being $C_{23}H_{26}O_8N.M.C_2H_5OH$, where M represents a monovalent metal.

Narceine behaves as a feeble monoacidic, tertiary base and yields well-crystallised salts. The hydrochloride, B.HCl, crystallises out when the alkaloid is dissolved in aqueous hydrochloric acid, and separates with $5\frac{1}{2}H_2O$ in the cold or with $3H_2O$ from hot solutions. If a methyl alcohol solution of hydrogen chloride is used the salt crystallises with 1 mol. of methyl alcohol, $B.HCl.CH_3OH$. The sulphate, $B.H_2SO_4.2H_2O$, forms slender needles.

Narceine gives a characteristic blood-red colour with chlorine water, followed by addition of ammonia. Weak iodine solution colours narceine blue. It dissolves in sulphuric acid with a brown colour, becoming blood-red on warming.

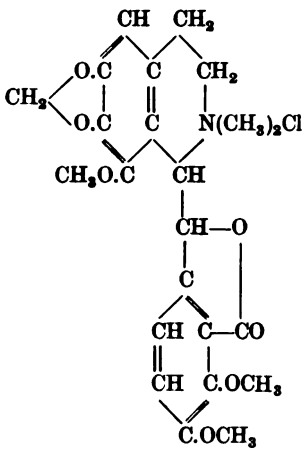
The alkaloid has been prepared synthetically[1] by heating narcotinemethochloride with caustic soda, when sodium chloride and narceine result according to the following equation:

$$\underset{\textit{Narcotinemethochloride}}{C_{22}H_{23}O_7N.CH_3Cl} + NaHO = \underset{\textit{Narceine}}{C_{23}H_{27}O_8N} + NaCl$$

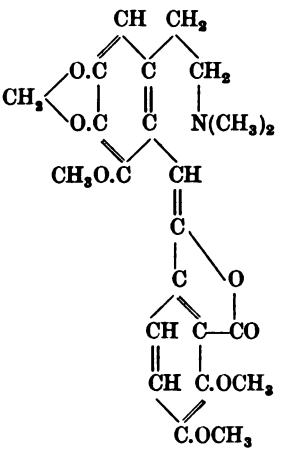
Narceine contains three methoxyl groups. It reacts with phenylhydrazine and hydroxylamine, furnishing a phenylhydrazone and an oxime. With alcohols in presence of hydrogen chloride it esterifies. From a study of these reactions, and in particular the partial synthesis of narceine from narcotine, Freund and Frankforter[1] have proposed to represent the alkaloid as related to narcotine in the

[1] Freund and Frankforter, *Annalen*, 1893, **277**, 31. *Cf.* Roser, *ibid.* 1888, **247**, 167.

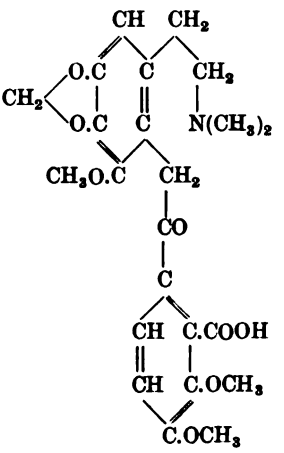
following way, and this has been confirmed by Freund and Oppenheimer's discovery [1] that narceine yields an oximino derivative, which on exhaustive methylation gives trimethylamine, hemipinic acid (3 : 4-dimethoxyphthalic acid), and 2-cyano-3-methoxy-4 : 5-methylenedioxy-1-vinylbenzene (cotarnonitrile), a substance first obtained by Roser from cotarnine.[2]



Narcotinemethochloride



Intermediate product

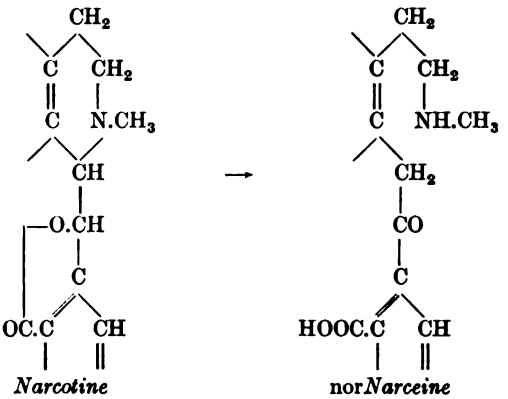


Narceine

It has been pointed out already that on heating in acetic acid

[1] *Berichte*, 1909, **42**, 1084. [2] *Annalen*, 1889, **254**, 338.

solution *l*-narcotine yields *dl*-narcotine (gnoscopine) and some *nor*-narceine. This latter change takes place in the following way :



Rabe has pointed out that this change is analogous with that of cinchonine into cinchonicine (p. 167).[1]

Oxynarcotine, $C_{22}H_{23}O_8N$. This alkaloid, which occurs in opium in minute quantities, was isolated by Beckett and Wright[2] from impure narceine. It crystallises from hot alcohol in small needles. Its close relationship to narcotine is shown by the formation from it of cotarnine, $C_{12}H_{15}O_4N$, and hemipinic acid, $C_{10}H_{10}O_6$, when it is oxidised by ferric chloride; narcotine under these circumstances furnishing cotarnine and opianic acid, $C_{10}H_{10}O_5$.

Papaverine, $C_{20}H_{21}O_4N$. This alkaloid was first obtained in 1848 by Merck,[3] who characterised it and prepared several of its derivatives. It occurs in the mixture of bases precipitated by ammonia from the mother liquors of the opium extract from which morphine and codeine hydrochlorides have been crystallised. From this mixture it is separated together with some narcotine by hot alcohol. The alkaloid is finally purified by conversion into the acid oxalate, which is nearly insoluble in alcohol, that of narcotine being soluble. From the acid oxalate the pure alkaloid is regenerated by the addition of calcium chloride to the aqueous

[1] *Berichte*, 1907, **40**, 3280. [2] *Journ. Chem. Soc.* 1876, **29**, 461.
[3] *Annalen*, 1848, **66**, 125 ; 1849, **72**, 50.

solution of the salt and precipitation of the free base with ammonia solution.

Papaverine crystallises in rhombic prisms or needles, m.p. 147°, $[\alpha]_D$ 0°, is insoluble in water, soluble in hot alcohol or chloroform, and slightly so in cold alcohol or ether. Papaverine behaves as a mono-acidic base and forms salts with acids, but since the base exerts only a mild soporific action, none of these are employed in medicine. The hydrochloride, B.HCl, forms monoclinic plates, m.p. 231°, sparingly soluble in water (1 in 37 at 18°). The acid oxalate, $B.H_2C_2O_4$, forms prisms, m.p. 199°, slightly soluble in water (1 in 388 at 10°) and almost insoluble in cold alcohol.

Papaverine gives a purple coloration, changing to black and green when dissolved in sulphuric acid containing iodic acid. With iodine in alcohol it yields a characteristic crystalline periodide. With sulphuric acid it gives no coloration in the cold, but becomes violet on warming.[1] According to Reichard[2] papaverine gives a green mass with sulphuric acid and sodium *ortho*arsenate on warming. Pictet and Kramers have pointed out that most of these colour reactions are due to the presence of cryptopine in commercial papaverine.[3]

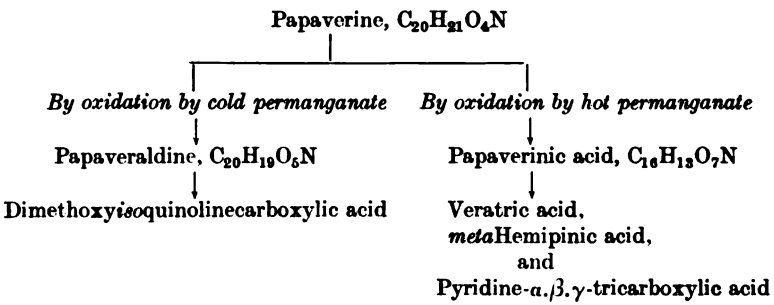
CONSTITUTION. Information regarding the structure of papaverine is principally due to the work of Goldschmiedt and collaborators.[4] Papaverine on treatment with hydriodic acid and red phosphorus furnishes four molecular proportions of methyl iodide and yields the new base papaveroline, $C_{16}H_9(OH)_4N$. It behaves as a tertiary amine and gives a methiodide, $B.CH_3I.4H_2O$, m.p. 195° (*dry*); the corresponding methohydroxide obtained by the action of alkali is crystalline and markedly alkaline in reaction.

Goldschmiedt stated that papaverine on reduction yielded tetrahydropapaverine, m.p. 200°–201°, together with an amorphous base.[5] By electrolytic reduction of papaveraldine (p. 246)

[1] Hesse, *J. prakt. Chim.* 1903 [ii], **68**, 190.
[2] *Pharm. Centr.-h.* 1907, **48**, 288. [3] *Berichte*, 1910, **43**, 1329.
[4] *Monatshefte*, 1883, **4**, 704; 1885, **6**, 372, 667, 956; 1886, **7**, 488; 1887, **8**, 510; 1888, **9**, 42, 327, 349, 679, 762, 778; 1889, **10**, 673, 692; 1893, **19**, 324.
[5] *Ibid.* 1886, **7**, 485; 1898, **19**, 324.

Freund and Beck obtained an amorphous *iso*tetrahydropapaverine yielding a crystalline hydriodide.[1] Pyman[2] has shown that Goldschmiedt's supposed tetrahydropapaverine is really a dihydropapaverine, $C_{20}H_{23}O_4N$, whilst his amorphous base and Freund and Beck's *iso*tetrahydropapaverine are identical and consist of tetrahydropapaverine, $C_{20}H_{25}O_4N$. This dihydropapaverine has been resolved into two optically isomeric forms by Pope and Peachey.[3] Pyman[4] supposed at first that it was 1 : 2-dihydropapaverine (*see* formula, p. 248), but in conjunction with Reynolds[5] has since then pointed out that its reactions are not altogether in harmony with that view. These authors have proposed the name PAVINE for this base. An isomeride, 3 : 4-dihydropapaverine, was prepared by Pictet and Finkelstein[6] in the course of their synthesis of laudanosine (p. 250).

Oxidation of Papaverine. The relationship of the principal substances formed by the oxidation of the alkaloid is shown in the following scheme :



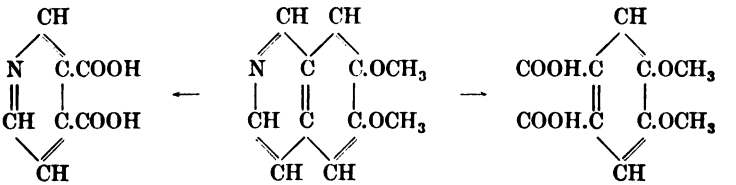
Papaveraldine, $C_{20}H_{19}O_5N$. This substance, the principal product of the action of cold acid permanganate on papaverine, forms colourless scales, m.p. 210°, yields well-crystallised yellow salts which are dissociated in water, and reacts as a tertiary base. It contains four methoxyl groups, and reacts with hydroxylamine as a ketone to form an oxime existing in two stereoisomeric forms. On

[1] *Berichte*, 1904, **37**, 3321.
[2] *Trans. Chem. Soc.* 1909, **95**, 1610.
[3] *Ibid.* 1898, **73**, 893.
[4] *Loc. cit.*
[5] *Trans. Chem. Soc.* 1910, **97**, 1320.
[6] *Compt. rend.* 1909, **148**, 925.

reduction with sodium amalgam in alcohol the *α*-oxime, m.p. 235°, furnishes the corresponding amine, papaveraldylamine, $C_{20}H_{20}O_4N.NH_2$. Miss Dobson and Professor W. H. Perkin have shown recently that the alkaloid, XANTHALINE, isolated from opium by T. and H. Smith,[1] is identical with papaveraldine.[2] On reduction with zinc dust in acetic acid papaveraldine yields the corresponding secondary alcohol, papaverinol.[3] When fused with potash it undergoes simple hydrolysis, furnishing veratric acid and a dimethoxy*iso*quinoline.

$$C_{20}H_{19}O_5N + H_2O = C_6H_3.COOH.(OCH_3)_2 + C_9H_5(OCH_3)_2N.$$
Papaveraldine *Veratric acid* *Dimethoxyisoquinoline*

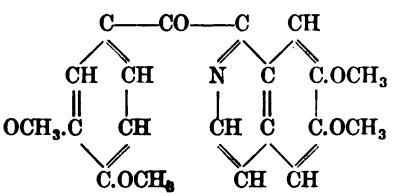
The constitution of the dimethoxy*iso*quinoline so produced is established by its conversion into cinchomeronic and *meta*hemipinic acids by oxidation with acid permanganate.



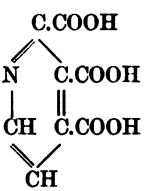
Cinchomeronic acid *Dimethoxyisoquinoline* meta*Hemipinic acid*

The position in which the veratryl residue is attached to the *iso*quinoline nucleus in papaveraldine and papaverine is determined by the formation of pyridine-*α*.*β*.*γ*-tricarboxylic acid in the energetic oxidation of papaverine by permanganate.

On the basis of these results Goldschmiedt[4] assigned the following formula to papaveraldine :



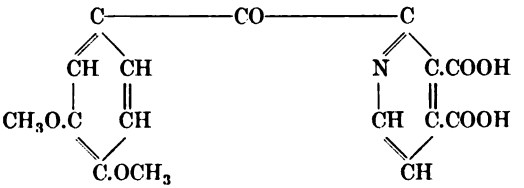
Papaveraldine



Pyridinet-α.β.γ-tricarboxylic acid

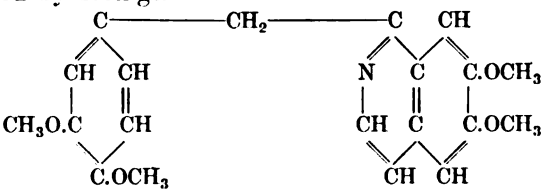
[1] *Pharm. Journ.* 1893 [iii], **52**, 793.
[2] *Trans. Chem. Soc.* 1911, **99**, 135.
[3] Stuchlik, *Monats.* 1900, **21**, 813.
[4] *Loc. cit.*

Papaverinic acid, $C_{16}H_{13}O_7N.H_2O$, crystallises in small tablets, m.p. 233°. It is dibasic, readily forms an anhydride, furnishes an oxime and a phenylhydrazone, and contains two methoxyl groups. These reactions and its formation from papaverine by oxidation with neutral permanganate are accounted for by the following formula :[1]



Papaverinic acid

The constitution of papaverine follows from that of papaveraldine, from which it differs in composition only by the substitution of two hydrogen atoms for one atom of oxygen. This change Goldschmiedt[2] assumed to be due to the conversion of a connecting—CH_2— group into the —CO— group of papaveraldine. The existence of such a —CH_2 group in papaverine has since been proved by Königs.[3]



Papaverine

The first attempt to synthesise papaverine was made by Fritsch[4] by condensing 3 : 4 : 3′ : 4′-tetramethoxydeoxybenzoin with acetalamine. This furnished an isomeride melting at a higher temperature than papaverine.

A complete synthesis was effected by Pictet and Gams,[5] who treated veratrole (*o*-dimethoxybenzene) with acetyl chloride and aluminium chloride, thus producing acetylveratrone, the oximino

[1] *Cf.* Goldschmiedt and Hönigschmid, *Monats.* 1903, **24**, 681.
[2] *Ibid.* 1888, **9**. 778.
[3] *Berichte*, 1899, **32**, 3612.
[4] *Annalen*, 1903, **329**, 37.
[5] *Compt. rend.* 1909, **149**, 210.

derivative of which was reduced and the resulting aminoacetylveratrone, $C_6H_3(OCH_3)_2.CO.CH_2.NH_2$, condensed with homoveratroyl chloride, $C_6H_3(OCH_3)_2.CH_2.COCl$, yielding homoveratroylaminoacetylveratrone, $C_6H_3(OCH_3)_2.CO.CH_2.NH.CO.CH_2.C_6H_3(OCH_3)_2$. This on reduction gave homoveratroylhydroxyveratrylamine, $C_6H_3(OCH_3)_2.CHOH.CH_2.NH.CO.CH_2.C_6H_3(OCH_3)_2$, which when boiled with phosphoric acid in xylene solution lost 2 mols. of water and yielded papaverine.

For the conversion of papaverine into glaucine, a near relative of the morphine group of alkaloids, *see* p. 259.

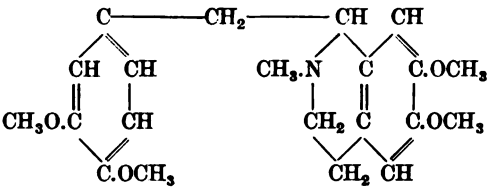
Laudanosine, $C_{21}H_{27}O_4N$. This alkaloid occurs in the liquor from which thebaine is precipitated, and is isolated by the method already described (p. 208). The crude alkaloid is purified by extracting with small quantities of ether, in which laudanosine is very soluble, and finally by precipitation with potassium iodide. The free alkaloid crystallises from hot benzene in needles, m.p. 89°, $[\alpha]_D^{15} + 103{\cdot}23°$ in alcohol, is soluble in alcohol, chloroform, hot benzene, or ether (1 in 19·3 at 16°), but insoluble in water or alkalis. The solution in alcohol is alkaline, and the alkaloid and its salts are bitter. The hydriodide, $B.HI.\frac{1}{2}H_2O$, forms small prisms readily soluble in alcohol, sparingly so in water, and the acid oxalate, $B.H_2C_2O_4.3H_2O$, prisms easily soluble in water. Laudanosine is not coloured by ferric chloride, but with ferric oxide and sulphuric acid gives a brown colour, changing to green when warmed at 150°. With sulphuric acid alone it gives a rose-red coloration, changing to deep reddish violet on warming to 150°.

Laudanosine contains four methoxyl groups. By "exhaustive methylation" it yields trimethylamine and laudanosen (tetramethoxy-*o*-vinylstilbene), $CH_2:CH.C_6H_2(OCH_3)_2.CH:CH.C_6H_3(OCH_3)_2$.[1] On oxidation with manganese dioxide and sulphuric acid it yields veratraldehyde and 4 : 5-dimethoxy-2 : β-methylaminoethylbenzaldehyde.[2]

The constitution of laudanosine has been determined by Pictet

[1] Decker and Galatty, *Berichte*, 1909, **42**, 1179.
[2] Pyman, *Trans. Chem. Soc.* 1909, **95**, 1267.

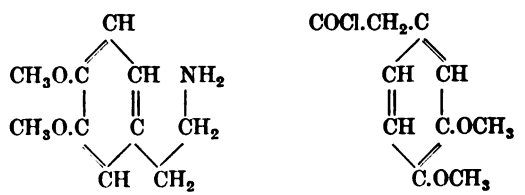
and Athanasescu,[1] who have prepared it by reducing papaverine methochloride and deracemising the *inactive* N-methyltetrahydropapaverine so obtained by fractional crystallisation of the quinate. Laudanosine must therefore be represented by the following formula :



Laudanosine

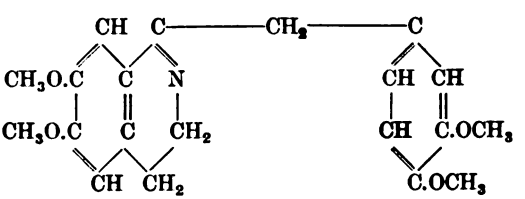
Racemic laudanosine, so prepared, crystallises from light petroleum or dilute alcohol in needles, m.p. 115°. The platinichloride, m.p. 160°, and the picrate, m.p. 174°, are crystalline.

A complete synthesis of laudanosine has been effected by Pictet and Finkelstein[2] by a process similar to that used for papaverine (p. 248), viz. the condensation of homoveratrylamine (I) with homoveratroyl chloride (II), giving homoveratroylhomoveratrylamine, which with phosphoric acid loses H_2O and yields 3 : 4-dihydropapaverine (III). This was converted into the methochloride and reduced to laudanosine (*see above*).



(I)

(II)



(III)

[1] *Berichte*, 1900, **33**, 2346. *Cf.* Pyman and Reynolds, *Trans. Chem. Soc.* 91), **97**, 1323.

[2] *Compt. rend.* 1909, **148**, 925.

For another synthesis of laudanosine and hydroxylaudanosine, *see* Gadamer.[1]

According to Hesse [2] laudanosine is the methyl ether of laudanine (*see below*).

Laudanine, $C_{20}H_{25}O_4N$. This isomeride of tetrahydropapaverine is isolated from opium as already described (p. 208). The crude laudanine thus obtained is purified by recrystallisation from dilute alcohol for the removal of small quantities of cryptopine, or it may be dissolved in acetic acid and the solution made alkaline with caustic soda when this impurity is precipitated, and the laudanine may then be isolated by addition of ammonium chloride. From laudanidine it is separated by repeated crystallisation of the hydrochloride.[3] It crystallises from dilute alcohol in trimetric prisms, m.p. 166°, $[\alpha]_D$ 0°, is easily soluble in chloroform or hot alcohol, and dissolves in solutions of soda or potash, forming metallic derivatives, which are precipitated by excess of alkali; it is nearly insoluble in ammonia solution. The hydriodide, $B.HI.H_2O$, is crystalline and sparingly soluble in water (1 in 500 at 15°).

With ferric chloride it gives a green coloration, and a deep red colour with ferric oxide and sulphuric acid.

According to Hesse it yields a mixture of laudanine methiodide and *r*-laudanosine when treated with methyl iodide in methyl alcohol,[4] so that inactive laudanosine would appear to be the methyl ether of laudanine.

The base contains three methoxyls and one hydroxyl group.[5]

*iso***Laudanine,** isomeric with laudanine, m.p. 76°, was prepared by Pictet and Kramers [6] by reducing trimethylpapaveroline methochloride with tin and hydrochloric acid. It gives blue colorations with sulphuric acid containing ferric chloride and with Fröhde's reagent.

Laudanidine, $C_{20}H_{25}O_4N$. This alkaloid occurs associated with its isomeride laudanine,[7] from which it may be separated by repeated

[1] *Arch. Pharm.* 1911, **249**, 680.
[2] *Journ. prakt. Chem.* 1902 [ii], **65**, 42.
[3] Hesse, *Annalen*, 1894, **282**, 209.
[4] *Journ. prakt. Chem.* 1902 [ii], **65**, 42.
[5] Hesse, *loc. cit.*
[6] *Arch. Sci. phys. nat.* 1903 [iv], **15**, 121.
[7] Hesse, *Annalen*, 1894, **282**, 209.

crystallisation of the hydrochlorides. Laudanidine closely resembles laudanine; it melts at 177° and has $[\alpha]_D$ — 87·8° in chloroform. It is probably the *lævo*-modification of laudanine.

Codamine, $C_{20}H_{25}O_4N$. The crude alkaloid, prepared as already described (p. 208), is purified by boiling with dilute sulphuric acid to remove meconidine, and is then regenerated by adding ammonia solution. It crystallises from ether in hexagonal prisms, m.p. 121°, but the salts are amorphous. The alkaloid is strongly alkaline, moderately soluble in water, and very soluble in alcohol; it is also dissolved by alkalis. It contains two methoxyl groups and one hydroxyl group. Nitric acid dissolves the alkaloid, forming a dark green liquid. Aqueous solutions are coloured green by ferric chloride.[1]

Pseudopapaverine, $C_{21}H_{21}O_4N$, was obtained by Hesse[2] from commercial papaverine. The hydrochloride, B.HCl, forms monoclinic crystals, m.p. 208°–210° (*decomp.*); the acid oxalate occurs in colourless needles, m.p. 196°. The base is readily soluble in chloroform and more soluble than papaverine in cold dry alcohol. It gives no coloration with sulphuric acid.

Papaveramine, $C_{21}H_{25}O_6N$, obtained by Hesse[3] in purifying papaverine, crystallises in colourless prisms, m.p. 128°–129°, and gives a crystalline hydrochloride, a very soluble acid oxalate, and an amorphous platinichloride. The alkaloid gives an intensely bluish-violet coloration with sulphuric acid.

Protopapaverine, $C_{19}H_{19}O_4N$, obtained by Hesse[3] from commercial papaverine, crystallises in yellow leaflets, m.p. 260° (*decomp.*), is sparingly soluble in alcohol and insoluble in ether or chloroform. The hydrochloride, $B.HCl.5H_2O$, forms yellow prisms, m.p. 200° (*dry*); the acid oxalate, $B.H_2C_2O_4.5H_2O$, forms yellow octahedra, m.p. 138° (*dry*). The alkaloid reacts with methyl iodide as a secondary amine. With cold sulphuric acid it gives a colourless solution which becomes violet on warming.

Meconidine, $C_{21}H_{23}O_4N$. This base was obtained by Hesse[4]

[1] Hesse, *Annalen*, 1870, **153**, 56. [2] *Journ. prakt. Chem.* 1903 [ii], **68**, 190.
[3] *Loc. cit.* [4] *Annalen*, 1870, **153**, 53.

by a complex fractionation of the mixed alkaloids precipitated from opium extract by soda solution. It is amorphous, yields amorphous salts, has m.p. 58°, is easily soluble in alcohol, ether, or caustic soda solution, and forms a green solution with sulphuric acid. The alkaloid exerts a mild tetanising action.

Lanthopine, $C_{23}H_{25}O_4N$, was obtained by Hesse [1] in the manner already described (p. 208). It forms a crystalline powder, m.p. 200°, and yields salts which are at first jellies, but finally crystallise. It is sparingly soluble in chloroform and insoluble in alkalis. With sulphuric acid the alkaloid gives a pale violet coloration, changing to brown on heating.

Protopine, $C_{20}H_{19}O_5N$ (*see* p. 381).

Cryptopine, $C_{21}H_{23}O_5N$. This base was obtained in the form of its acid oxalate from thebaine residues by T. and H. Smith,[2] and may be isolated by the method already described (p. 208). According to Pictet and Kramers [3] commercial papaverine frequently contains up to 4 per cent. of cryptopine, and to this are due some of the colour reactions usually ascribed to papaverine.

It crystallises from alcohol in prisms, m.p. 218°, $[\alpha]_D 0°$, is soluble in alcohol, but sparingly soluble in ether or benzene. The salts separate as jellies, but can usually be crystallised. The aurichloride forms brownish-yellow needles, m.p. 205° (*decomp.*), and the platinichloride concentrically arranged needles, m.p. 204° (*decomp.*). Cryptopine is not reduced by nascent hydrogen. It contains two methoxyl groups and a $:N.CH_3$ group, and probably also a dioxymethylene group, since it gives a green coloration with sulphuric and gallic acids. It contains no hydroxyl or carbonyl groups. With sulphuric acid it gives a violet colour, changing to green on warming to 150°. Cryptopine is mildly hypnotic in action, but in addition is mydriatic.

Tritopine, $C_{42}H_{54}O_7N_2$ or $(C_{21}H_{27}O_3N)_2O$. This diacidic alkaloid was isolated by Kauder [4] by treatment of thebaine residues

[1] *Annalen*, 1870, **153**, 53; 1872, *Suppl.* **8**, 280.
[2] *Pharm. Journ.* 1867, **27**, 595, 716. [3] *Berichte*, 1910, **43**, 1329.
[4] *Arch. Pharm.* 1890, **228**, 119.

with oxalic acid, whereby the very soluble acid oxalate of tritopine is formed. It crystallises from alcohol in needle-like plates, m.p. 182°, is easily soluble in chloroform or in alkaline solutions, but not in ether, and closely resembles in properties the laudanine group of isomerides. Tritopine is said to be physiologically inactive.

Rheadine, $C_{21}H_{21}O_6N$, occurs especially in all parts of the red poppy, *Papaver Rhœas*, and in very minute amount in opium.[1] It crystallises in colourless prisms, m.p. 232° (*decomp.*), 245°–247° (Pavesi), and is sparingly soluble in alcohol, ether, chloroform, or water. It is alkaline to litmus, but does not easily form salts with acids. It gives a purple coloration with moderately strong hydrochloric or sulphuric acid, which disappears on addition of alkali, but returns when the solution is acidified. On treatment with strong acids rheadine is converted into RHEAGENINE, rectangular leaflets, m.p. 223° (235°–237°, Pavesi), from alcohol, which is strongly basic and, though tasteless itself, gives bitter salts. The hydriodide forms prisms and is sparingly soluble in water. Rheadine is not toxic.

Physiological Action of Opium Alkaloids

The foregoing discussion of the opium alkaloids shows that as regards chemical constitution they fall into two groups: (1) The *morphine* group, including morphine, codeine, thebaine; and (2) the *narcotine* group, including narcotine, narceine, papaverine, as its principal members. In physiological action there is, however, no well-marked distinction between these two groups. The most characteristic feature of the physiological action of the whole of the opium alkaloids is their simultaneous depressing and exciting action on the central nervous system. The five chief members, morphine, papaverine, codeine, narcotine, and thebaine, all exhibit this peculiarity, and as the series is descended in the order just given the narcotic action diminishes, and the power of reflex stimulation increases until in thebaine a strychnine-like effect is exhibited.

[1] Hesse, *Annalen*, 1864–65, *Suppl.* **4**, p. 50; 1866, **140**, 145; 1869, **149**, 35. *Cf.* Pavesi, *Abstr. Chem. Soc.* 1906, ii, 483.

Vahlen[1] has attributed the characteristic action of morphine to the phenanthrene group, and Bergell and Pschorr[2] have pointed out that whilst phenanthrene itself has no action on rabbits, the 2-, 3-, and 9-hydroxyphenanthrenes cause tetanic convulsions. Loeb and Oldenburg state that whilst dihydromorphine and dihydrocodeine resemble the parent alkaloids in action, tetrahydrothebaine no longer causes tetanus, and they connect this property with the presence of an ethylenic linkage. In the case of dihydromorphine re-oxidation to morphine may occur in the organism, but this is less likely with tetrahydrothebaine.[3]

MORPHINE. This alkaloid exerts both a depressing and stimulating action on the central nervous system, the former being produced mainly in the brain, the latter mainly in the spinal cord. In the cat there is also some stimulation in the brain, but in man the depressing action dominates the whole nervous system. Respiration is slowed by morphine; in many cases it may be deeper at first, though the amount of air taken in per minute is reduced. In the higher animals death ensues from arrest of respiration. Morphine has little effect on the circulation, and this is also true of the peripheral muscles and nerves. The pupil of the eye is much contracted in morphine poisoning until just before asphyxia, when it is widely dilated. The alkaloid causes a slight fall in body temperature.

Morphine is excreted mainly by the digestive tract, but after large doses it also occurs in traces in the urine.

The continued use of morphine enables considerable tolerance for the alkaloid to be acquired, so that large doses are required to produce any effect. Morphine is usually fatal to man in doses of 0·2 to 0·3 grm.

PAPAVERINE is a comparatively weak poison, but in the nature of its effects stands between morphine and codeine. It produces light sleep when taken in comparatively small doses, and this does not become deeper when the dose is increased. On the other hand,

[1] *Arch. exp. Path. Pharm.* 1902, **47**, 368.
[2] *Zeit. Physiol. Chem.* 1903, **38**, 16.
[3] *Verh. Ges. deut. Naturf. A.* 1912 [ii], **2**, 481.

the reflex irritability is increased, and large doses may cause some tetanising action. It has more tendency than either morphine or codeine to slow the heart.

CODEINE resembles morphine in its general effect, but its depressant action is less marked and less prolonged, whilst its stimulating action involves not only the spinal cord but also the lower parts of the brain. In small doses in man it induces sleep, which is not so deep as that caused by morphine; in large doses it causes restlessness and increased reflex excitability rather than sleep. The respiration is slowed less than by morphine. The pupil is contracted at first, but is dilated in the excitement stage of the intoxication.

The artificial alkaloids, DIONINE (ethylmorphine) and PERONINE (benzylmorphine), somewhat resemble codeine in their action. HEROINE (diacetylmorphine) resembles morphine in its general action, but is stated to affect respiration to a greater extent than morphine, without producing mental depression.

NARCOTINE in general resembles codeine in its action, but is less depressant. It is much less poisonous than either morphine or codeine. It was at one time used in India as a remedy for malaria, but has long been superseded by quinine for this purpose. HYDROCOTARNINE resembles narcotine in its action, but is even less depressant. NARCEINE has been recommended as a hypnotic, but is believed to have very little action when pure, probably owing to the instability of its salts and the insolubility of the alkaloid itself. OXYNARCOTINE is described as a feeble narcotic poison.

THEBAINE stands at the other end of the series from morphine. In thebaine the depressing action on the central nervous system has almost disappeared, and this alkaloid resembles strychnine rather than morphine in its action, though it is much less active than strychnine.

Very few of the rarer opium alkaloids have been completely examined physiologically. LAUDANOSINE and LAUDANINE are stated to be similar to thebaine in their action, laudanine being the more poisonous. MECONIDINE is asserted to exert an effect similar

to that of thebaine, but to be much weaker. CRYPTOPINE and PROTOPINE produce in frogs narcosis, similar to that caused by morphine. In mammals there is no depression, but restlessness and convulsions are produced. These two alkaloids also paralyse the sensory nerve terminations somewhat like cocaine. Their action on the heart is more marked than that of narcotine and papaverine.

Of the derivatives of the opium alkaloids two are of special importance in medicine, viz. apomorphine and cotarnine.

APOMORPHINE. In the conversion of morphine into apomorphine the depressing action on the central nervous system is almost wholly lost, but the stimulant action remains and is exercised over the whole central nervous system, but especially on the " vomiting " centre of the medulla. In very small doses apomorphine may not produce vomiting, though the secondary symptoms, such as increased perspiration, which usually accompany this may be shown. The emetic action is due to direct action on the medulla oblongata, and not to irritation of the stomach. According to Hildebrandt [1] thebaine antagonises the emetic action of apomorphine in dogs, and Harnack and Hildebrandt [2] have shown that α- and β-chloromorphides are also anti-emetics, the former being the more powerful.

COTARNINE. This decomposition product of narcotine has come into use in medicine as a styptic in uterine hæmorrhage. It resembles hydrastinine in physiological action (*see* p. 279).

Alkaloids of other Papaver Spp.

The following species of *Papaver* have also been examined for alkaloids :

Species	Alkaloidal constituents	Reference
P. dubium	*Aporheine*, $C_{18}H_{16}O_2N$, amorphous ; salts crystalline. Tetanising poison *Aporheidine*, crystalline, m.p. 124°–125°	Pavesi (*Abstr. Chem. Soc.* 1905, i, 368 ; 1907, i, 870)

[1] *Arch. exp. Path. Pharm.* 1911, **65**, 54. [2] *Ibid.* p. 38.

Alkaloids of other Papaver Spp. (continued)

Species	Alkaloidal constituents	Reference
P. hybridum	*Rheadine* (*see* p. 254) and a second alkaloid	Pavesi (*Abstr. Chem. Soc.* 1906, ii, 483)
P. lateritium	Phenolic alkaloid, amorphous	Gadamer and Klee (*Arch. Pharm.* 1911, **249**, 39)
P. orientale	Phenolic alkaloid, crystalline, m.p. 204°–205°	
P. Rhœas	*Rheadine* (*see* p. 254)	Hesse (*Annalen*, 1866, **140**, 146); Pavesi (*loc. cit.*)

ALKALOIDS OF *GLAUCIUM FLAVUM*

The stem, leaves, and flowers of this plant were examined by R. Fischer [1] and found to contain glaucine and protopine (*see* p. 381), whilst the root contained protopine, traces of chelerythrine (*see* p. 378) and sanguinarine (*see* p. 381). Glaucine is best separated from the protopine with which it occurs by converting the mixture of alkaloids into hydrochlorides and extracting with chloroform, in which the glaucine salt is soluble.

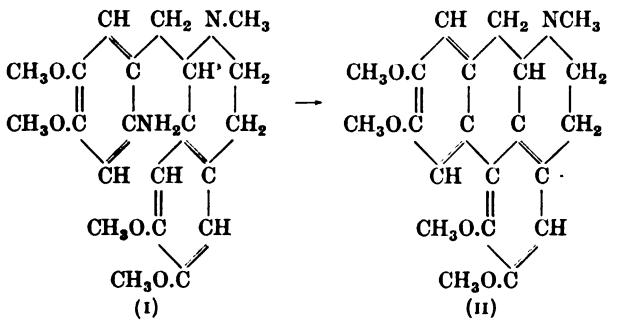
Glaucine, $C_{21}H_{25}O_4N$, was obtained by Probst [2] from *Glaucium flavum*, but was first prepared in a pure state by R. Fischer.[3] It crystallises in yellow rhombic prisms, m.p. 119°–120°, $[\alpha]_D$ + 113·3° in alcohol, is readily soluble in alcohol or chloroform, fairly so in ether, and sparingly so in benzene or hot water. The hydrochloride, $B.HCl.3H_2O$, forms colourless crystals, and the hydrobromide, B.HBr, pale pink crystals, m.p. 235°. The alkaloid itself is tasteless, but the salts are bitter. Glaucine dissolves in sulphuric acid, forming a colourless liquid which becomes bright blue after some hours. If the mixture is heated it rapidly becomes violet. Nitric

[1] *Arch. Pharm.* 1901, **239**, 426. [2] *Annalen*, **31**, 241. [3] *Loc. cit.*

acid gives a transient green tint; Fröhde's reagent (sulphomolybdic acid in sulphuric acid) yields a green passing into blue.

Glaucine behaves as a tertiary base and contains four methoxyl groups. It exerts narcotic properties, depresses the action of the heart, and also shows the tetanising action characteristic of some of the papaveraceous alkaloids.

Glaucine was synthesised by Gadamer [1] by treating a diazotised solution of N-methyltetrahydroaminopapaverine (*formula* I) with copper powder, when phenanthreno-N-methyltetrahydropapaverine, which proved to be *dl*-glaucine (*formula* II), was formed, thus:



(I) (II)

Glaucine (Gadamer)

The *dl*-glaucine thus prepared has m.p. 137°–139°, and on recrystallisation of the *d*- and *l*-hydrogen tartrates furnishes the corresponding salts of *l*- and *d*-glaucine, from which the free bases are obtainable, the *d*-glaucine thus produced being identical with the natural alkaloid.

ALKALOIDS OF *DICENTRA* SPECIES

The roots of four species of *Dicentra* have been examined and shown to contain the following alkaloids:

D. Cucullaria. Protopine and two alkaloids, provisionally termed *c* and *d*. Alkaloid *c* crystallises in rosettes of needles, m.p. 230°–231° (*decomp.*), is very sparingly soluble in alcohol and slightly in chloroform. It is colourless, but rapidly becomes yellow in the light.

[1] *Arch. Pharm.* 1911, **249**, 680.

Alkaloid *d* forms granular crystals, m.p. 215°, and is fairly soluble in alcohol.[1]

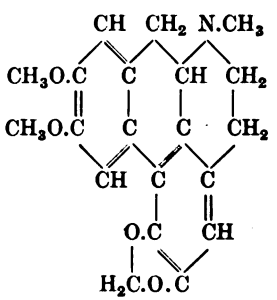
D. formosa. Protopine and at least two other alkaloids which were separated by fractional crystallisation of the hydrobromides from dilute alcohol. The one giving the less soluble hydrobromide had m.p. 168·5°–169° (? dicentrine, *see below*), and the other m.p. 142·5°. They resembled homochelidonine and chelidonine respectively to some extent.[2]

D. pusilla. Protopine and dicentrine.

Dicentrine, $C_{20}H_{21}O_4N$, crystallises from ether, alcohol, or ethyl acetate in prisms, m.p. 168°–169°, $[\alpha]_D$ + 62·1° in chloroform, and yields well-crystallised salts. The methiodide, $B.CH_3I.H_2O$, m.p. 224°, crystallises from dilute alcohol. The alkaloid contains two methoxyl groups.[3]

According to Iwakawa [4] dicentrine produces narcosis in small doses, and in large doses stimulates the medullary centres and causes convulsions. It weakens the heart and paralyses the respiratory centre.

Gadamer has suggested the following constitution for dicentrine,[5] because of its similarity to glaucine (p. 258).



Dicentrine (Gadamer)

D. spectabilis contains protopine.[6] Protopine is described at p. 381.

[1] Fischer and Soell, *Pharm. Arch.* 1902, **5**, 121.
[2] Heyl, *Arch. Pharm.* 1903, **241**, 313. [3] Asahina, *ibid.* 1909, **247**, 201.
[4] *Arch. exp. Path. Pharm.* 1911, **64**, 369. [5] *Arch. Pharm.* 1911, **249**, 680.
[6] Gadamer, *Apoth. Zeit.* 1901, **16**, 621.

THE ALKALOIDS OF *CORYDALIS* SPP.

This series of alkaloids occurs in the roots of *Corydalis tuberosa* and certain other species of the same genus. The following names and formulæ have been assigned to these alkaloids :

Group I	Corydaline, $C_{22}H_{27}O_4N$. Dehydrocorydaline, $C_{22}H_{23}O_4N$. Corybulbine, $C_{21}H_{25}O_4N$. *iso*Corybulbine, $C_{21}H_{25}O_4N$.
Group II	Corycavine, $C_{23}H_{23}O_6N$. Corycavamine, $C_{21}H_{21}O_5N$. Corycavidine, $C_{22}H_{25}O_5N$.
Group III	Bulbocapnine, $C_{19}H_{19}O_4N$. Corytuberine, $C_{19}H_{21}O_4N$. Corydine, $C_{20}H_{23}O_4N$.

OTHER CORYDALIS ALKALOIDS. Makoshi has obtained from Chinese corydalis tubers (*C. ambigua*) corydaline, dehydrocorydaline, corybulbine, protopine, and two new alkaloids, of which one has the formula $C_{20}H_{17}O_4N$, is isomeric with berberine, and is a quaternary base ; the hydrochloride forms red needles, and the aurichloride reddish-brown needles decomposing at 280°. The alkaloid can be reduced, giving a colourless substance, not identical with tetrahydroberberine. The second new alkaloid occurs in greyish-white needles, m.p. 197°–199°.[1] In Japanese corydalis roots (*C. Vernyi*) the same author[2] found only protopine and dehydrocorydaline. The occurrence of protopine in *C. tuberosa* roots is doubtful, and it does not occur in the seeds of *C. lutea* or *C. nobilis*.[3] Gadamer[4] has obtained protopine from the sub-aerial parts of *C. tuberosa*, together with an alkaloid, $C_{18}H_{14}O_5(OMe)_2.NMe$, m.p. 137·5°, $[\alpha]_D^{20}$ + 96·8°, first obtained by Haars[5] along with a second new alkaloid, $C_{21}H_{21}O_8N$, m.p. 230°, $[\alpha]_D^{20}$ — 112·8°. To these Gadamer[6] added a fourth alkaloid, giving a crystalline perchlorate, and a fifth, which was amorphous and yielded only amorphous derivatives. None of these were phenolic. In addition he obtained

[1] *Arch. Pharm.* 1908, **246**, 381.
[2] *Ibid.* p. 401.
[3] Schmidt, *ibid.* p. 575.
[4] *Ibid.* 1911, **249**, 224.
[5] *Ibid.* 1905, **243**, 154.
[6] *Loc. cit.*

two new phenolic bases closely related to glaucine. At the same time Gadamer showed that Gaebel's supposed new alkaloid from *C. tuberosa* roots [1] is a mixture (possibly a molecular combination) of corycavidine with corycavine. According to Heyl [2] *C. aurea* roots contain protopine and an alkaloid melting at 148°–149°, and *C. solida* (*C. bulbosa*) roots contain two new alkaloids, melting at 145° and 132°–133° respectively.

The following method of isolating the chief corydalis alkaloids is recommended by Gadamer, Ziegenbein, and Wagner : [3] The finely ground root is exhausted with 94 per cent. alcohol, the solvent removed by distillation, the residue acidified with acetic acid and diluted with water. After cooling, the liquid is filtered and the filtrate shaken with ether. Ammonia is then added and the mixture shaken with successive quantities of ether until alkaloids are no longer removed. The greater part of the ether is distilled off and the residual liquid set aside, when it deposits a mixture of corydaline, bulbocapnine, corycavine, and corybulbine, which are separated in this order by successive extraction of the crystalline mass with boiling alcohol. The mother liquor on concentration to a syrup deposits corydaline. The residue left on completely removing the remaining solvent is converted into the hydrobromides and fractionally precipitated with ammonia, when it yields in turn corydaline, corybulbine, *iso*corybulbine, corycavamine, corycavine, corydine, and bulbocapnine. The ammoniacal aqueous solution still contains some corytuberine, which is recovered by evaporating the liquid to a syrup, adding ammonia and extracting with chloroform.

The purification of corydaline obtained in the foregoing processes is carried out by converting the crude alkaloid into the hydrochloride and adding dilute soda to an aqueous solution of the latter, when corydaline with some corycavine is precipitated, whilst any bulbocapnine passes into the alkaline solution and can be regenerated by carbon dioxide. The two former alkaloids are best separated by repeated crystallisation from absolute alcohol, cory-

[1] *Arch. Pharm.* 1910, **248**, 207. [2] *Apoth. Zeit.* 1910, Nos. 5 and 17.
[3] *Arch. Pharm.* 1902, **240**, 19.

cavine accumulating in the earlier and corydaline in the later fractions. Advantage may also be taken of the greater solubility of corydaline hydrochloride in dilute hydrochloric acid over that of the corycavine salt.

The separation of these alkaloids into three groups is due to Gadamer, Ziegenbein, and Wagner.[1] Group I consists of weakly basic alkaloids which are readily oxidised by iodine to berberine-like compounds. Group II includes stronger bases which are attacked by iodine solution. Group III comprises the strongest bases of the series; these are all oxidised by iodine and contain free phenolic hydroxyl groups, so that they are soluble in alkaline liquids.

Group I

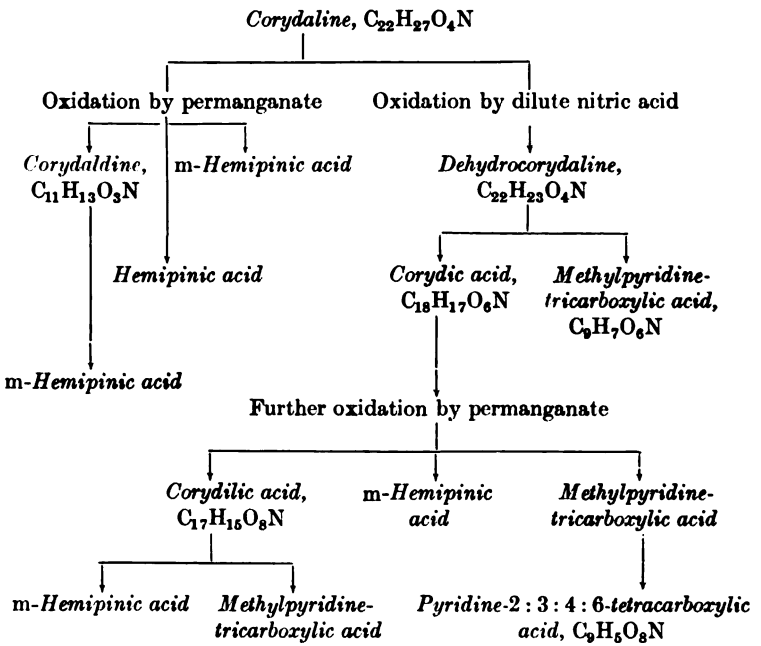
Corydaline, $C_{22}H_{27}O_4N$. This, the principal alkaloid of *Corydalis* roots, was discovered in 1826 by Wackenroder[2] and was subsequently obtained and examined by several investigators, but not in a pure state until 1866, when Wicke[3] analysed well-crystallised specimens of the salts of the alkaloid and assigned to it the formula $C_{18}H_{19}O_4N$. Birsmann[4] examined corydaline and adopted for it the formula $C_{22}H_{23}O_4N$, which Dobbie and Lauder[5] altered to $C_{22}H_{29}O_4N$. Freund and Josephi[6] found that the alkaloid was better represented by the formula $C_{22}H_{27}O_4N$, and this is now generally adopted.

Corydaline crystallises from alcohol in short prisms, m.p. 135°, $[\alpha]_D^{20} + 317°$ in chloroform, is sparingly soluble in cold alcohol, but dissolves readily on warming, is easily soluble in ether or chloroform, insoluble in water or alkalis. It forms well-crystallised salts, of which the hydriodide, B.HI, obtained by double decomposition of the hydrochloride with potassium iodide, forms pale yellow prisms of indefinite melting-point; the nitrate, $B.HNO_3$, crystallises from alcohol in tablets, m.p. 198°; the hydrochloride,

[1] *Loc. cit.* [2] *Berz. Jahr.* 1826, **7**, 220. [3] *Annalen*, 1866, **137**, 274.
[4] *Inaug. Diss. Dorpat.* 1888. [5] *Trans. Chem. Soc.* 1892, **61**, 244.
[6] *Annalen*, 1893, **277**, 1. *Cf.* Ziegenbein, *Arch. Pharm.* 1896, **234**, 492; Martindale, *ibid.* 1898, **236**, 214.

B.HCl.$2H_2O$, columnar crystals, m.p. 206°–207° ; the aurichloride, $(B.HCl)_2.AuCl_3$, crystallises from dilute alcoholic hydrochloric acid in orange-coloured needles, m.p. 207°. The platinichloride forms brown crystals, m.p. 227°. The most characteristic salt is corydaline ethyl sulphate, $B.C_2H_5HSO_4.H_2O$, which crystallises in large prisms, m.p. 152·5°.

CONSTITUTION. Corydaline contains four methoxyl groups. It reacts with methyl iodide, forming corydaline methiodide, and therefore contains a tertiary nitrogen atom. Further insight into the constitution of the alkaloid has been obtained principally by the study of its oxidation by permanganate and similar agents, by which means the alkaloid may be gradually broken down, as shown in the following tabular arrangement : [1]



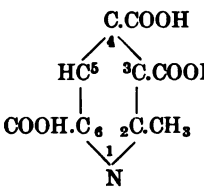
The ultimate products of oxidation are therefore pyridine-2 : 3 : 4 : 6-tetracarboxylic, hemipinic, and *meta*hemipinic acids,

[1] Dobbie and Lauder, *Trans. Chem. Soc.* 1902, **81**, 145 ; 1903, **83**, 605. *Cf.* Haars, *Arch. Pharm.* 1905, **243**, 165.

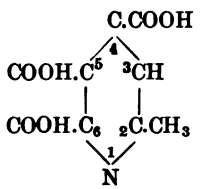
furnishing evidence of the existence in the molecular complex of the alkaloid of two benzene rings and at least one pyridine ring.

Methylpyridinetricarboxylic acid, $C_9H_7O_6N$. This substance was obtained [1] by oxidising corydic acid with permanganate. It crystallises in prisms, m.p. 208°, and furnishes well-crystallised salts. When dissolved in potash solution and treated with permanganate it is oxidised to a tetracarboxylic acid, $C_9H_5O_8N$, which is identical with pyridine-2 : 3 : 4 : 6-tetracarboxylic acid.

The formation of this acid makes it possible to assign with considerable certainty a position to the methyl group of the methylpyridinetricarboxylic acid from which it is derived.[2] Assuming that corydaline contains an *iso*quinoline nucleus, then, in the opening of the aromatic ring of this complex by oxidation, there must be formed a carboxyl group in the α-position (*see* I *and* II *below*); the two remaining carboxylic groups are probably formed by the destruction of a ring joined to the pyridine ring by the carbon atoms 3 : 4- or 4 : 5-. The methyl group must therefore be in position 2. These considerations lead to the adoption of one of the two following formulæ for the methylpyridinetricarboxylic acid formed from corydaline, of which Dobbie and Lauder prefer I :



(I)

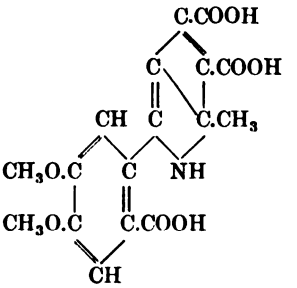


(II)

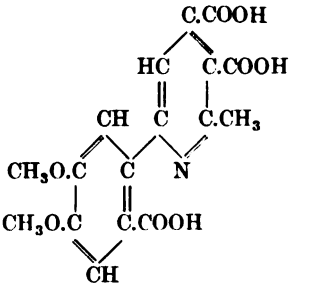
Corydilic acid, $C_{17}H_{15}O_8N$. This crystallises from alcohol in needles with $2H_2O$, m.p. 228°, and is formed by the oxidation of corydic acid (*see below*) with permanganate. On further treatment with this reagent it furnishes the methylpyridinetricarboxylic acid already described, and *meta*hemipinic acid. It is tribasic and

[1] Dobbie and Marsden, *Trans. Chem. Soc.* 1897, **71**, 657.
[2] Dobbie and Lauder, *ibid.* 1902, **81**, 152.

contains two methoxyl groups.[1] These properties and reactions led Dobbie and Lauder[2] to assign to this acid the following constitution (I), which has been modified by Haars to formula II,[3] the chief difference being that Haars regards corydilic acid as a tertiary base, since it gives a methiodide :

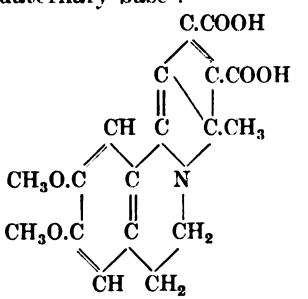


(I)
Corydilic acid
(Dobbie and Lauder)

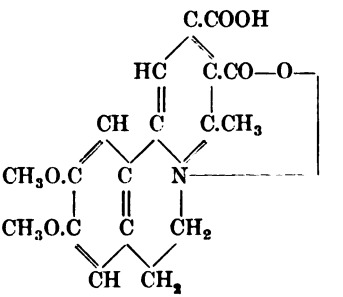


(II)
Corydilic acid
(Haars)

Corydic acid, $C_{18}H_{17}O_6N$,[4] is formed by the oxidation of dehydrocorydaline with dilute nitric acid. It crystallises in yellow leaflets with $2H_2O$, m.p. 218°, or with $1H_2O$, m.p. 224°, is a dibasic acid, contains two methoxyl groups and a tertiary nitrogen atom. When oxidised by permanganate it furnishes corydilic acid and a dibasic acid, $C_{16}H_{17}O_6N$. Dobbie and Lauder[2] assign formula I to corydic acid, which Haars[5] has modified as shown in formula II, since in his experiments the dimethyl ester of the acid formed salts as a quaternary base :



(I)
Corydic acid (Dobbie and Lauder)

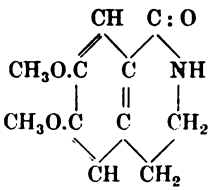


(II)
Corydic acid (Haars)

[1] Dobbie and Marsden, *Trans. Chem. Soc.* 1897, **71**, 657.
[2] *Loc. cit.*
[3] *Arch. Pharm.* 1905, **243**, 165.
[4] Dobbie and Marsden, *loc. cit.*
[5] *Loc. cit.*

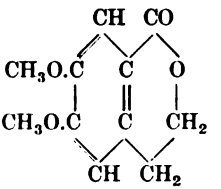
CORYDALDINE, $C_{11}H_{13}O_3N$, was obtained by Dobbie and Lauder by oxidising corydaline with permanganate. It forms prismatic crystals, m.p. 175°, and reacts with nitrous acid, giving nitrosocorydaldine, m.p. 185°, which when warmed with sodium hydroxide solution loses nitrogen and passes into the lactone of hydroxyethylveratric acid (II). The latter contains two methoxyl groups, and on oxidation gives *meta*hemipinic acid. With hydrochloric acid at 150° it furnishes a phenol, giving reactions similar to those of the catechol derivative obtained by Perkin (*see* p. 290) in the same way from hydroxyethylpiperonylcarboxylic anhydride, with which it is probably identical.

Dobbie and Lauder[1] assign the following formula to corydaldine:



(I)

Corydaldine



(II)

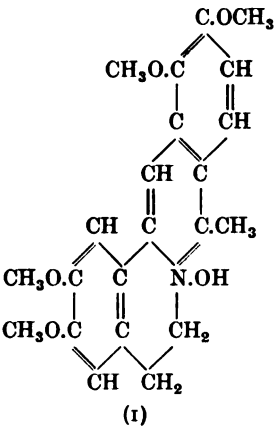
Hydroxyethylveratric anhydride

DEHYDROCORYDALINE, $C_{22}H_{23}O_4N$. This alkaloid occurs in *Corydalis tuberosa* roots and also in those of *C. Vernyi*, *C. ambigua*, and *C. solida*, and is formed by the gentle oxidation of corydaline.[2] It is a yellowish crystalline powder, m.p. 112°–113° (*decomp.*). The salts are crystalline; the hydrochloride, $B.HCl.4H_2O$, yellow leaflets; aurichloride, $B.HAuCl_4$, red-brown needles, m.p. 219°; the hydriodide, $B.HI.2H_2O$, small yellow needles. Like berberine it unites with one molecule of chloroform to form a colourless crystalline compound, m.p. 154°. Dehydrocorydaline contains four methoxyl groups and gives a crystalline oxime, m.p. 165°. On reduction it furnishes *iso*CORYDALINE, $C_{22}H_{27}O_4N$, m.p. 135°, together with *r-meso*corydaline, m.p. 158°, which by crystallisation

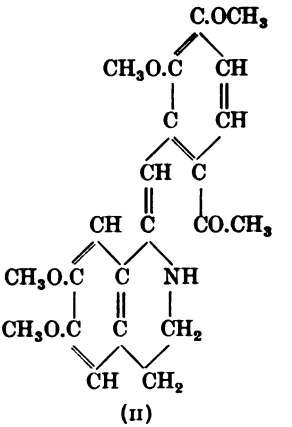
[1] *Trans. Chem. Soc.* 1899, **75**, 670.

[2] Schmidt, *Arch. Pharm.* 1896, **234**, 489; Haars, *ibid.* 1905, **243**, 165. *Cf.* Dobbie and Marsden, *Trans. Chem. Soc.* 1897, **71**, 659.

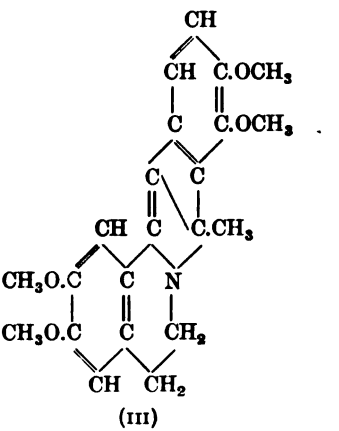
of the *d*-camphorsulphonate can be partially separated into *l*-corydaline and *d*-corydaline, neither of which is identical with natural corydaline.[1] According to Haars dehydrocorydaline has the formula $C_{22}H_{25}O_5N$, and in solution is a quaternary base (formula I), whilst in the free state it has the keto-structure (formula II). These differ slightly from the formula (III) assigned by Dobbie and Lauder[2] to the base :



(I)



(II)



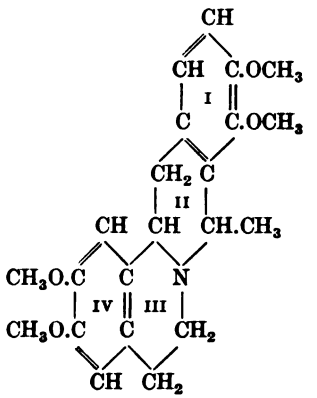
(III)

Dehydrocorydaline exhibits many analogies with berberine (p. 285); thus both are yellow and both are easily reduced, forming

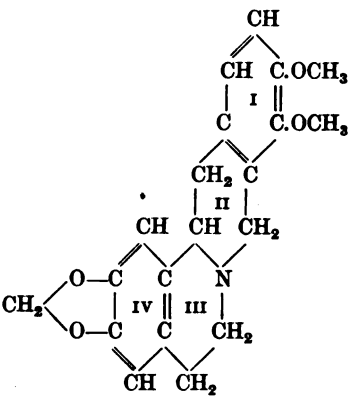
[1] Gadamer, Ziegenbein, and Wagner, *Arch. Pharm.* 1902, **240**, 19. *Cf.* Haars, *ibid.* 1905, **243**, 165. [2] *Trans. Chem. Soc.* 1902, **81**, 148.

the colourless alkaloids corydaline and so-called tetrahydroberberine (p. 297) respectively.

On the basis of the results briefly summarised above, Dobbie and Lauder [1] assigned the following constitution to corydaline:



Corydaline (Dobbie and Lauder)



Tetrahydroberberine

which makes it differ from tetrahydroberberine only in having two methoxyl groups in place of a dioxymethylene group in ring IV and a methyl group substituted for a hydrogen atom in ring II.

Corybulbine, $C_{21}H_{25}O_4N$. This alkaloid was isolated from commercial corydaline by Freund and Josephi [2] in 1893 by precipitation of the crude hydrochloride with caustic soda solution in which corybulbine is soluble. It crystallises from boiling absolute alcohol in needles, m.p. 238°, $[\alpha]_D$ + 330·3° in chloroform, is insoluble in water, slightly soluble in methyl alcohol or ether, readily soluble in chloroform, acetone, or hot benzene. The hydrochloride, B.HCl, is slightly soluble in hot water, from which it crystallises in yellowish prismatic crystals, m.p. 245°–250° (*decomp.*). The platinichloride and aurichloride are amorphous.

When treated with iodine, corybulbine is oxidised to dehydrocorybulbine, $C_{21}H_{21}O_4N$, m.p. 210°–211°, and the latter on reduction regenerates an optically inactive form of the parent base.[3] When heated with methyl iodide in presence of potash, corybulbine is

[1] *Loc. cit.* *Cf.* Haars, *loc. cit.* [2] *Annalen*, 1893, **277**, 1.
[3] Bruns, *Arch. Pharm.* 1903, **241**, 634.

converted into corydaline,[1] from which it differs only in possessing a hydroxyl in place of a methoxyl group. Evidence of the existence of the hydroxyl group is found in the solubility of the alkaloid in alkalis and in the formation of acetylcorybulbine, m.p. 160°. The position of the hydroxyl group in corybulbine has not been ascertained with certainty, but since the alkaloid does not give corydic acid by oxidation with nitric acid, Dobbie, Lauder, and Paliatseas[2] suggest that it must occur in ring IV (*see* corydaline formula, p. 269).

***iso*Corybulbine,** $C_{21}H_{25}O_4N$, was first obtained by Gadamer, Ziegenbein, and Wagner,[3] and was subsequently examined by Bruns.[4] It separates from alcohol in colourless voluminous leaflets, m.p. 179°–180°, $[\alpha]_D$ + 299·8° in chloroform, and closely resembles corybulbine. It contains three methoxyl groups, and on oxidation with iodine yields dehydro*iso*corybulbine; the hydriodide of the latter is reduced by zinc and sulphuric acid to *i-iso*corybulbine, m.p. 165°–167°.

Group II

Corycavine, $C_{23}H_{23}O_6N$. This alkaloid was isolated by Freund and Josephi[5] from corydalis roots and was subsequently examined by Gadamer, Ziegenbein, and Wagner[6] and by Gaebel.[7] It crystallises from hot absolute alcohol in rhombic tablets, m.p. 218°–219°, $[\alpha]_D$ 0°, and is insoluble in alkalis. The hydrochloride, $B.HCl.H_2O$, forms needles melting at 219°; the hydriodide, $B.HI.H_2O$, small yellowish needles, m.p. 236°; the platinichloride, $(B.HCl)_2.PtCl_4$, yellowish crystals, m.p. 214° (*decomp.*); the aurichloride, $B.HAuCl_4$, has m.p. 178°–179° (*decomp.*). Corycavine reacts with methyl iodide as a tertiary base, forming a methiodide (rhombic tablets, m.p. 218°). It contains one dioxymethylene group, but no hydroxyl. According to Gaebel corycavine on exhaustive methylation yields finally trimethylamine and an amorphous non-nitrogenous substance.

[1] Dobbie, Lauder, and Paliatseas, *Trans. Chem. Soc.* 1901, **79**, 87.
[2] *Loc. cit.* [3] *Arch. Pharm.* 1902, **240**, 19. [4] *Loc. cit.*
[5] *Loc. cit.* [6] *Loc. cit.* [7] *Arch. Pharm.* 1910, **248**, 207.

Corycavamine, $C_{21}H_{21}O_5N$, was first obtained by Gadamer, Ziegenbein, and Wagner[1] and is best purified by recrystallisation of the nitrate. The free base forms rhombic columns, m.p. 149°, $[\alpha]_D^{20}$ + 166·6° in chloroform. It contains no methoxyl groups, but probably a dioxymethylene group. The hydrobromide and hydriodide crystallise in needles, but the platinichloride is amorphous. When warmed with acetic anhydride or heated alone at 180° it is converted into an optically inactive modification, m.p. 213°–214°, which resembles cryptopine (p. 253), but is not identical with it.

Corycavidine, $C_{22}H_{25}O_5N$, was described by Gadamer.[2] It crystallises from hot chloroform with one molecule of the solvent, melts at 212°–213°, has $[\alpha]_D^{20}$ + 203·1° in chloroform, and yields a crystalline hydrochloride and nitrate and an amorphous red aurichloride, m.p. 170° (*decomp.*). It contains two methoxyl groups and a =NMe group, and appears to be corycavamine in which a dioxymethylene group is replaced by two methoxyls. Like corycavamine, when heated at 209° it is converted into an inactive modification, m.p. 193°–195°. On exhaustive methylation it yields eventually trimethylamine and a neutral substance.

Group III

Bulbocapnine, $C_{19}H_{19}O_4N$. This alkaloid was isolated by Freund and Josephi[3] from corydalis roots. It crystallises from hot dry alcohol in rhombic needles, m.p. 199°, $[\alpha]_D$ + 237·1° in chloroform, is insoluble in water, readily soluble in chloroform or alkalis, but is precipitated from its solutions in the latter by excess of carbon dioxide. The hydrochloride forms needles, m.p. 270° (*approx.*); the platinichloride is crystalline, m.p. 200° and 230° (*decomp.*). The methiodide, m.p. 257°, forms brilliant needles. The base was formerly regarded as a partially demethylated dehydrocorydaline, the latter being supposed to have the formula, $C_{22}H_{25}O_4N$, thus :

$C_{18}H_{13}(OCH_3)_4N$	$C_{18}H_{13}(OH)_3(OCH_3)N$
Dehydrocorydaline	*Bulbocapnine*

[1] *Loc. cit.* [2] *Arch. Pharm.* 1911, **249**, 30. [3] *Annalen*, 1893, **277**, 10.

but the observations of Gadamer and Ziegenbein [1] and of Dobbie and Lauder [2] indicated that such a relationship between the alkaloids did not exist, and this has been proved recently by the investigations of Gadamer and Kuntze.[3] They showed that bulbocapnine contained one methoxyl, one hydroxyl, and a dioxymethylene group. On "exhaustive methylation" it yielded trimethylamine and 3 : 4-dimethoxy-5 : 6-methylenedioxy-8-vinylphenanthrene, and on these grounds formula I (p. 273) was assigned to it.

Corydine, $C_{20}H_{23}O_4N$, was first prepared by Merck [4] and was subsequently examined by Gadamer and collaborators.[5] It crystallises from alcohol with $\frac{1}{2}C_2H_5OH$, m.p. 124°–125°, or 149° (*dry*), $[\alpha]_D^{20} + 204{\cdot}3°$ in chloroform, and is readily soluble in alcohol or chloroform. It contains three methoxyl groups and one hydroxyl group, and on oxidation with iodine yields dehydrocorydine hydriodide, $C_{20}H_{19}O_4N.HI$. This on reduction yields *i*-corydine, m.p. 165°–167°, which on recrystallisation of the *d*-tartrate yields *l*-corydine $[\alpha]_D^{20} - 206{\cdot}2°$ in chloroform. Corytuberine (*see below*) on methylation with diazomethane yields a mixture of corydine and *iso*corydine, so that these two alkaloids are monomethyl ethers of corytuberine, as shown by the formula on p. 273.

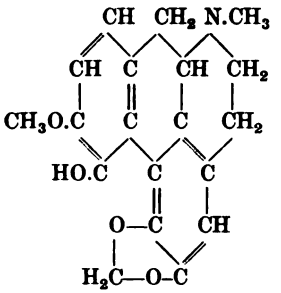
*iso***Corydine,** $C_{20}H_{23}O_4N$, is obtained along with corydine (*see above*) when corytuberine is methylated with diazomethane or methyl sulphate.[6] It crystallises in glistening four-sided tablets, m.p. 185°, $[\alpha]_D^{20} + 195{\cdot}3°$ in chloroform, and yields a methiodide, m.p. 213°–214° (*decomp.*), $[\alpha]_D^{20} + 143{\cdot}3°$.

Corytuberine, $C_{19}H_{21}O_4N.5H_2O$. This alkaloid was obtained by Dobbie and Lauder [7] from commercial corydaline by exhausting the latter with boiling water. It crystallises in silky needles, m.p. 240°, $[\alpha]_D^{20} + 282{\cdot}65°$ in alcohol, is insoluble in benzene, ether, or chloroform, but dissolves readily in alkalis. The salts are crystalline. It reacts with methyl iodide, forming a crystalline

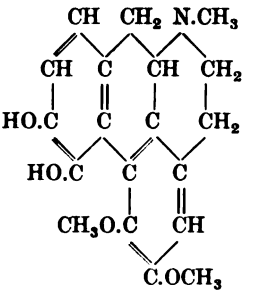
[1] *Arch. Pharm.* 1902, **240**, 81. [2] *Trans. Chem. Soc.* 1903, **83**, 612.
[3] *Arch. Pharm.* 1911, **249**, 503, 598. [4] *Abstr. Chem. Soc.* 1893, i, 492.
[5] *Arch. Pharm.* 1902, **240**, 81 : 1911, **249**, 503, 669.
[6] Gadamer, *Arch. Pharm.* 1911, **249**, 485, 669.
[7] *Trans. Chem. Soc.* 1893, **63**, 485.

methiodide, contains two methoxyl and two hydroxyl groups.[1] Gadamer[2] finds that on methylation with methyl sulphate or diazomethane it yields a mixture of two monomethyl ethers, one of which is identical with corydine and the other is isomeric and has been named *iso*corydine (*see* p. 272). On "exhaustive methylation" corytuberine yields eventually trimethylamine and 3 : 4 : 5 : 6-tetramethoxy-8-vinylphenanthrene.

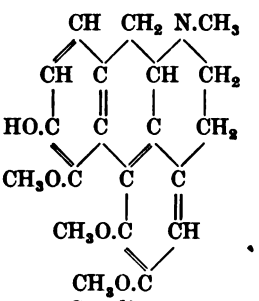
It is clear from these results that bulbocapnine, corydine, *iso*-corydine, and corytuberine are all closely related, and Gadamer[3] on the basis of these investigations has assigned to them the following formulæ :



Bulbocapnine



Corytuberine



Corydine[4]

Physiological Action of Corydalis Alkaloids

Neither corydalis root nor the alkaloids it contains have been used in medicine, though the roots are reputed to possess

[1] Gadamer, Ziegenbein, and Wagner, *Arch. Pharm.* 1902, **240**, 81.
[2] *Ibid.* 1911, **249**, 641. [3] *Loc. cit.*
[4] *iso*Corydine differs from corydine merely in the interchange of hydroxyl and methoxyl in positions 3 and 4 in the phenanthrene nucleus.

antiperiodic properties. The physiological action of the chief alkaloids has been investigated by Peters,[1] who showed that they are divided physiologically into three groups corresponding with the three chemical groups already referred to. The alkaloids of the corydaline group cause paralysis of the spinal cord. Those of the corycavine group stimulate the motor centres, whilst those of the bulbocapnine group resemble codeine in action and cause increased reflex excitability in frogs. All the corydalis alkaloids except corytuberine somewhat resemble morphine and the allied alkaloids in action, affecting the heart and producing narcosis in frogs.

ALKALOIDS OF *HYDRASTIS CANADENSIS*

The plant *Hydrastis canadensis*, " Golden Seal," belongs to the natural order Ranunculaceæ, and is, as its name implies, a native of North America. It contains at least three alkaloids, HYDRASTINE, BERBERINE, and CANADINE, of which the first is the chief physiologically active constituent. The rhizome is generally stated to yield about 1·5 per cent. of hydrastine and 4 per cent. of berberine, but Messrs. Caesar and Loretz[2] give the following percentages of hydrastine in *Hydrastis* rhizome for the seasons indicated :

1906–07	2·68 to 4·04
1907–08	3·57 to 4·22
1908–09	3·39 to 3·73
1909–10	2·63 to 4·06
1910–11	2·60 to 4·44

Preparation. The finely powdered hydrastis rhizome is extracted with alcohol, the extract concentrated, and a slight but distinct excess of sulphuric acid added, when impure berberine sulphate separates. The filtrate is nearly neutralised with ammonia solution, evaporated to a syrupy consistence and poured into water to precipitate resin, &c. The filtrate from this is treated with ammonia solution in excess, when it furnishes crude hydras-

[1] *Arch. exp. Path. Pharm.* 1903, **51**, 130.
[2] *Jahresberichte* for the years named.

tine, which may be purified by reprecipitation from dilute sulphuric acid solution by ammonia, and recrystallisation from boiling alcohol,[1] or the rhizome may be extracted with dilute acetic acid, the extract evaporated to a syrup, and excess of dilute sulphuric acid added. The filtrate on neutralisation with ammonia gives a precipitate containing much hydrastine, and on adding excess of ammonia to the filtrate a further supply of hydrastine, mixed with canadine, is obtained. From both these precipitates hydrastine is obtainable by recrystallisation from ethyl acetate.[2]

Hydrastine may be prepared more rapidly by extracting the ground rhizome with ether and dissolving the residue left on distilling off the solvent in hot alcohol, when nearly pure hydrastine crystallises out on cooling.[3]

Estimation of Hydrastine and Berberine in Hydrastis Rhizome. The great difference in the physiological activity of hydrastine and berberine renders necessary a method of estimation of the former alkaloid at least, in hydrastis rhizome intended for use in medicine.

No process of estimation is given for hydrastis rhizome or its preparations in the British Pharmacopœia. The United States Pharmacopœia (8th Rev.) gives the following process: Fifteen grammes of the rhizome in No. 60 powder are allowed to stand ten minutes with 150 c.c. of ether, and a further thirty minutes after adding 5 c.c. ammonia solution (sp. gr. 0·958 at 25°), the 250 c.c. flask containing the mixture being shaken at intervals. Fifteen cubic centimetres of water are added and the flask shaken till the drug coheres in masses and 100 c.c. of the ethereal extract can be poured off into a separating funnel. The alkaloid in this is extracted by shaking successively (for one minute each time) with (*a*) 15 c.c. *N*-sulphuric acid, (*b*) 5 c.c. *N*-sulphuric acid and 5 c.c. distilled water, and (*c*) 5 c.c. distilled water, the combined acid and aqueous extracts being then rendered distinctly alkaline and the

[1] Power, *Pharm. Journ.* 1884–85 [iii], **15**, 297.
[2] Schmidt and Wilhelm, *Arch. Pharm.* 1888, **226**, 329.
[3] Freund and Will, *Berichte*, 1886, **19**, 2797.

free alkaloid extracted by shaking in succession with 25, 20, and 15 c.c. of ether. The ethereal extracts are run into a tared beaker, the solvent evaporated, the residue dried at 100° and its weight, *w*, noted. The percentage of hydrastine in the rhizome is 10*w*. The United States Pharmacopœia requires hydrastis rhizome to contain not less than 2·5 per cent. of hydrastine as determined by this method.

The German Pharmacopœia (V) gives the following process: Six grammes of the rhizome in moderately fine powder are mixed with 60 grm. of ether and 10 c.c. of dilute ammonia solution, and occasionally shaken during three hours. Forty grammes of the ethereal extract (= 4 grm. of rhizome) are filtered into a flask and the solvent distilled off. The residue is dissolved in 10 c.c. of 1 per cent. hydrochloric acid, the solution filtered, using two portions, each 5 c.c., of 1 per cent. hydrochloric acid, followed by a little distilled water to wash out the flask and the small filter used, the washings being added to the filtrate, which is then mixed with 40 c.c. of ether in a separating funnel, enough dilute ammonia solution being added to make the solution alkaline. Shaking is continued for two minutes. The aqueous alkaline layer is then run off and 30 c.c. of the ethereal solution (= 3 grm. rhizome) run into a tared flask, the solvent distilled off, the residue dried at 100° and weighed. It should weigh at least 0·075 grm., corresponding to 2·5 per cent. of hydrastine in the rhizome.

Hydrastis Preparations. The United States Pharmacopœia gives the following methods for the *fluid extract* and the *tincture*: Ten cubic centimetres of fluid extract are mixed with 85 c.c. of distilled water containing 2 grm. of potassium iodide, and the mixture made up to 100 c.c. with distilled water and then shaken for several minutes. Fifty cubic centimetres of the mixture are placed in a separating funnel, made alkaline with ammonia solution (sp. gr. 0·958 at 25°), and the alkaloid extracted by shaking first with 30 c.c. of ether for several minutes, and then with 20 c.c. for one minute. The ethereal liquids are run into a tared flask, the solvent distilled off, and the residue dried at 100° and weighed. It should

weigh 0·2 grm., corresponding to 2 grm. of hydrastine in 100 c.c. of the extract. For another process, *see* van der Haar.[1]

In the case of the tincture, 100 c.c. are evaporated at 100° to 10 c.c., and the process is carried out as for the fluid extract. The tincture should contain 0·4 grm. of hydrastine in 100 c.c.

A method of separately estimating hydrastine and berberine in hydrastis rhizome has been proposed by Gordin and Prescott,[2] depending on (1) the isolation of the hydrastine by extraction with ether and its precipitation as pentaiodide by standard iodine solution, and (2) extraction of the berberine from the rhizome, previously freed from hydrastine, with alcohol, and estimation of this as described on p. 287.

Hydrastine, $C_{21}H_{21}O_6N$. This alkaloid was first isolated in a pure state by Perrins [3] from the rhizome of *Hydrastis canadensis*. It was subsequently investigated by Mahla [4] and by Power.[5] Mahla assigned to it the formula $C_{22}H_{24}O_6N$, which later analyses by Freund and Will [6] and van Eykman [7] have displaced in favour of the formula given above.

Hydrastine forms rhombic prisms, m.p. 132°, from alcohol. It has a bitter taste, is alkaline to litmus, almost insoluble in water, easily soluble in chloroform (1 in 2 at 25°) or benzene, and less so in alcohol (1 in 135 at 25°) or ether (1 in 124 at 25°). In chloroform, hydrastine has $[\alpha]_D$ − 67·8°, but according to Carr and Reynolds in dry alcohol it is − 49·8° and in 50 per cent. alcohol + 115°.[8] Hydrastine is dextrorotatory in acid solution.

The salts with acids are unstable in water and generally not well crystallised: the hydrochloride, B.HCl, is a microcrystalline powder, which is dextrorotatory: the hydriodide periodide, B.HI.I_5, is a dark brown powder; the platinichloride, $B_2.H_2PtCl_6$, is an amorphous

[1] *Pharm. Weekblaad*, 1911, **48**, 1302.
[2] *Arch. Pharm.* 1899, **237**, 439. *Cf.* Gordin, *ibid.* 1901, **239**, 638.
[3] *Pharm. Journ.* 1862 [ii], **3**, 546. [4] *Silliman's Journ.* 1863, **36**, 57.
[5] *Pharm. Record*, 1884, September 10; *Pharm. Journ.* 1884–5 [iii], **15** 297; 1885–6 [iii], **16**, 1092.
[6] *Berichte*, 1887, **20**, 88. [7] *Rec. Trav. Chim.* 1886, **5**, 291.
[8] *Trans. Chem. Soc.* 1910, **97**, 1334. *Cf.* Freund and Will, *Berichte*, 1886, **19**, 2797.

yellow precipitate, but the picrate, $B.C_6H_2(NO_2)_3OH.H_2O$, forms fine yellow needles. The alkaloid gives ill-defined metallic derivatives, especially with the alkalis.

Hydrastine when dissolved in sulphuric acid gives with ammonium molybdate an olive-green colour, whilst a solution in dilute sulphuric acid gives a blue fluorescence with an aqueous solution of permanganate (1 in 10). Iodine solution precipitates a characteristic hydriodide periodide as a dark brown powder, and soluble chromates yield insoluble hydrastine chromate, which gives a fugitive red colour with sulphuric acid.[1]

Physiological Action. Hydrastine stimulates first the centres of the medulla oblongata, producing slowing of the pulse, constriction of blood-vessels, increased blood-pressure, and quickened respiration. Large doses eventually paralyse the medulla and the spinal cord. Apart from this action on the central nervous system, it weakens and paralyses the heart in mammals. In spite of its similarity to narcotine in constitution, hydrastine exercises no narcotic effect. It appears to be excreted in the urine unchanged. Hydrastine has been used as an internal styptic, as in uterine hæmorrhage, but for such purposes hydrastinine (*see below*) is preferable since it causes greater constriction of the peripheral blood-vessels and has less action on the heart.

Hydrastis rhizome has been used as a stomachic, probably owing to the berberine it contains, but is also employed, like hydrastine, as an internal styptic.

Constitution of Hydrastine. Hydrastine contains two methoxyl groups, and with alkyl iodides reacts as a tertiary amine. It does not react with hydroxylamine or phenylhydrazine. With oxidising agents it furnishes on the one hand pyridine derivatives such as apophyllenic acid, and on the other aromatic substances such as hemipinic and opianic acids. When fused with potash, hydrastine furnishes protocatechuic acid.[2]

The first important insight into the inner structure of the base

[1] *Cf.* Lyons, *Pharm. Journ.* 1885-86 [iii], **16**, 880.
[2] Power, *loc. cit.*

was obtained when Freund and Will [1] observed that by the action of dilute nitric acid it undergoes hydrolytic oxidation, furnishing opianic acid, C_6H_2[COH : COOH : OMe : OMe = 1 : 2 : 3 : 4], and a new base, hydrastinine, $C_{11}H_{13}O_3N$, thus :

$$\underset{\textit{Hydrastine}}{C_{21}H_{21}O_6N} + H_2O + O = \underset{\textit{Opianic acid}}{C_{10}H_{10}O_5} + \underset{\textit{Hydrastinine}}{C_{11}H_{13}O_3N}.$$

This reaction is analogous with the similar hydrolytic oxidation of narcotine to opianic acid and cotarnine (*see* p. 233), and hydrastinine is allied to cotarnine in constitution and physiological action.

HYDRASTININE, $C_{11}H_{13}O_3N$, has acquired special importance on account of its extensive use in medicine. It crystallises in colourless glancing needles, m.p. 116°–117°, from light petroleum, is soluble in non-ionising organic solvents to a colourless solution, but dissolves in alcohol and sparingly in water, forming fluorescent yellow solutions. It is optically inactive.

It forms salts with the mineral acids, losing at the same time a molecule of water; thus the hydrochloride has the formula $C_{11}H_{11}O_2N.HCl$. This salt, which is the form in which the alkaloid is used in medicine, occurs in pale yellowish needles, has a bitter taste, melts at 212°, is very soluble in water or alcohol, 1 in 286 of chloroform, or 1 in 300 of ether at 25°. Its aqueous solution shows a blue fluorescence, especially when dilute, is neutral to litmus, and is not precipitated by ammonia solution, but dilute sodium hydroxide solution added drop by drop causes turbidity, which disappears on shaking. On standing, this liquid then deposits crystalline hydrastinine. Bromine water gives, with an aqueous solution of the salt, a yellow precipitate, which is soluble in ammonia solution. A crystal of the salt gives a deep yellow colour with sulphuric acid, or a reddish-brown colour if the sulphuric acid contains a trace of nitric acid.[2]

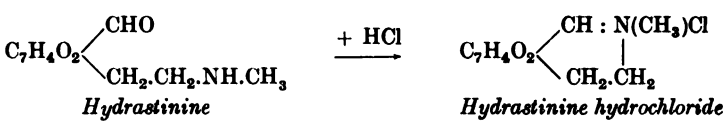
In its physiological action hydrastinine differs from hydrastine in causing no disturbance of the centres of motion and feeling

[1] *Berichte*, 1887, **20**, 88.

[2] *See also* Reichard, *Pharm. Zentr.-h.* 1911, **52**, 1253.

except in very large doses, which paralyse the nervous system. The arterial tension is increased even more than by hydrastine, and the effect lasts longer because there is no depression of the heart. It appears to have no direct action on uterine muscle, and its efficacy in arresting uterine hæmorrhage appears to be due to constriction of the blood-vessels. When applied to the eye in 10 per cent. solution it causes dilatation of the pupil. The alkaloid is used in medicine as an internal styptic.

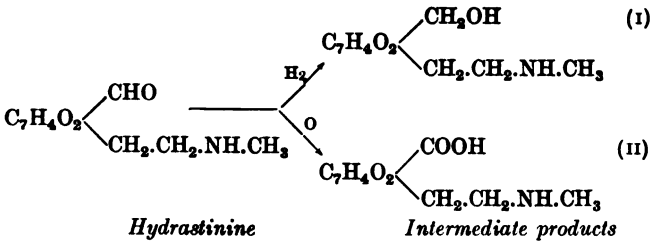
Reactions. Hydrastinine contains a methyl group linked to nitrogen;[1] it reacts with hydroxylamine forming an oxime, m.p. 145°–146°, with acetic anhydride forming acetylhydrastinine, and with benzoyl chloride to form benzoylhydrastinine. When treated with aqueous solution of potassium hydroxide it yields *oxyhydrastinine*, $C_{11}H_{11}O_3N$, rosettes of needles, m.p. 97°–98°, b.p. above 350°, and *hydrohydrastinine*, $C_{11}H_{13}O_2N$, m.p. 66°, both of which are crystalline.[2] It has already been mentioned that in forming salts hydrastinine loses the elements of a molecule of water. These reactions indicate that hydrastinine (1) is a econdary amine, (2) contains an aldehyde grouping, and (3) contains two side-chains from which water may readily be eliminated on addition of an acid. Roser,[3] to explain these reactions, formulated hydrastinine and its salts thus:



Hydrastinine — *Hydrastinine hydrochloride*

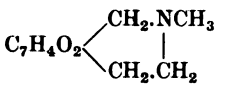
Its conversion into oxyhydrastinine and hydrohydrastinine by the action of potassium hydroxide recalls the similar behaviour with this reagent of aromatic aldehydes, which are thereby converted into a mixture of the corresponding aromatic alcohol and acid. This change may therefore be represented thus:

[1] Herzig and Mayer, *Monats.* 1897, **18**, 379.
[2] Freund and Will, *Berichte*, 1887, **20**, 88, 2400.
[3] *Annalen*, 1888, **249**, 172. *Cf.* Freund, *Berichte*, 1889, **22**, 2329.

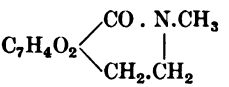


Hydrastinine *Intermediate products*

Product I by loss of water forms hydrohydrastinine, and product II in like manner gives oxyhydrastinine:



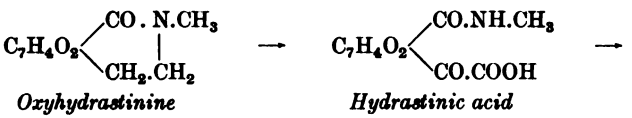
Hydrohydrastinine



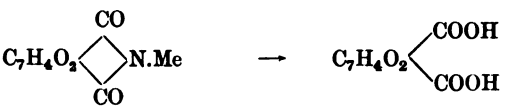
Oxyhydrastinine

Further insight into the constitution of oxyhydrastinine has been obtained by study of (1) its oxidation products, (2) its products of "exhaustive methylation."[1]

Alkaline permanganate converts oxyhydrastinine into hydrastinic acid, $C_{11}H_9O_6N$: this in turn is oxidised by dilute nitric acid to the methylimide of hydrastic acid, which when warmed with potassium hydroxide furnishes methylamine and hydrastic acid, $C_9H_6O_6$. These changes may be represented thus:



Oxyhydrastinine *Hydrastinic acid*

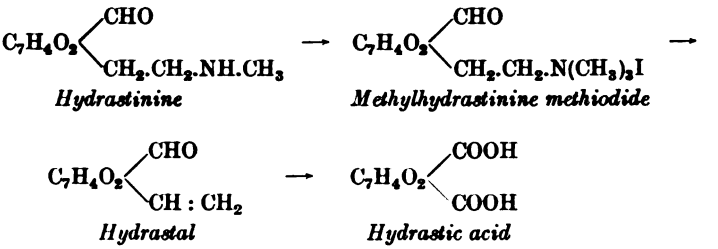


Hydrastic acid methylimide *Hydrastic acid*

Hydrastic acid also results from "exhaustive methylation" of hydrastinine. The latter as a secondary amine gives with methyl iodide a mixture of hydrastinine hydriodide and methylhydrastinine

[1] Freund and collaborators, *Berichte*, 1889, **22**, 456, 1156, 2322, 2329; *Annalen*, 1892, **271**, 320.

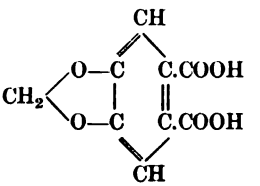
methiodide. The latter on distillation with alkali yields trimethylamine and an aldehyde, hydrastal, $C_{10}H_8O_3$, which on oxidation furnishes hydrastic acid, $C_9H_6O_6$.[1]



Hydrastinine — *Methylhydrastinine methiodide*

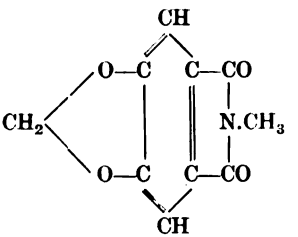
Hydrastal — *Hydrastic acid*

Hydrastic acid, $C_9H_6O_6$, needles, m.p. 175°, is a dibasic acid, and on melting passes into an anhydride. When fused with potassium hydroxide it furnishes a mixture of protocatechuic acid and catechol. On heating with strong nitric acid the methylene ether of dinitrocatechol is formed, whilst phosphorus pentachloride converts it into nor*meta*hemipinic acid. These observations are explained by the following formula, representing hydrastic acid as 4 : 5-dioxymethylenephthalic acid :

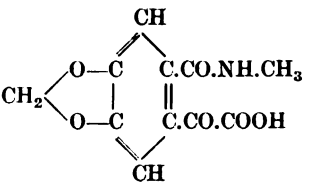


Hydrastic acid

Utilising this formula for hydrastic acid, the formulæ for the intervening products back to hydrastinine may be written as follows :

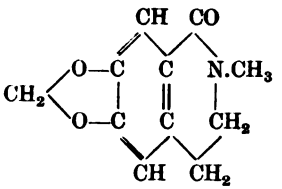


Hydrastic acid methylimide

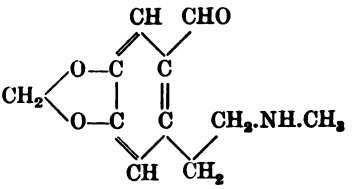


Hydrastinic acid

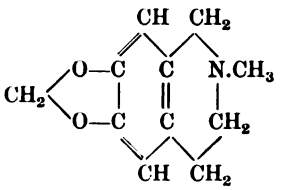
[1] Freund, *Berichte*, 1889, **22**, 2320.



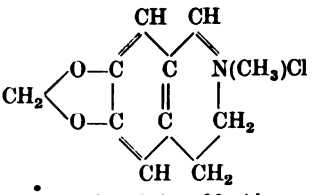
Oxyhydrastinine



Hydrastinine (Roser)

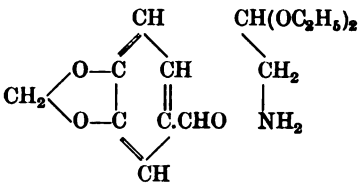


Hydrohydrastinine

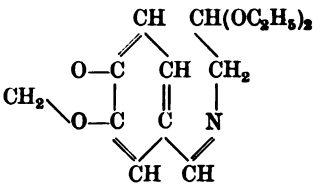


Hydrastinine chloride

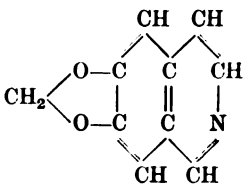
This formula for hydrastinine has been confirmed by Fritsch's synthesis [1] of this base by condensing piperonal with aminoacetal, and treating the piperonylideneaminoacetal so produced with sulphuric acid, thereby converting it into methylenedioxy*iso*quinoline. The methiodide of the latter on reduction furnished hydrohydrastinine hydriodide. The various steps in this synthesis are graphically represented thus :



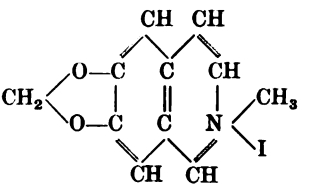
Piperonal *Aminoacetal*



Piperonylideneaminoacetal

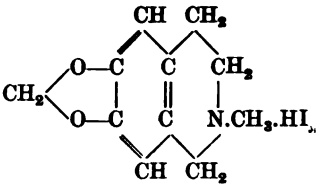


Methylenedioxyisoquinoline



Methylenedioxyisoquinoline methiodide

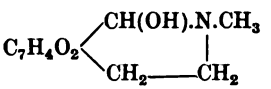
[1] *Annalen*, 1895, **286**, 18.



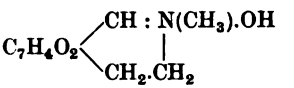
Hydrohydrastinine hydriodide

Decker has shown[1] that formylpiperonylamine, $CH_2:O_2:C_6H_3.CH_2.CH_2.NH.COH$, obtained by heating homopiperonylamine formate at 160°–170°, on heating with phosphorus pentoxide yields 6 : 7-methylenedioxy-3 : 4-dihydro*iso*quinoline, which with methyl iodide yields hydrastinine hydriodide. By an extension of this reaction[2] a series of substituted hydrastinines has been prepared. Freund[3] has described the preparation of substituted hydrastinines from tetrahydroberberine. Quite recently Pyman and Remfry have prepared hydrastinine from cotarnine.[4]

Dobbie and Tinkler[5] have suggested that since hydrastinine in solution in ether or chloroform has an absorption spectrum almost identical with that of hydrohydrastinine, whilst the absorption spectra of its solutions in water or alcohol resemble those of the salts, it may exist in two forms represented by formulæ *I* and *II*, *I* representing it in the solid state, or dissolved in ether or chloroform, and the other representing it dissolved in water or alcohol.



Hydrastinine I
(*carbinol form*)

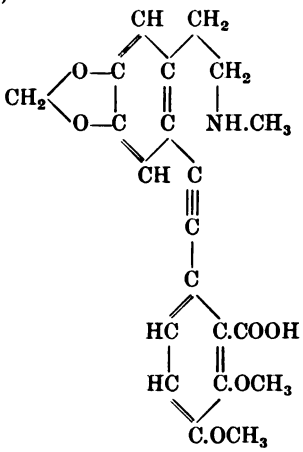


Hydrastinine II
(*ammonium form*)

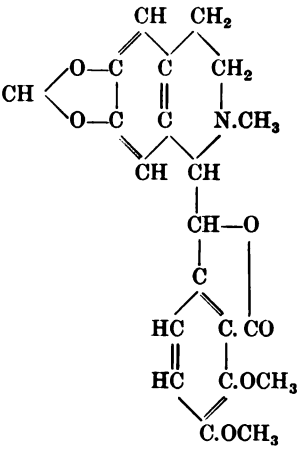
The suitable combination of the formulæ for hydrastinine and opianic acid (p. 279) to represent the parent alkaloid, hydrastine, may be made in several ways. Thus Freund,[6] taking into consideration the fact that the two products of hydrolysis each contained an aldehyde group whilst hydrastine itself had none, suggested

[1] *German Patent* 234850, 1911.
[2] *Farbenfabrik* vorm. Fr. Baeyer & Co., *German Patent* 235358, 1911.
[3] *Ibid.* 241136, 1911.
[4] *Trans. Chem. Soc.* 1912, **101**, 1595.
[5] *Ibid.* 1904, **85**. 1006.
[6] *Berichte*, 1889, **22**, 2337.

that the combination must occur by condensation between these two groups, and in this way arrived at the following representation (I) :



(I)
Hydrastine (Freund)



(II)
Hydrastine (Roser)

This formula, however, represents hydrastine as a secondary amine, though the alkaloid reacts with alkyl iodides on the whole as a tertiary amine. Moreover, hydrastine forms salts with alkalis rather as a lactone than as a free acid. These and other considerations led Roser to suggest the alternative formula (II) given above, which is in better agreement with these reactions.[1]

Berberine, $C_{20}H_{17}O_4N.H_2O$ or $C_{20}H_{19}O_5N$. This second alkaloidal constituent of *Hydrastis canadensis* is somewhat widely distributed in the vegetable kingdom and occurs in species belonging to a number of different natural orders. Some of the occurrences are as follows :

Natural Order	*Species*
Ranunculaceæ . . .	*Coptis Teeta, C. trifolia, Hydrastis canadensis, Zanthorhiza apiifolia.*

[1] *Annalen*, 1889, **254**, 357. *Cf.* Freund and Rosenburg, *Berichte*, 1890, **23**, 404 ; Freund, *Annalen*, 1892, **271**, 311 ; and Schmidt, *Arch. Pharm.* 1893, **231**, 541.

Natural Order	*Species*
Berberidaceæ . . .	*Berberis vulgaris, B. Aquifolium* (*B. repens*), *B. buxifolia, B. glauca, B. ætnensis, B. nervosa*, and other species; *Leontice thalictroides, Nandina domestica.*
Leguminoseæ . . .	*Andira inermis.*
Menispermaceæ . . .	*Coscinium fenestratum.*
Papaveraceæ . . .	*Argemone mexicana, Chelidonium majus, Stylophorum diphyllum.*
Anonaceæ	*Xylopia polycarpa* (*Cœlocline polycarpa*).
Rutaceæ	*Xanthoxylon clava Herculis* and other species, *Orixa* (*Celastrus*) *japonica, Toddalia aculeata, Evodia meliæfolia.*

It has been stated to occur in *Podophyllum peltatum* rhizome, but this was disproved by Power.[1] Similarly Gordin[2] has shown that it does not occur in calumba root (p. 372), pareira brava root (p. 416), *Menispermum canadense*, or *Jeffersonia diphylla.*

The alkaloid was first isolated by Chevalier and Pelletan from the bark of *Xanthoxylon clava Herculis*[3] and called "xanthopicrit." It was found independently by Buchner and Herberger[4] in barberry root bark, *Berberis vulgaris*, and was examined by Fleitmann.[5] The formula now assigned to the alkaloid was first used by Perrins, who identified berberine with "xanthopicrit."[6]

From *Hydrastis canadensis* or other sources berberine is usually isolated as the crude sulphate, as described on p. 274. From this the alkaloid may be recovered by the action of ammonia and recrystallised from hot water or alcohol.[7] Gaze[8] recommends the acetone compound of berberine as a means of purification. For the preparation of this, 50 grm. of crude berberine sulphate are dissolved in 1000 grm. of water, and 500 grm. of acetone added. The mixture is then made alkaline with sodium hydroxide solution when the acetone compound is precipitated as a lemon-yellow powder. For the recovery of berberine from this compound, Gaze recommended boiling 2 grm. of the substance with 50 c.c. of dry

[1] *Amer. Journ. Pharm.* 1878, **50**, 370.
[2] *Arch. Pharm.* 1902, **240**, 146.
[3] *Journ. chim. med.* 1826, **2**, 314.
[4] *Annalen, Suppl.* 1835, **24**, 228.
[5] *Annalen*, 1846, **59**, 60.
[6] *Journ. Chem. Soc.* 1862, **15**, 339.
[7] Lloyd, *Pharm. Journ.* 1879–80 [iii], **10**, 125.
[8] *Arch. Pharm.* 1890, **228**, 604.

alcohol containing 5 c.c. of chloroform, but Gordin and Merrell [1] state that this gives rise to berberine hydrochloride, $B.HCl.2H_2O$, not berberine itself.

For the estimation of berberine Gordin [2] has suggested the precipitation of the alkaloid as sulphate by adding alcoholic sulphuric acid to an alcoholic solution of the alkaloid; the precipitate is subsequently suspended in water and decomposed by the addition of potassium iodide solution, by which means the insoluble berberine hydriodide is precipitated and the liberated sulphuric acid is then titrated with $N/40$ potassium hydroxide solution. This method may be applied to the estimation of berberine in plants if the crude alkaloid is first purified through the acetone compound.[3] In the case of hydrastis rhizome the hydrastine must first be extracted from the rhizome by dry ether (*see* p. 275).

Troeger and Linde [4] have pointed out that berberine may be estimated by precipitation with a known excess of an aqueous solution of β-naphthalenethiosulphonate, previously standardised by means of $N/100$ iodine solution, the excess of the precipitant being determined by titration of the filtrate with $N/100$ iodine solution.

Berberine crystallises from water in long, silky, reddish-yellow needles with $5\frac{1}{2}H_2O$; dried at 100°, the crystals retain $2\frac{1}{2}H_2O$; from chloroform it forms triclinic tablets containing $1CHCl_3$, m.p. 179°; the acetone compound, $B.C_3H_6O$, forms reddish-yellow tablets. Berberine melts indefinitely, decomposing above 110°, and is completely liquid only at 160° (*decomp.*). It is slightly soluble in cold water (1 in 4·5 at 21°) or alcohol (1 in 100), but readily soluble in the hot liquids; slightly soluble in benzene or chloroform and insoluble in ether or light petroleum. The aqueous solution is bitter to the taste, neutral to litmus, and optically inactive. The salts are formed with the loss of $1H_2O$: they are mostly of dull yellow colour and crystallise well. The hydrochloride, $C_{20}H_{17}O_4N.HCl.2H_2O$, small needles; the hydriodide, $C_{20}H_{17}O_4N.HI$, is sparingly soluble in cold water (1 in 2130); the nitrate forms greenish-yellow needles and the

[1] *Arch. Pharm.* 1901, **239**, 226.
[2] *Ibid.* 1901, **239**, 638.
[3] Gordin and Prescott, *ibid.* 1899, **237**, 439.
[4] *Ibid.* 1900, **238**, 4.

sulphate slender yellow needles; both these are sparingly soluble in cold water, and even less so in dilute solutions of the corresponding acids. The phosphate, $C_{20}H_{17}O_4N.2H_3PO_4.1\frac{1}{2}H_2O$, is bright yellow and crystalline.[1] The aurichloride, the platinichloride, and carbonate can be crystallised, the first from alcoholic hydrochloric acid.

An aqueous solution of berberine gives a precipitate of the characteristic crystalline nitrate on addition of nitric acid (sp. gr. 1·185). On reduction with sulphuric acid and zinc the aqueous solution becomes colourless owing to the formation of the so-called tetrahydroberberine (p. 297). Chlorine water, added to berberine hydrochloride dissolved in water, gives a reddish coloration. For other reactions, *see* Hirschhausen.[2] For the detection of berberine in plants Gordin [3] recommends the following method: The plant (5–20 grm.) is extracted with hot alcohol, the dry extract mixed with water (20–40 c.c.) and the solution, cleared by ground talc if necessary, filtered. To a few cubic centimetres of the filtrate, potassium iodide (10 per cent.) solution is added, when, if berberine is present, the hydriodide will be precipitated. If a precipitate forms, berberine is isolated from 10 c.c. of the filtrate by adding 1–2 c.c. of 10 per cent. sodium hydroxide solution and 5 c.c. of acetone, and warming to 50°. The solution is then set aside. If no crystals separate in two hours, 30 c.c. of water are added and the solution set aside over-night. Crystals of berberine-acetone will then form if the filtrate contained more than 0·1 per cent. of the alkaloid.

Berberine is not toxic in the ordinary sense to the larger animals and man. In rabbits it produces respiratory disturbance and paresis. Drugs containing berberine as their chief constituent, *e.g.* barberry bark, have been used chiefly as tonics and stomachics.

Constitution of Berberine. Our knowledge of the chemistry of berberine is chiefly due to W. H. Perkin, jun.[4]

When heated with hydriodic acid, berberine yields two mole-

[1] Shedden, *Pharm. Journ.* 1900 [iv], **11**, 89.
[2] *Zeit. anal. Chem.* 1885, **24**, 157. [3] *Arch. Pharm.* 1902, **240**, 146.
[4] *Trans. Chem. Soc.* 1889, **55**, 63; 1890, **57**, 991; 1910, **97**, 305.

cular proportions of methyl iodide and is thereby converted into BERBEROLINE, $C_{18}H_{13}O_4N$. The latter is amorphous, gives an amorphous sulphate, and dissolves in alkaline solutions, forming dark violet liquids.

When berberine is oxidised in warm alkaline solution with potassium permanganate (Perkin [1]) an interesting series of derivatives is obtained, of which the following are the more important: *Berberal*, $C_{20}H_{17}O_7N$; *Anhydroberberilic acid*, $C_{20}H_{17}O_8N$; *Berberilic acid*, $C_{20}H_{19}O_9N$.

Berberilic acid, $C_{20}H_{19}O_9N$, m.p. 177°–182°, crystallises from methyl alcohol on addition of water. It is dibasic and furnishes a dimethyl ester, m.p. 173°. When heated to about 180°, the acid loses $1H_2O$, and passes into ANHYDROBERBERILIC ACID, $C_{20}H_{17}O_8N$, which is one of the most easily obtained oxidation products of berberine. It forms colourless needles, m.p. 236°, soluble in alkali and alkali carbonate solutions with the formation of salts of berberilic acid. When ammonium berberilate formed in this way is dried under reduced pressure a molecular proportion of ammonia is lost with the formation of the ammonium salt of the anhydro-acid, from which other salts have been obtained, and in particular the methyl ester, m.p. 178°. Anhydroberberilic acid appears therefore to be formed from berberilic acid by an intramolecular condensation between a carboxyl group and a hydrogen of a neighbouring group.

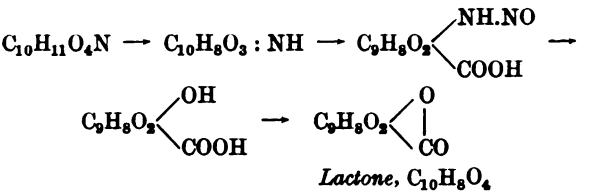
When berberilic acid is heated with dilute sulphuric acid it undergoes hydrolysis, as shown by the following equation:

$$\underset{\textit{Berberilic acid}}{C_{20}H_{19}O_9N} + H_2O = \underset{\textit{Hemipinic acid}}{C_{10}H_{10}O_6} + \underset{\textit{Aminoethylpiperonyl-carboxylic acid}}{C_{10}H_{11}O_4N}$$

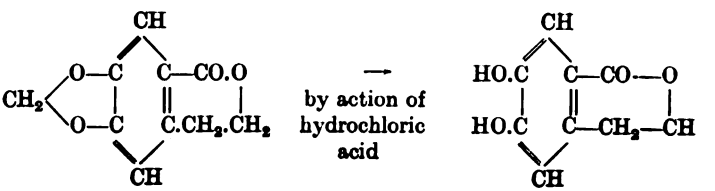
The identity of the non-nitrogenous acid hydrolytic product with hemipinic acid is shown by the facts that it crystallises in lustrous prisms, m.p. 159°–160°, furnishes protocatechuic acid on fusion with potash, and in all its reactions agrees with the hemipinic acid obtained by Goldschmiedt from narcotine and which has the constitution $C_6H_2[OCH_3 : OCH_3 : COOH : COOH = 1 : 2 : 3 : 4]$.

[1] *Loc. cit.*

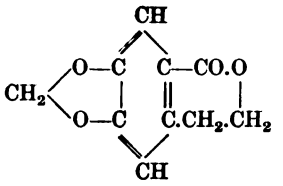
The nitrogenous product of the hydrolysis of berberilic acid crystallises in large tabular crystals, m.p. 180°–182°, readily forms well-crystallised salts with acids, and also possesses weak acid properties. When boiled with water or when heated at its melting-point it forms an anhydride, $C_{10}H_9O_3N$, which with nitrous acid gives a nitrosoamine that is decomposed by alkalis, evolving nitrogen and yielding a lactone, $C_{10}H_8O_4$, colourless needles, m.p. 126°. These changes may be represented thus :



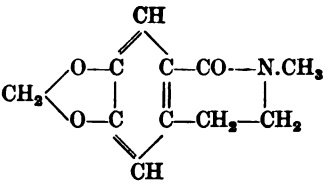
The lactone dissolves in alkalis, giving salts of the corresponding acid, $C_{10}H_{10}O_5$, and when heated in sealed tubes with dilute hydrochloric acid is decomposed with the liberation of carbon and the formation of a new crystalline substance, $C_9H_8O_4$, m.p. 220°–225°, having all the characters of a catechol derivative. This last change is analogous with that observed by Fittig and Remsen in the case of piperonylic acid, which when heated with dilute hydrochloric acid decomposes into carbon and protocatechuic acid. It was therefore probable that the lactone, $C_{10}H_8O_4$, was a piperonyl derivative, in which case the change outlined can be regarded as taking place in the following way :



Such a substance is closely related to oxyhydrastinine (p. 280) obtained previously by Freund from hydrastinine, as comparison of formulæ I and II shows :



(I)

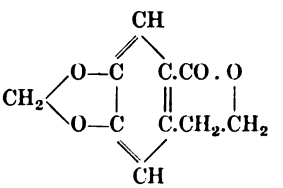


(II)

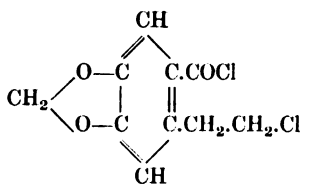
Oxyhydrastinine

The proof of this was furnished by Perkin's synthesis [1] of oxyhydrastinine from the berberine derivative $C_{10}H_8O_4$, which may now be called ω-hydroxyethylpiperonylcarboxylic acid anhydride.

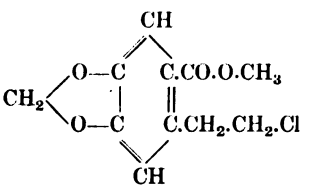
This synthesis was accomplished by treating the anhydride (I) with phosphorus pentachloride, thereby converting it into ω-chloroethylpiperonylcarboxylic acid chloride (II), which was then poured into absolute methyl alcohol and so converted into the chloromethylic ester (III).



(I)

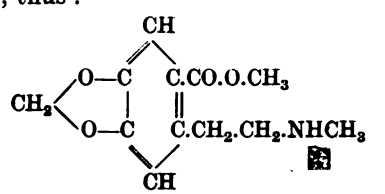


(II)

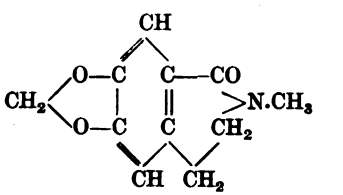


(III)

This on treatment with methylamine formed oxyhydrastinine (IV), thus :



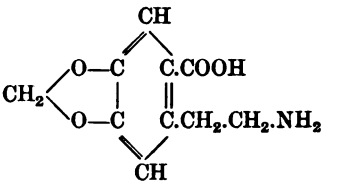
Intermediate amino-compound



(IV) *Oxyhydrastinine*

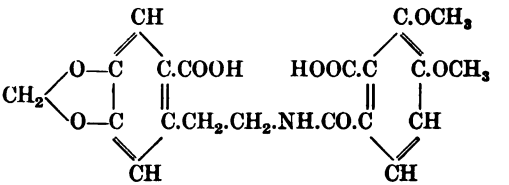
[1] *Trans. Chem. Soc.* 1890, **57**, 1034.

From this synthesis it follows that the nitrogenous hydrolytic product of berberilic acid must be ω-aminoethylpiperonylcarboxylic acid.[1]



ω-Aminoethylpiperonylcarboxylic acid

By combining this formula with that of hemipinic acid the following formula for berberilic acid is obtained :

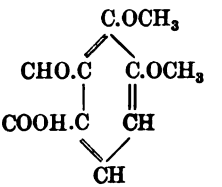


Berberilic acid (Perkin)

The validity of this formula has been proved by the synthesis of anhydroberberilic acid from hemipinic acid and ω-aminoethylpiperonylcarboxylic acid,[1] and from the anhydro-acid berberilic acid can be obtained by the action of alkalis as already stated (p. 289).

Berberal, $C_{20}H_{17}O_7N$. This substance is obtained from the parent alkaloid only with great difficulty, It crystallises in colourless glancing leaflets, m.p. 148°–150°. When hydrolysed by boiling with dilute sulphuric acid it furnishes ψ-opianic acid and the ω-aminoethylpiperonylcarboxylic acid anhydride similarly obtained from berberilic acid (p. 290).

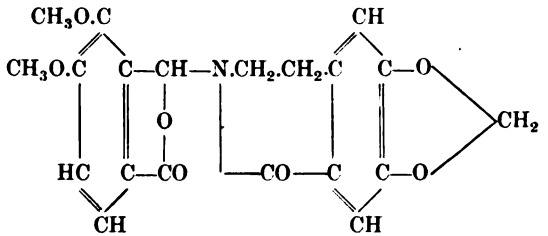
ψ-Opianic acid was found to be the semialdehyde corresponding to hemipinic acid, and has therefore the following constitution :



ψ-Opianic acid

[1] Perkin, *loc. cit.*

It was found possible to recombine ψ-opianic acid with the anhydro-base, $C_{10}H_9O_3N$, to form berberal, and Perkin and Robinson [1] have recently assigned the following formula to this substance, which differs a little from that originally given to this product : [2]



Berberal (Perkin and Robinson, 1910)

By combining opianic acid,

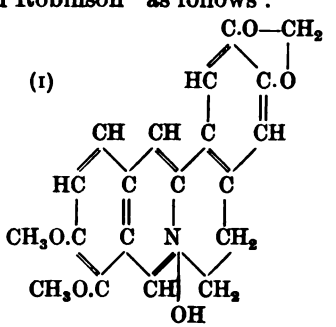
$$C_6H_2[MeO : MeO : COOH : CHO = 1 : 2 : 3 : 4],$$

with the anhydride $C_{10}H_9O_3N$, an isomeric substance, iso*berberal*, needles, m.p. 185°, has been obtained.[3]

Oxyberberine, $C_{20}H_{17}O_5N$. This alkaloid, the first product of the action of potassium permanganate on berberine, crystallises in lustrous, colourless (when pure) plates, m.p. 198°–200°, from xylene. When even traces are dissolved in 50 per cent. sulphuric acid and a drop of nitric acid is added to the solution a deep brown colour is produced, changing to intense violet. Oxyberberine has been synthesised recently by Pictet and Gams (*see* p. 296).

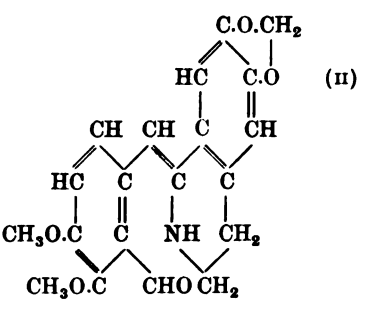
From a consideration of these reactions Perkin assigned a formula to berberine [4] which has recently been slightly modified by Perkin and Robinson [5] as follows :

(I)



Berberine (ammonium form)
(Perkin and Robinson)

(II)



Berberinal (aldehyde form)
(Perkin and Robinson)

[1] *Trans. Chem. Soc.* 1910, **97**, 321. [2] Perkin, *ibid.* 1890, **57**, 1002.
[3] Perkin, *loc. cit.* [4] *Loc. cit.* [5] *Loc. cit. Cf.* Faltis, *Monatshefte*, 1910, **31**, 557.

The necessity for at least two formulæ to represent berberine was shown by Gadamer,[1] who observed that on adding barium hydroxide to berberine sulphate solution a brownish-red, strongly alkaline solution of the free base (berberinium hydroxide of Gadamer, formula I, p. 293) is obtained, which with excess of sodium hydroxide yields berberinal (supposed aldehyde form of berberine, formula II), which differs from ordinary solid berberine (ammonium form) in being soluble in ether. This furnishes an oxime, m.p. 165°, and on treatment with concentrated sodium hydroxide yields oxyberberine, $C_{20}H_{17}O_5N$ (*see* p. 293), and dihydroberberine (so-called), $C_{20}H_{19}O_4N$, thus behaving like an aromatic aldehyde (*compare* hydrastinine, p. 280), the former being the acid anhydride and the latter the anhydride of the primary alcohol corresponding to the aldehyde berberinal. Faltis has suggested[2] that this reaction is in reality analogous with that between quinoline methiodide and alkalis,[3] and that the products formed are oxyberberine and tetrahydroberberine (*dl*-canadine). Tinkler[4] has, however, observed that ordinary berberine and its salts show the same ultra-violet absorption spectra, whilst Gadamer's "berberinal" shows an absorption spectrum almost identical with that of Freund and Beck's α-methyldihydroberberine,[5] which would appear to be a derivative of a carbinol form of berberine. Further, the absorption spectrum of the hydro-product formed by the action of alkalis on "berberinal" is similar to that of the supposed "berberinal" and is quite distinct from that of tetrahydroberberine, so that these observations lend no support to Faltis' suggestion referred to above. The position therefore is that berberine can theoretically exist in three forms, of which two are known, viz. the ammonium form (I) and the carbinol form (III), whilst the aldehyde form (II) has not been obtained. Tinkler proposes to replace Gadamer's name "berberinal" for the carbinol

[1] *Arch. Pharm.* 1901, **239**, 648; *Chem. Zeit.* 1902, **26**, 291; *Arch. Pharm.* 1905, **243**, 31; Voss and Gadamer, *ibid.* 1910, **248**, 43. *Cf.* Roser, *Chem. Zeit.* 1902, **26**, 385.

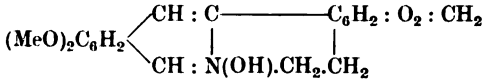
[2] *Monatshefte*, 1910, **31**, 557.

[3] Decker, *Berichte*, 1903, **36**, 2568.

[4] *Trans. Chem. Soc.* 1911, **99**, 1340.

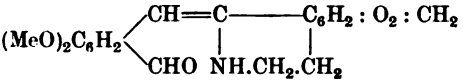
[5] *Berichte*, 1904, **37**, 4677.

form by "berberinol." The condensed formulæ for these three forms are as follows :



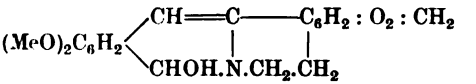
Ammonium form = ordinary berberine and berberine salts

(I)



Aldehyde form ; not known

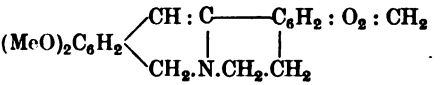
(II)



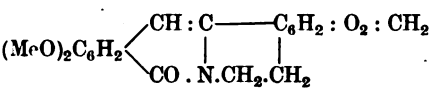
Carbinol form

(III)

By the action of strong alkalis the carbinol form is converted into dihydroberberine and oxyberberine, thus :



Dihydroberberine



Oxyberberine

Bland, Perkin and Robinson have shown that on treating oxyberberine with hydrochloric acid it is converted into *iso*oxyberberine, apparently by the opening of the reduced pyridine ring, thus : [1]

Synthesis of Oxyberberine. Confirmation of Perkin and Robinson's formula for berberine is afforded by Pictet and Gams' recent syntheses of this alkaloid and of oxyberberine.[2] Bouveault and

[1] *Trans. Chem. Soc.* 1912, **101**, 262.

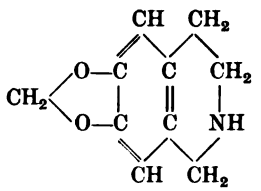
[2] *Compt. rend.* 1911, **152**, 1102; **153**, 386.

Wahl showed that piperonal condenses with nitromethane in presence of sodium methoxide and methyl alcohol to yield piperonylidene-nitromethane ; this on oxidation furnishes homopiperonaldoxime,[1] which Medinger [2] found was reduced by sodium and alcohol to homopiperonylamine :

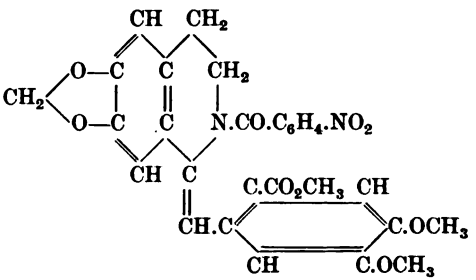
$CH_2 : O_2 : C_6H_3.CH_2.CH : NOH$ — *Homopiperonaldoxime*

$CH_2 : O_2 : C_6H_3.CH_2.CH_2.NH_2$ — *Homopiperonylamine*

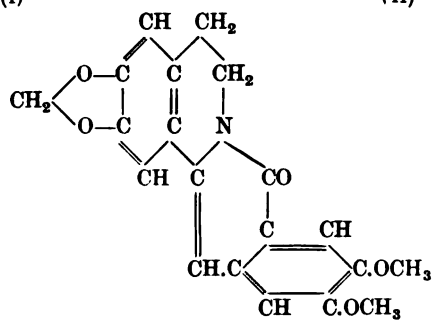
Pictet and Gams treated this amine with formaldehyde in presence of hydrochloric acid, thereby converting it into methylenedioxytetrahydro*iso*quinoline (norhydrohydrastinine) (I). The *o*-nitrobenzoyl derivative of this reacts with the methyl ester of opianic acid in presence of sulphuric acid to give the compound (II), which crystallises in needles, m.p. 103°–105°, and on treatment with potassium hydroxide in alcohol yields Perkin's oxyberberine (III) by hydrolysis and subsequent elimination of water between the carboxyl and imino groups.



(I)



(II)



(III)

Oxyberberine

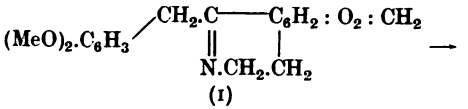
[1] *Compt. rend.* 1902, **135**, 41.

[2] *Monats.* 1906, **27**, 237.

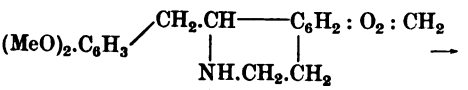
Synthesis of Berberine. This was accomplished by Pictet and Gams by an extension of the method just described. Homoveratroylhomopiperonylamine,

$$CH_2 : O_2 : C_6H_3.CH_2.CH_2.NH.CO.CH_2.C_6H_3(OCH_3)_2,$$

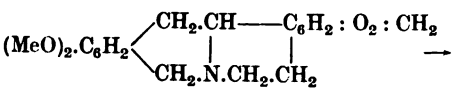
loses $1H_2O$ when heated with phosphoric anhydride in xylene, forming the compound (I), which on reduction with tin and hydrochloric acid furnishes veratroylnorhydrohydrastinine (II). On treating this with methylal in presence of hydrochloric acid a $—CH_2$ group is inserted between the veratroyl ring and the imino group, yielding tetrahydroberberine (III), and this on oxidation yields berberine (IV). These steps are shown by the following condensed formulæ :



(I)

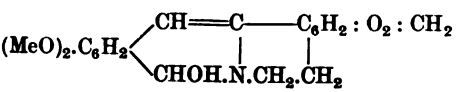


(II)



(III)

Tetrahydroberberine (*dl*-Canadine)



(IV)

Berberine

By the application of the Grignard reaction to berberine, Freund has prepared a series of α-alkyldihydroberberines.[1]

Canadine, $C_{20}H_{21}O_4N$. In 1873 Hale[2] obtained indications of a third alkaloid in *Hydrastis canadensis*, and this was confirmed by Burt.[3] This third alkaloid was isolated in a pure state from

[1] *Berichte*, 1904, **37**, 3334, 4673; 1907, **40**, 2604. *Cf.* E. Merck, *German Patent* 179212, 1907.

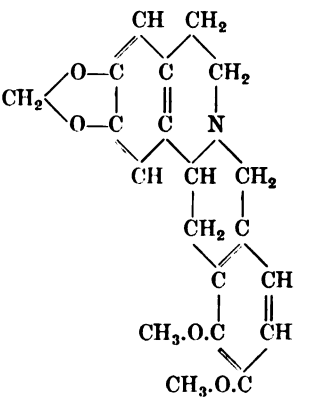
[2] *Amer. Journ. Pharm.* 1873, **45**, 247.

[3] *Pharm. Journ.* 1875–76 [iii], **6**, 467.

hydrastis rhizome and named canadine by Schmidt and Wilhelm,[1] and was subsequently examined by Schmidt.[2] It is best separated from crude hydrastine (*see* p. 277) by fractional crystallisation of the nitrates, canadine nitrate being less soluble than the hydrastine salt.

The alkaloid forms silky needles, m.p. 132·5°, insoluble in water, but readily soluble in ether; lævorotatory, $[\alpha]_D$ — 298° in chloroform. The hydrochloride and nitrate are crystalline, lævorotatory, and slightly soluble in water. Canadine gives an olive-green colour changing to brownish black with sulphovanadic acid, and a similar colour changing to brownish red with Fröhde's reagent.

Gadamer,[3] by fractional crystallisation of tetrahydroberberine *dextro-o*-bromocamphorsulphonate, has isolated a lævorotatory alkaloid identical with canadine, which is therefore to be regarded as *lævo*tetrahydroberberine. The *d*- form melts at 139°–140°.



Canadine

The peculiar isomerism of the ammonium compounds derived from tetrahydroberberine is discussed by Voss and Gadamer.[4]

Canadine in small doses causes drowsiness and depression. In large quantities it gives rise to transient excitement succeeded by depression and paralysis of the central nervous system. Its injection is followed by violent peristalsis of the intestine with diarrhœa.

[1] *Arch. Pharm.* 1888, **226**, 329. [2] *Ibid.* 1894, **232**, 136.
[3] *Ibid.* 1901, **239**, 648; Voss and Gadamer, *ibid.* 1910, **248**, 43.
[4] *Ibid.* 1910, **248**, 43. *Cf.* McDavid, Perkin and Robinson, *Trans. Chem. Soc.*, 1912, **101**, 1220.

It is said to have no influence on the blood-pressure, although the racemic modification obtained by reducing berberine causes constriction of the blood-vessels and consequent rise of blood-pressure, in opposition to berberine, which reduces the blood-pressure.

ALKALOIDS OF *BERBERIS* SPECIES

The root barks of *Berberis vulgaris* and of *Berberis Aquifolium* are used in medicine, the former in Europe and the latter in the United States. *B. vulgaris* contains three alkaloids, berbamine, berberine, and oxyacanthine.[1] Parsons,[2] Stubbe and Rüdel [3] have shown that the same three alkaloids also occur in *Berberis Aquifolium*.[4]

The berberine is best isolated as the sulphate as described already (p. 287). Berbamine and oxyacanthine remain in the mother liquors. They are precipitated by the addition of sodium hydroxide solution, dissolved in ether, and the residue left on evaporation of this solvent dissolved in acetic acid. Sodium sulphate is then added to this solution, when oxyacanthine sulphate is precipitated. The filtrate from this is treated with sodium nitrate, which precipitates berbamine nitrate. From these two salts the alkaloids are regenerated in the usual way, converted into the hydrochlorides, and these recrystallised from water.

Berbamine, $C_{18}H_{19}O_3N$. This alkaloid crystallises with $2H_2O$ from alcohol in small leaflets, m.p. 156° (*dry*), or anhydrous from light petroleum in warty masses, m.p. 197°–210°. The salts crystallise well. The sulphate, $B_2.H_2SO_4.4H_2O$, forms small leaflets or needles; the platinichloride, $B_2.H_2PtCl_6.5H_2O$, is a crystalline yellow precipitate, and the aurichloride is amorphous.

According to Rüdel [5] berbamine gives the same colour reactions as oxyacanthine (p. 300) and is probably the next lower homologue of that alkaloid.

[1] Polex, *Arch. Pharm.* 1836 [ii], **6**, 271; Wacker, *Jahresb.* 1861, 545; Hesse, *Berichte*, 1886, **19**, 3190.

[2] *Pharm. Journ.* 1882–83 [iii], **13**, 46. [3] *Arch. Pharm.* 1891, **229**, 631.

[4] *Cf.* Pommerehne, *Ibid.* 1895, **233**, 127. [5] *Loc. cit.*

Oxyacanthine, $C_{19}H_{21}O_3N$. This substance crystallises from ether or alcohol in needles, m.p. 208°–214° (Hesse), 202°–204° (Rüdel), or from light petroleum in warty masses, m.p. 175°–185° (Rüdel). It is dextrorotatory, $[\alpha]_D$ + 174° 5′ in alcohol, + 131·6° in chloroform. The hydrochloride, $B.HCl.2H_2O$, forms colourless needles and is dextrorotatory in aqueous solution, $[\alpha]_D$ + 163·6°: the nitrate, $B.HNO_3.2H_2O$, forms small needles, m.p. 195°–200° (*decomp.*), and is sparingly soluble in water. The platinichloride and aurichloride are both amorphous.

According to Hesse, oxyacanthine is converted by alcoholic potassium hydroxide into the potassium salt of β-oxyacanthine, which is reconverted into oxyacanthine by addition of a large excess of acid. Pommerehne [1] has shown that one oxygen atom is present as a hydroxyl group and the other two as methoxyl groups, and that the base forms a methiodide, m.p. 248°–250° (*dry*).

Oxyacanthine dissolves in nitric acid, forming a yellowish-brown solution. It is not coloured by sulphuric acid, but on further addition of nitric acid a yellow coloration changing to red is observed. Molybdic acid in sulphuric acid gives a dirty violet tint changing to yellowish green. Bromine water gives a yellow precipitate. Oxyacanthine liberates iodine from potassium iodide in dilute acid solution and gives a blue coloration with a mixture of potassium ferricyanide and ferric chloride.

[1] *Loc. cit.*

VI. GLYOXALINE GROUP

ALKALOIDS OF *PILOCARPUS*, SPP. (JABORANDI)

THE leaves of the South American plant *Pilocarpus Jaborandi* were first employed therapeutically in 1874 by Dr. Coutinho of Pernambuco, by whom they were sent to Europe. At first the leaves were referred to *P. pennatifolius*, but in a subsequent investigation by Holmes the latter botanist showed that up to 1893 the jaborandi of commerce was obtained from the first-mentioned plant, although small quantities of the leaves of *P. pennatifolius* had on various occasions been placed on the market. Since 1896 the leaves of both these species have been unobtainable in commerce, and their place has been taken by the leaves of *P. microphyllus*. The leaves of *P. spicatus* and *P. trachylophus* have also appeared on the English market from time to time.

The drug was first examined in 1875 by Hardy,[1] who isolated from it an alkaloid to which he gave the name pilocarpine. This base was prepared independently a few months later by Gerrard,[2] who succeeded in obtaining several of its salts in a crystalline condition. Some years later Harnack and Meyer[3] isolated a second amorphous alkaloid, jaborine, which according to Jowett[4] is merely a mixture of the various alkaloidal constituents of the drug. In 1885 Harnack and Meyer[5] discovered a third alkaloid, pilocarpidine, in jaborandi, and the existence of this alkaloid has been confirmed by Jowett,[4] though it does not occur in the jaborandi of present-day commerce. In 1897 a fourth alkaloid was isolated by Petit and Polonowsky[6] from the leaves of *Pilocarpus*

[1] *Bull. Soc. chim.* 1875 [ii], **24**, 497.
[2] *Pharm. Journ.* 1875 [iii], **5**, 865, 965; 1877, **7**, 255.
[3] *Annalen*, 1880, **204**, 67.
[4] *Trans. Chem. Soc.* 1900, **77**, 474, 851; 1901, **79**, 581, 1331.
[5] *Chem. Centr.* 1885, 628.
[6] *Journ. Pharm.* 1897 [vi], **5**, 370, 430, 475; **6**, 8.

microphyllus and named by them pilocarpidine [β-pilocarpine (Brühl), *iso*pilocarpine (Jowett)], apparently under the impression that it was identical with Harnack and Meyer's base. A fifth alkaloid, pilosine, has been obtained by Pyman. Petit and Polonowsky have stated that *P. spicatus* leaves contain φ-pilocarpine and ψ-jaborine.

The principal facts relating to the origin and chemistry of jaborandi are shown in the following table :

Name of plant	Commercial name	Synonym	Constituents	Amount of total alkaloid per cent.	Amount of crystalline pilocarpine nitrate obtained per cent.
P. Jaborandi (Holmes)	Pernambuco jaborandi	Formerly regarded as *P. pennatifolius*	pilocarpine *iso*pilocarpine (?) pilocarpidine	0·72[1]	0·67
P. pennatifolius (Lemaire)	Paraguay jaborandi	*P. selloanus*	pilocarpine *iso*pilocarpine	0·2 to 0·3	
P. microphyllus (Stapf)	Maranham jaborandi	—	pilocarpine *iso*pilocarpine pilosine	0·765 to 0·783[2]	0·45[1]
P. racemosus	Guadeloupe jaborandi	—	pilocarpine		0·12[3]
P. trachylophus (Holmes)	Ceara jaborandi	—	Not known	0·4[1]	
P. spicatus (St. Hilaire)	Aracati jaborandi	—	ψ-pilocarpine ψ-jaborine	0·16[1]	

The United States Pharmacopœia (8th Rev.) gives the following process for the determination of the total alkaloids in jaborandi leaves : Ten grammes of leaves in No. 60 powder are mixed with 2 c.c. of ammonia water (sp. gr. 0·958 at 25°) and 3 c.c. of chloroform, and packed firmly in a cylindrical percolator, the lower opening of which is closed with a wad of cotton-wool. The drug is percolated slowly with chloroform containing 2 per cent. of ammonia water until exhausted (usually about 100 c.c. of solvent are enough).

[1] Paul and Cownley, *Pharm. Journ.* 1896 [iv], 3, 1.
[2] Evans, *Analytical Notes*, 1906, p. 21; 1908, p. 20; 1909, p. 35.
[3] Jowett and Pyman, *Proc. Chem. Soc.* 1912, **28**, 268.

The percolate is placed in a separator and the alkaloids extracted from it by shaking (*a*) with 15 c.c. *N*-sulphuric acid, (*b*) with 2 c.c. *N*-sulphuric acid mixed with 8 c.c. of water, and (*c*) with 10 c.c. of water. The combined acid extract is made alkaline with ammonia and shaken out with 20, 15, and 10 c.c. of chloroform. The residue left on evaporating the combined chloroform solutions is dissolved in 7 c.c. *N*/10 sulphuric acid and titrated back with *n* c.c. of *N*/50 potassium hydroxide solution, using cochineal or iodeosin as indicator. The percentage of total alkaloids is given by the formula $(7 - n/5)0{\cdot}2$. It should not be less than 0·5.

Jowett has pointed out [1] that the estimation of the total alkaloids is of little value since *iso*pilocarpine is less active than pilocarpine, and has suggested the following method for the examination of the total alkaloid with a view to obtaining an approximate idea of the amount of pilocarpine present:

The varnish obtained by extracting the total alkaloids by any suitable process is dissolved in a small quantity of a saturated alcoholic solution of pilocarpine nitrate, and to the solution a strong, freshly prepared alcoholic solution of nitric acid is added until the mixture is distinctly acid. A small crystal of pilocarpine nitrate is added and the whole set aside two hours to crystallise. The mixture is vigorously stirred, any crystals which have separated are filtered off, washed with a saturated alcoholic solution of pilocarpine nitrate, dried and weighed. This may for most purposes be taken as pilocarpine nitrate, but it should be examined by the determination of its melting-point and specific rotation. The former constant should be between 164° and 174°, and from the rotation found the percentage of pilocarpine (*p*) present may be calculated from the formula $p = 100(n—38{\cdot}5)/43{\cdot}7$, where *n* is the observed specific rotation.

The alkaloids of jaborandi leaves may be prepared as follows: The finely powdered leaves are extracted with alcohol containing 1 per cent. of hydrochloric acid. The solvent is distilled off, the aqueous residue filtered, made just neutral by addition of ammonia,

[1] *Year-Book of Pharmacy*, 1899, 36, 435.

and evaporated to a low bulk. Excess of ammonia is then added and the free alkaloids shaken out with chloroform. The latter is distilled off, the residue dissolved in a small volume of water and neutralised by dilute nitric acid. The nitrates which crystallise out are separated into pilocarpine and *iso*pilocarpine nitrate by recrystallisation from alcohol.

Pilocarpine, $C_{11}H_{16}O_2N_2$. Pilocarpine is a colourless oil, b.p. 260°/5 mm. (partially isomerised on distillation), $[\alpha]_D + 100{\cdot}5°$ freely soluble in water, alcohol, or chloroform, but almost insoluble in ether or light petroleum. The salts of pilocarpine with acids crystallise well; the nitrate, $B.HNO_3$, forms well-defined prisms, m.p. 178°, $[\alpha]_D + 82{\cdot}9°$, and dissolves in 6·4 parts of water at 20°; the hydrochloride, B.HCl, prisms, m.p. 204°–205°, $[\alpha]_D + 91{\cdot}74°$. The nitrate and hydrochloride are chiefly used in medicine. Jowett suggests the following characters for these salts in a condition of sufficient purity for this purpose. *Nitrate*, white distinct crystals, m.p. 176°–178°, $[\alpha]_D + 81°$ to 83° in water, soluble in 6 to 7 parts of water or 146 of alcohol (95 per cent.) at 15°, almost insoluble in ether or chloroform; a concentrated aqueous solution gives no precipitate with ammonia or with aqueous solutions of sodium or potassium hydroxide. *Hydrochloride*, white deliquescent crystals, m.p. 200°–204° (*dry*), $[\alpha]_D + 90°$ to 92° in water, soluble in less than its own weight of water, or in 10 parts of dry alcohol. A concentrated aqueous solution gives no precipitate with ammonia and only a few oily drops, which rapidly redissolve, with aqueous solutions of sodium or potassium hydroxide.[1]

The hydrobromide forms small prisms, m.p. 185°, $[\alpha]_D + 77{\cdot}05°$; the aurichloride, $B.HAuCl_4.H_2O$, small lemon-yellow needles, m.p. 117°–130° (*dry*); and the picrate, characteristic long needles, m.p. 147°. Pilocarpine dissolves in dilute soda solution, and the rotation is thereby reduced due to the formation of the sodium salt of pilocarpic acid, $C_{11}H_{18}O_3N_2$, of which pilocarpine is the lactone, and in like manner barium and copper salts, $(C_{11}H_{15}O_3N_2)_2Cu$, may be prepared. The pilocarpates are amorphous.

[1] *Pharm. Journ.* 1899, July 29.

***iso*Pilocarpine**, $C_{11}H_{16}O_2N_2$ (*Pilocarpidine*, Petit and Polonowsky; *β-Pilocarpine*, Bruhl). When pilocarpine is heated alone, or, better, when a solution in alcoholic soda is boiled, it is converted into the isomeride, *iso*pilocarpine. The latter is found in the leaves of *Pilocarpus microphyllus*, and according to Jowett frequently occurs in the pilocarpine nitrate of commerce. It is a colourless viscid oil, b.p. 261°/10 mm., $[\alpha]_D$ + 42·8°, readily soluble in water, alcohol, or chloroform. It forms crystalline salts with acids; the nitrate crystallises from water in prisms, m.p. 159°, $[\alpha]_D$ + 35·68°; the hydrochloride, $(B.HCl)_2.H_2O$, has m.p. 127° or 159° (*dry*), whilst the aurichloride, $B.HAuCl_4$, forms lemon-yellow needles, m.p. 158°–159°. When *iso*pilocarpine is dissolved in water and a molecular proportion of soda added, the rotation is reduced to zero due to the formation of sodium *iso*pilocarpate.

METAPILOCARPINE. According to Pinner this second isomeride is formed when pilocarpine hydrochloride is heated at 225°–235° during one to two hours. It differs from pilocarpine and *iso*pilocarpine chiefly in yielding less soluble salts. In the free state it has the composition $C_{11}H_{18}O_3N_2$, but in its salts it appears to exist as $C_{11}H_{16}O_2N_2$.

Constitution of Pilocarpine and iso*Pilocarpine*. The constitution of pilocarpine was first seriously investigated by Hardy and Calmels,[1] who assigned to it a formula which was shown later on by various investigators to be untenable. Our present knowledge of the two alkaloids is mainly due to Jowett.[2] On oxidation with permanganate, *iso*pilocarpine yields the following products:

iso*Pilocarpine*, oxidised by permanganate, yields
↓
Homopilopic acid, $C_8H_{12}O_4$.
Pilopic acid, $C_7H_{10}O_4$.

Pilopic acid, $C_7H_{10}O_4$. The mixture of acids obtained by the oxidation of *iso*pilocarpine with permanganate is best separated into its constituents by fractional distillation of the ethyl esters. In

[1] *Compt. rend.* 1886, **102**, 1116, 1251, 1562; **103**, 277; 1887, **105**, 68.
[2] *Loc. cit.*

this way a large fraction of an ester, $C_9H_{14}O_4$, b.p. 290°–300°, is obtained, which on hydrolysis furnishes pilopic acid, $C_7H_{10}O_4$, crystallising in silky plates, m.p. 104°, $[\alpha]_D$ + 36·1°. When pilopic acid is digested in the cold with barium hydroxide a salt of the composition $(C_7H_9O_4)_2Ba$ is formed, but when the acid is boiled with a solution of barium hydroxide for an hour, and the filtrate, after removal of excess of baryta by a current of carbon dioxide, is evaporated and excess of alcohol added, a barium salt of the formula $C_7H_{10}O_5Ba$ is obtained; the latter by double decomposition with silver nitrate gives a silver salt of the composition $C_7H_{10}O_5Ag_2$. Pilopic acid appears therefore to be a lactonic acid furnishing by hydration of the lactone group the hydroxy-acid $C_7H_{12}O_5$.

When fused with potash, pilopic acid is converted into *normal* butyric acid. The constitution of pilopic acid is discussed below.

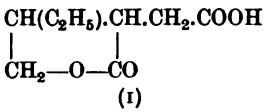
Homopilopic Acid, $C_8H_{12}O_4$, is obtained by hydrolysis of the highest boiling fraction of ethyl ester prepared from the mixture of acids resulting from the oxidation of *iso*pilocarpine with permanganate. It is a viscid colourless oil, b.p. 235°–237°/20 mm., $[\alpha]_D$ + 45·4°. With cold baryta water the acid furnishes a microcrystalline barium salt of the formula $(C_8H_{11}O_4)_2Ba$, and with boiling baryta water the salt of the hydroxy-acid $C_8H_{12}O_5Ba$. It is therefore a lactonic acid like pilopic acid.

When fused with excess of potash it furnishes α-ethyltricarballylic acid, $COOH.CH(C_2H_5).CH(COOH).CH_2.COOH$.

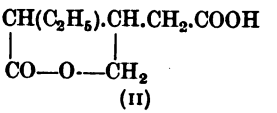
This acid could be formed from any one of the three isomeric hydroxy-acids of the following formulæ:

$CH_2OH.CH(C_2H_5).CH(COOH).CH_2.COOH$
$COOH.CH(C_2H_5).CH(CH_2OH).CH_2.COOH$
$COOH.CH(C_2H_5).CH(COOH).CH_2.CH_2OH$

Homopilopic acid is very stable, and is probably therefore the γ-lactonic acid of one of these three hydroxy-acids. Further, pilopic acid seems to be produced from its higher homologue by loss of carbon dioxide and oxidation of the contiguous carbon atom. Of the four γ-lactonic acids derived from the three hydroxy-acids formulated above only the two following answer these conditions:



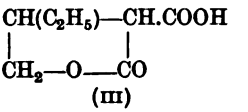
(I)



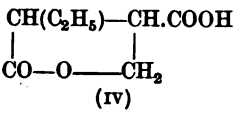
(II)

Homopilopic acid (Jowett)

and these lead to the following possible formulæ for pilopic acid :



(III)



(IV)

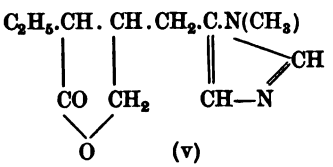
Pilopic acid (Jowett)

A substance having formula III would probably lose carbon dioxide on heating, whereas pilopic acid is stable even at 200°. It is probable, therefore, that homopilopic acid is represented by formula II and pilopic acid by formula IV.

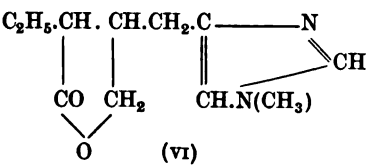
Jowett has also shown that pilocarpine, like *iso*pilocarpine, yields homopilopic acid when oxidised by permanganate.[1]

In the oxidation of the two alkaloids Jowett has pointed out that the nitrogen atoms are eliminated as ammonia and methylamine.

From these and other experimental results Pinner and Schwarz [2] suggested that pilocarpine could be represented by formula V, and subsequently Jowett confirmed the validity of this formula to a certain extent by the preparation of a series of disubstituted glyoxalines from *iso*pilocarpine by distillation with soda-lime,[3] although he pointed out that the reactions of the alkaloid were equally well accounted for by formula VI,



(V)



(VI)

since it is impossible at present to decide whether the dialkyl-

[1] *Trans. Chem. Soc.* 1903, **83**, 451. *Cf.* Pinner and collaborators, *Berichte*, 1900, **33**, 1424, 2357 ; 1901, **34**, 727 ; 1902, **35**, 204, 2443.

[2] *Berichte*, 1902, **35**, 2441.

[3] *Trans. Chem. Soc.* 1903, **83**, 442.

glyoxalines produced on distillation with soda-lime are 1 : 4 or 1 : 5 derivatives, though Pyman has recently brought forward evidence for the view that they are 1 : 5 derivatives, thus supporting formula v.[1] The same author[2] has recently synthesised several glyoxaline derivatives allied to pilocarpine.

The relationship existing between pilocarpine and *iso*pilocarpine is at present uncertain; both alkaloids furnish homopilopic acid when oxidised with permanganate, but with bromine pilocarpine is converted into bromocarpinic acid, $C_{10}H_{15}O_4N_2Br$, whilst *iso*pilocarpine is changed into dibromo*iso*pilocarpinic acid, $C_{11}H_{14}O_4N_2Br_2$, and similarly oxidation with chromic acid leads to the formation of pilocarpoic acid, $C_{11}H_{16}O_5N_2$, in the case of pilocarpine, but with *iso*pilocarpine total disruption of the molecule occurs.[3] In spite of these differences in reactivity it appears probable that the alkaloids are stereoisomeric and that in the formation of *iso*pilocarpine from pilocarpine, under the influence of heat alone or by the action of alkali hydroxides, partial racemisation occurs, which would account for the lower specific rotation of the former. In support of this view may also be quoted the facts (1) that the absorption spectra of the nitrates of the two alkaloids are identical, although, as has been pointed out by Hartley,[4] such spectra are merely those of the acid modified by the presence of the alkaloids, and (2) that in the action of alkalis on pure *iso*pilocarpine or pure pilocarpine an equilibrium mixture of both alkaloids is formed.[5]

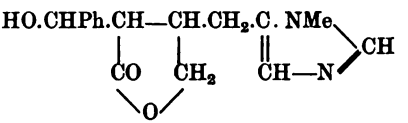
Pilocarpidine, $C_{10}H_{14}O_2N_2$. This alkaloid was first obtained by Harnack[6] from *Pilocarpus Jaborandi*, and later by Merck from the same source, being found in the mother liquors from crystallisation of pilocarpine nitrate. According to Jowett[7] it does not occur in the leaves of *Pilocarpus microphyllus*. The free base is a viscid

[1] *Trans. Chem. Soc.* 1910, **97**, 1820. [2] *Ibid.* 1912, **101**, 530.
[3] Jowett, *loc. cit.* [4] *Proc. Chem. Soc.* 1903, p. 122.
[5] Jowett, *Trans. Chem. Soc.* 1905, **87**, 908. *Cf.* Pinner, *Berichte*, 1905, **38**, 1510.
[6] *Annalen*, 1887, **238**, 230.
[7] *Trans. Chem. Soc.* 1900, **77**, 474.

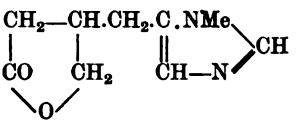
oil, $[\alpha]_D$ + 81·3° (less in presence of alkali), miscible with water. The salts crystallise well; the nitrate, $B.HNO_3$, in colourless prisms, m.p. 137°, $[\alpha]_D$ + 73·2°, soluble in water (1 in 2 at 15°). The aurichloride, unlike that of pilocarpine, is very soluble in water, but crystallises from acetic acid, m.p. 124°–125°. The platinichloride, $(B.HCl)_2PtCl_4.4H_2O$, forms yellow needles, m.p. 187° (*dry*). The picrate, unlike the corresponding salts of pilocarpine and *iso*pilocarpine, is an oil.

Pilocarpidine reacts with methyl iodide to form a methiodide, $C_{10}H_{14}O_2N_2.CH_3I$, from which a methochloride platinichloride, $(B.CH_3.Cl)_2.PtCl_4$, m.p. 178°, is obtainable. When warmed with caustic potash solution at 200°, pilocarpidine yields dimethylamine. By repeated evaporation with acids, it is said to be converted into jaboridine, $C_{10}H_{12}O_3N_2$, obtained by Parodi from "false jaborandi" (leaves of *Piper reticulatum*).

Pilosine, $C_{16}H_{18}O_3N_2$, occurs in the mother liquors from the isolation of pilocarpine and *iso*pilocarpine from *P. microphyllus* leaves, has m.p. 187° (*corr.*), $[\alpha]_D$ + 39·9°, and on distillation with potash solution gives benzaldehyde and *pilosinine*, $C_9H_{12}O_2N_2$. Both alkaloids resemble pilocarpine in physiological action, but are much weaker. The following formulæ are assigned to them: [1]



Pilosine



Pilosinine

Jaborine, $C_{22}H_{32}O_4N_4$, was obtained by Harnack and Meyer [2] from the leaves of *Pilocarpus Jaborandi*. According to Jowett it is a mixture of pilocarpine, *iso*pilocarpine, and extractive matter.

ψ-Pilocarpine and **ψ-Jaborine** were obtained by Petit and Polonowsky [3] from *Pilocarpus spicatus* (Aracati jaborandi). The former is a colourless syrup giving a nitrate, small needles, m.p. 142°, and a hydrochloride, prisms, m.p. 198°. ψ-Jaborine

[1] Pyman, *Proc. Chem. Soc.* 1912, **28**, 267.

[2] *Annalen*, 1880, **204**, 67. [3] *Chem. Centr.* 1897, i. 1126.

is also amorphous; its nitrate forms lamellæ, m.p. 158°, and the hydrochloride, needles, m.p. 222°. Both are optically inactive.

Physiological Action of Jaborandi Alkaloids

Pilocarpine causes increased secretion by the salivary, lachrymal, gastric, and other glands, the solids of the secretions being increased as well as the fluids, though to a less extent; this action is inhibited by atropine, indicating that pilocarpine acts on the nerve endings in the secretory cells. The muscles of a number of organs are contracted after administration of pilocarpine. Taken internally or applied locally, pilocarpine causes contraction of the pupil of the eye. The heart is slowed by the alkaloid in general, though in some cases it is accelerated and there is a rise in blood-pressure. The respiratory centre is not directly affected by small doses, but large doses produce convulsive movements and rapid and laboured respiration, and eventually the respiration becomes slow and weak, and asphyxia occurs. On the whole pilocarpine resembles muscarine in action, but is much less poisonous.

Pilocarpine is chiefly used in medicine as a diaphoretic in dropsy and similar diseases. It has also been employed in ophthalmic surgery as a substitute for physostigmine to contract the pupil and reduce the intraocular pressure. It has been employed as an antidote to atropine, but it does not antagonise the action of atropine in the central nervous system.

*iso*Pilocarpine and pilocarpidine are stated to have the same general action as pilocarpine, but are much weaker, pilocarpidine being the least active of the three. Pilocarpic acid is inactive.[1] Jaborine was supposed to exhibit an action similar to that of atropine, but in view of Jowett's statement that jaborine is a mixture of pilocarpine and *iso*pilocarpine this statement lacks confirmation.

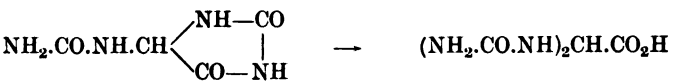
ALKALOIDS OF *SYMPHYTUM OFFICINALE*

From this plant Greimer[2] obtained two poisonous alkaloids, *consolidine* and *symphytocynoglossine*, both of which exerted a

[1] Marshall, *Journ. Physiol.* 1904, **31**, 123. [2] *Arch. Pharm.* 1900, **238**, 505.

paralysing action on the central nervous system. From the rhizome Titherley and Coppin have obtained allantoin.

Allantoin, $C_4H_6O_3N_4$. This substance occurs naturally in the allantois and in urine, but has also been found in a number of plants, *e.g.* shoots of the plane tree (*Platanus orientalis*),[1] horse-chestnut (*Æsculus Hippocastanum*),[2] beetroot,[3] bread, peas, and French beans,[4] tobacco seeds,[5] *Datura Metel* seeds,[6] and in comfrey rhizome (*Symphytum officinale*).[7] Its occurrence to the extent of 0·67 per cent. in the last-named plant is of interest since Macalister and Bramwell have shown[8] that to its remedial action is due the use of this rhizome as a remedy for sores and ulcers. Allantoin crystallises in needles, m.p. 227°, from boiling water. On hydrolysis by alkalis it furnishes ammonia and carbamide, and on treatment with cold potassium hydroxide solution yields allantoic acid.[9] Allantoin is a monoureide of the following formula :[10]



Allantoin *Allantoic acid*

and was synthesised by Grimaux[11] by condensing carbamide with glyoxylic acid,[12] and by Michael[13] by the action of mesoxalic acid on carbamide.

For other alkaloids of the glyoxaline group, *see under* ergot, p. 383.

[1] Schulze and Barbieri, *Journ. prakt. Chem.* 1882 [ii], **25**, 147.
[2] Schulze and Booshard, *Zeits. physiol. Chem.* 1892, **9**, 425.
[3] von Lippmann, *Berichte*, 1896, **29**, 2652.
[4] Ackroyd, *Bio-chem. Journ.* 1911, **5**, 403.
[5] Spurti and Perciabosco, *Gazzetta*, 1906, **36**, 626.
[6] De Plato, *Chem. Soc. Abstr.* 1910, ii, 742.
[7] Titherley and Coppin, *Pharm. Journ.* 1912 [iv], **34**, 92.
[8] *Brit. Med. Journ.* 1912, **1**, 10, 12.
[9] Behrend and Schultz, *Annalen*, 1909, **365**, 36.
[10] *Cf.* Dakin, *J. Biol. Chem.* 1910, **7**, 153 ; Biltz, *Berichte*, 1910, **43**, 1999.
[11] *Ann. Chim. Phys.* 1877 [v], **11**, 389.
[12] *Cf.* Simon and Chavanne, *Compt. rend.* 1906, **143**, 51.
[13] *Amer. Chem. Journ.* 1883, **5**, 198.

VII. PURINE GROUP

THIS group includes the important alkaloids occurring in the stimulant foodstuffs, tea, coffee, cocoa, kola, guarana, maté, &c., together with a few others which are found especially in the embryos of leguminous plants. The most important compound of this group occurring in nature is uric acid, which has been used as a raw material for the preparation of a number of the alkaloids and is now employed commercially in some cases for their manufacture, the uric acid being extracted for this purpose from guano. The alkaloids concerned are as follows :

Caffeine, $C_8H_{10}O_2N_4$, found in tea, coffee, kola, maté, and guarana.

Theobromine, $C_7H_8O_2N_4$, found in cocoa.

Theophylline, $C_7H_8O_2N_4$, found in tea.

Xanthine, $C_5H_4O_2N_4$, found in tea.

Hypoxanthine, $C_5H_4ON_4$, found in black pepper.

Inosine, a pentoside of hypoxanthine, found in yeast and beetroot.

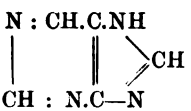
Guanine, $C_5H_5ON_5$, found in guano and leguminous seedlings.

Adenine, $C_5H_5N_5$, found in tea and beetroot.

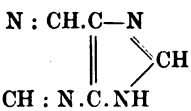
Vernine, a pentoside of adenine found in *Vicia* seedlings.

In addition a number of compounds of this class are found in animals, *e.g.* uric acid, methyl- and dimethyl-xanthines, methyl-guanine, &c., but these do not come within the scope of this volume.

Purine, which may be regarded as the parent of this group of compounds, has been synthesised by E. Fischer[1] and has formula I, though it may also react in the sense of formula II.[2]



(I)



(II)

[1] *Berichte*, 1898, **31**, 2550.

[2] Fischer, *ibid.* 1899, **32**, 435.

Caffeine (*Theine*), $C_8H_{10}O_2N_4$. This is the principal alkaloidal constituent of tea and coffee and of the similar stimulant foodstuffs, kola (used throughout West Africa), maté and guarana (both used in South America). It also occurs to a small extent in cocoa beans.[1] The percentages present in these various products are as follows:

Tea, 1 to 4·8. Kola nuts, 2·7 to 3·6.
Coffee, 1 to 1·5. Maté, 1·25 to 2·0.
Guarana, 3·1 to 5·0.

It occurs in most cases partly free and partly combined, as caffeine chlorogenate.[2]

Caffeine is largely prepared from waste tea or tea dust by extracting this with boiling water, treating the decoction with litharge, and concentrating the filtrate until crystallisation occurs, the caffeine being recrystallised from boiling water.

The following processes for the estimation of the total alkaloids in tea, coffee, and kola are available:

Tea and Coffee. The following modification of Stahlschmidt's process is recommended by Allen:[3] Six grammes of tea (or 12 grm. of coffee) in fine powder are boiled with 500 c.c. of water for six hours under a reflux condenser, the extract filtered off, diluted with water to 600 c.c., heated to boiling, and colouring matter removed by adding 4 grm. of lead acetate in powder and stirring well. Five hundred cubic centimetres of the filtrate are collected, concentrated to 50 c.c., and the excess of lead precipitated with sodium phosphate. The filtrate and washings from this are evaporated to 40 c.c. and the caffeine extracted by shaking with successive portions of chloroform until no more alkaloid is removed. The combined chloroform solutions are collected in a tared flask and the residue left on evaporating off the solvent dried and weighed. Its weight represents the amount of alkaloid present in 5 grm. of tea or 10 grm. of coffee.

Kola Nuts. Dieterich gives the following process[4] for the

[1] Schmidt, *Annalen*, 1883, **217**, 306. [2] Gorter, *Annalen*, 1908, **358**, 327.
[3] *Commercial Organic Analysis*, vol. vi, p. 607.
[4] *Pharm. Zeit.* 1897, No. 8.

estimation of the total alkaloids (caffeine and theobromine): Ten grammes of the finely powdered drug are mixed with 10 grm. of quicklime and the mixture extracted in a Soxhlet apparatus with chloroform, the solvent distilled off for the most part, the residue warmed with 20 c.c. *N*-hydrochloric acid and the acid solution filtered, the flask and the filter being washed, and the washings added to the filtrate previously placed in a separator. The liquid is now made alkaline with ammonia solution and then extracted three times with chloroform, using 20 c.c. each time. The chloroform is evaporated from the combined chloroform solution and the residue dried till of constant weight.

Caffeine crystallises with 1 mol. of water from hot water, or anhydrous from alcohol, in slender, silky needles; it becomes anhydrous at 100°,[1] melts at 234°–235° (*dry*), and sublimes at 176°. At 25° 1 part of caffeine dissolves in the following quantities of the solvents named: water 45·6, alcohol 53·2, ether 375, chloroform 8. One part of caffeine is dissolved at the boiling-point by the following quantities of the solvents named: ether 339, acetic ether 23·9, benzene 18·9, chloroform 6·4. The alkaloid is bitter to the taste. It is a weak base, neutral to litmus, and furnishes salts that are decomposed when their aqueous solutions are evaporated. The double salts are more stable; the mercurichloride, $B.HgCl_2$, forms colourless needles, m.p. 246°, and the aurichloride, $B.HAuCl_4.2H_2O$, golden-yellow leaflets, m.p. 243° or 248·5° (*dry*). When warmed with water the aurichloride loses 2HCl and forms aurichlorcaffeine, $C_8H_9(AuCl_2)O_2N_4$, as a yellow amorphous precipitate.[2] "Caffeine citrate," the form in which the alkaloid is principally used in medicine, is prepared by evaporating to dryness a solution of equal weights of caffeine and citric acid in water. It is a colourless powder which dissolves unchanged in a little water, deposits caffeine on dilution, the solution becoming clear on further addition of water. The solubility of caffeine in water is increased by the presence of lithium benzoate, sodium metaphosphate, salicylate,

[1] *Cf.* Tassilly, *Bull. Soc. chim.* 1897 [iii], **17**, 596.
[2] Dunstan and Shepheard, *Trans. Chem. Soc.* 1893, **63**, 198.

or benzoate; potassium bromide and other salts, and combinations such as caffeine sodio-salicylate and caffeine sodio-benzoate, prepared by dissolving caffeine in such solutions and evaporating to dryness, are used in medicine. Caffeine forms similar compounds with salicylic and gallic acids.[1] The alkaloid also forms additive compounds with pyrogallol and phloroglucol.[2]

Caffeine dissolves in sulphuric acid, forming a colourless solution, but if a crystal of potassium dichromate is added the solution becomes yellowish green and finally green. In common with uric acid and all the alkaloids of this group it gives the murexide test, *i.e.* if a small quantity of the alkaloid is evaporated to dryness with nitric acid, or with hydrochloric acid and potassium chlorate, on the water-bath, the residue gives with ammonia a rich purple colour that is destroyed by the addition of fixed alkalis. Caffeine is not precipitated by Mayer's reagent, but gives a colourless precipitate, soluble in excess, with a solution of tannin.

Constitution. The relationship of caffeine to theobromine and theophylline and to xanthine (*see* p. 321) is shown by its formation from derivatives of these substances. When theobromine is heated with methyl iodide, potassium hydroxide, and alcohol, it undergoes methylation and caffeine is formed. Similarly the silver derivative of theophylline when warmed with methyl iodide yields caffeine. Further, when the silver derivative of methylxanthine is treated with methyl iodide, caffeine is produced. The relationship of these four alkaloids is therefore as follows:

Xanthine, $C_5H_4O_2N_4$.

Theophylline, $C_7H_8O_2N_4$ (dimethylxanthine).

Theobromine, $C_7H_8O_2N_4$ (dimethylxanthine).

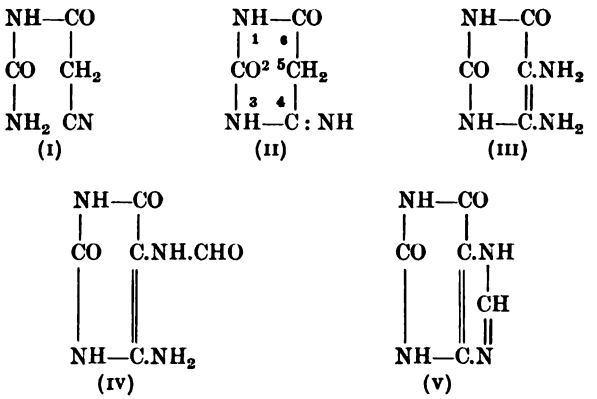
Caffeine, $C_8H_{10}O_2N_4$ (trimethylxanthine).

A method for the conversion of caffeine into theophylline and xanthine has been described by Fischer and Ach.[3]

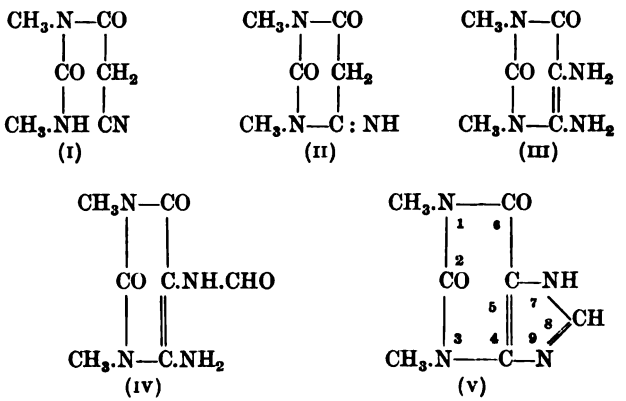
Caffeine has been synthesised by Fischer and Ach,[4] and more

[1] Brissemoret, *Bull. Soc. chim.* 1906 [iii], **35**, 316.
[2] Ultée, *Chem. Weekbl.* 1910, **7**, 32. [3] *Berichte*, 1906, **39**, 423.
[4] *Ibid.* 1895, **28**, 3135.

recently by Traube.[1] The latter used the following method: Carbamide treated with cyanoacetic acid in presence of phosphorus oxychloride yielded cyanoacetylcarbamide (I), and this treated with sodium hydroxide, followed by acetic acid, gave 4-amino-2 : 6-dioxypyrimidine (II). The latter furnished an oximino derivative, which on reduction yielded 4 : 5-diamino-2 : 6-dioxypyrimidine (III), and this as an *o*-diamine condensed with formic acid to yield a formyl derivative (IV), which on heating at 100°–220° yielded xanthine (V).

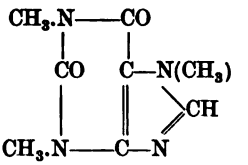


By a precisely similar series of reactions starting from dimethylcarbamide, Traube obtained theophylline (1 : 3-dimethylxanthine) thus:



[1] *Berichte*, 1900, **33**, 1371, 3035.

and this on methylation as described already yielded caffeine (1:3:7-trimethylxanthine or 1 : 3 : 7-trimethyl-2 : 6-dioxypurine) thus :



Caffeine

Theobromine, $C_7H_8O_2N_4$, is the chief alkaloid in cocoa beans, but is also found in small quantities in kola nuts and leaves [1] and in tea leaves. For the preparation of theobromine the ground beans are extracted with light petroleum to remove fat, the residue of fat-free beans is made into a paste with lime and extracted with 80 per cent. alcohol until exhausted of alkaloid. For the estimation of the total alkaloids of cocoa beans the following process, due to Dekker,[2] is available :

Ten grammes of powdered cocoa beans are mixed with 5 grm. of magnesia and boiled under a reflux apparatus during one hour with 300 c.c. of water. The decoction is filtered off, the residue again boiled with water during fifteen minutes and the second decoction filtered. The combined filtrates are evaporated to dryness on the water-bath, the residue mixed with sand and extracted in a Soxhlet apparatus with chloroform The solvent is distilled off and the residue dried and weighed. The quantity of total alkaloid in cocoa beans varies from 1·2 to 2·2 per cent., whilst the husks contain about 0·5 per cent. About half the theobromine appears to be present in a free state.

The recorded results show much greater variation than this, probably due to the use of methods of estimation which do not remove the whole of the theobromine. It is stated that caffeine may be fairly completely separated from theobromine by extraction with cold benzene, in which theobromine is practically insoluble.

Theobromine forms microscopic crystals belonging to the

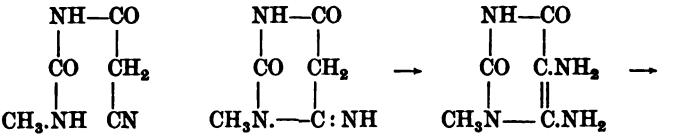
[1] Dekker, *Rec. Trav. chim.* 1903, **22**, 143.

[2] *Loc. cit.* and *Rev. Intern. Falsif.* 1903, **48**, 36.

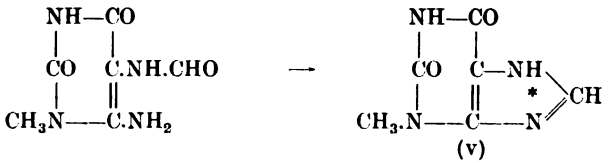
rhombic system, melts at 329°–330° in a closed capillary tube, sublimes at 290°–295°, and is sparingly soluble in most solvents. One part of theobromine is soluble in the following quantities of the solvents named at 15°: water 1800, dry alcohol 3570, chloroform 3845, ether 25,000, ethyl acetate 3845, benzene 100,000.[1] At their boiling-points 1 grm. of the alkaloid is dissolved by the following quantities of solvent: ether 3125, carbon tetrachloride 4703,[2] chloroform 100,[3] water 150. It is a weak base, neutral to litmus. The salts are decomposed more or less completely by water and in some cases by alcohol. The hydrochloride, $B.HCl.H_2O$, is crystalline, and yields the free base when dried at 100°. The platinichloride, $B_2.H_2PtCl_6.4H_2O$, forms golden-yellow monoclinic prisms. Theobromine forms a series of metallic derivatives of which the most characteristic is silver-theobromine, $AgC_7H_7O_2N_4$, obtained by warming a solution of the alkaloid in ammonia with silver nitrate. Sodium-theobromine is also of considerable importance since it orms very soluble compounds with sodium chloride and with sodium salts of organic acids, *e.g.* sodium acetate, formate, benzoate, or salicylate, and such compounds are used in medicine (*see* p. 325), as well as similar double salts containing lithium, since they are usually more soluble than theobromine.

Theobromine, like caffeine, gives the murexide test (p. 315): it is not precipitated by iodine solution or by Mayer's reagent.

Constitution. Theobromine has been synthesised by Fischer[4] and by Traube.[5] The latter utilised a series of reactions parallel with that described on p. 316, starting with methylcarbamide as a raw material, which furnishes as an end product 3-methylxanthine (v):



[1] Dekker, *Sch. Woch. Pharm.* 1902, **40**, 436.
[2] Göckel, *Chem. Zeit.* 1897, p. 402.
[3] Dekker, *loc. cit.*
[4] *Berichte*, 1897, **30**, 1845.
[5] *Ibid.* 1900, **33**, 3035.



(v)

3-Methylxanthine on treatment with methyl iodide and alkali undergoes methylation at the point marked * (formula v), yielding 3 : 7-dimethylxanthine identical with natural theobromine.

Theophylline, $C_7H_8O_2N_4$. This isomeride of theobromine is much less important than its allies theobromine and caffeine. It occurs in small quantities in tea, and was obtained therefrom by Kossel [1] by the following process: An alcoholic extract of tea was concentrated to a syrup and set aside until caffeine ceased to crystallise out. The filtrate from this was diluted with water, acidified with dilute sulphuric acid, set aside for some hours and then filtered. The filtrate was made alkaline with ammonia solution, silver nitrate solution added, and the mixture allowed to stand during twenty-four hours. The precipitate was then collected and dissolved in warm, diluted nitric acid. On cooling, silver-adenine and silver-hypoxanthine crystallised out. From the filtrate, ammonia precipitated silver-theophylline, which was collected, suspended in water, and decomposed by hydrogen sulphide. On concentrating the filtrate, xanthine and finally theophylline crystallised out. More theophylline was obtained from the mother liquor by precipitating it with mercuric nitrate and decomposing the mercury-precipitate with hydrogen sulphide.

Theophylline crystallises, with $1H_2O$, in thin monoclinic tablets or needles (from hot water), melts at 264°, is sparingly soluble in cold, but readily in hot water. It is a weak base, neutral to litmus, and yields salts with acids, as well as derivatives with metals. The hydrochloride, $B.HCl.H_2O$, loses all its water and acid at 100°. The aurichloride forms lemon-yellow needles. Theophylline gives the murexide reaction (p. 315) and in general resembles theobromine; thus it furnishes soluble double salts with organic sodium salts, and

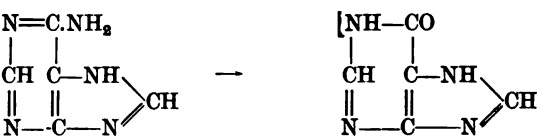
[1] *Zeits. physiol. Chem.* 1889, **13**, 298.

one of these, sodium-theophylline-sodium acetate, as well as theophylline itself, has been used in medicine.

Constitution. Theophylline has been synthesised by Fischer and Ach [1] and by Traube,[2] whose method has been described already (p. 316) in connection with the synthesis of caffeine. It is 1 : 3-dimethylxanthine (1 : 3-dimethyl-2 : 6-dioxypurine). For medicinal purposes theophylline is prepared synthetically by Traube's method or from uric acid as a starting-point.

Hypoxanthine (*Sarcine*), $C_5H_4ON_4$, is widely distributed both in animals and plants. Among the latter it occurs in mustard, black pepper, melon, barley, and other seeds, as well as in potatoes, yeast, beetroot, and in lupin and other seedlings. According to Kruger it does not occur in tea.[3] Probably in all cases it is a decomposition product of nucleins. Its isolation has been described already (*see* p. 319).

It forms microscopic needles, decomposes at 150°, and is sparingly soluble in cold water (1 in 1400 at 19°), more so in hot water (1 in 69·5 at 100°), readily in acids or alkalis. It is a weak monoacidic base and, like other alkaloids of this group, forms metallic derivatives. Its constitution is determined by the fact that it is formed from adenine (6-aminopurine : p. 322) by the action of nitrous acid.[4]



Adenine (6-aminopurine) — *Hypoxanthine* (6-oxypurine)

INOSINE, $C_{10}H_{12}O_5N$. The carnine which occurs in meat extract and also in yeast and beetroot (Lippmann) has been shown by Haiser and Wenzel [5] to be a molecular mixture of hypoxanthine (*see*

[1] *Berichte*, 1895, **28**, 3135. [2] *Ibid.* 1900, **33**, 3035.
[3] *Chem. Soc. Abstr.* 1896, i, 450. *Cf.* Kossel, *loc. cit.*
[4] *Cf.* Fischer, *Berichte*, 1897, **30**, 555, 2228 ; Traube, *Annalen*, 1904, **331**, 64.
[5] *Monats.* 1908, **29**, 157 ; 1909, **30**, 147, 377 ; 1910, **31**, 357. *Cf.* Levene and Jacobs, *Berichte*, 1909, **42**, 335, 1198, 2102, 3247 ; Neuberg and Brahn, *Biochem. Zeits.* 1909, **17**, 293.

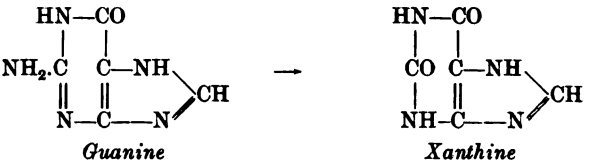
ve) and inosine. The latter can be separated by washing carnine ·atedly with water or by treating it with acetic anhydride and ium acetate. In the latter case inosine is obtained as the acetate, tening needles or plates, m.p. 236° (*decomp.*). Inosine itself ns slender silky needles, m.p. 215° (*decomp.*), $[\alpha]_D^{18} - 49{\cdot}2°$, ingly soluble in water (1·615 in 100 at 20°). It is hydrolysed dilute sulphuric acid into hypoxanthine and *d*-ribose, m.p. ·87°, the osazone of which melts at 163°.

Xanthine, $C_5H_4O_2N_4$, occurs somewhat commonly in the nal organism, but is also found in small quantities in yeast, beet-·, lupin and *Vicia* seedlings, and in tea. Its isolation from tea has ı described under theophylline (p. 319).

Xanthine crystallises in microscopic, glancing plates (with O) when a dilute warm alkaline solution is acidified with ic acid and allowed to cool slowly. It becomes anhydrous 25°–130°, is sparingly soluble in cold water (1 in 14,151 at , rather more soluble in hot water (1 in 1500 at 100°), and ily soluble in alkalis or acids. A process for its identification been given by Fischer.[1] It is a very weak base, yielding able salts with acids and derivatives with metals. It gives murexide reaction (*see* p. 315). Xanthine has been syn-ised by Fischer[2] and also by Traube (*see* p. 316) and shown e 2 : 6-dioxypurine.

Guanine, $C_5H_5ON_5$, occurs commonly in animal organisms, has also been found in small quantities in yeast, sugar-cane, in beetroot.[3] It is usually prepared from guano.[4] It is a e crystalline powder, insoluble in water and very sparingly ble in ammonia. It has been synthesised by Fischer[5] and also Traube.[6] It is 2-amino-6-oxypurine, as shown by the formation ı ıt of xanthine (*see above*) by the action of nitrous acid, or by ng with hydrochloric acid.[7]

[1] *Berichte*, 1898, **31**, 2550.
[2] *Ibid.* 1897, **30**, 2232.
[3] Lippmann, *ibid.* 1896, **29**, 2653.
[4] Strecker, *Annalen*, 1861, **118**, 152.
[5] *Berichte*, 1897, **30**, 553, 2226.
[6] *Ibid.* 1900, **33**, 1378.
[7] Fischer, *ibid.* 1910, **43**, 805.

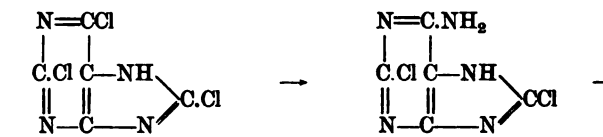


Guanine *Xanthine*

VERNINE, $C_{10}H_{13}O_5N_5.2H_2O$, was obtained by Schulze and collaborators[1] from lupin seeds and from the embryos of *Vicia sativa*, *Trifolium pratense*, and other plants, and by Lippmann from beet-root residues. It crystallises in small prisms, $[\alpha]_D^{20}$ — 60° in alkali, is readily soluble in hot water, but sparingly so in cold water. It forms amorphous compounds with mercuric and silver nitrates, and when boiled with hydrochloric acid furnishes guanine, and a pentose, probably *d*-ribose. According to Schulze and Trier,[2] Levene and Jacobs' guanosine [3] is identical with vernine.

A second guanine pentoside has been found by Andrlik [4] in molasses, but Schulze and Trier have shown [5] that this is identical with vernine (guanine-*d*-ribose).

Adenine, $C_5H_5N_5$, occurs in the pancreas and in small quantities in yeast, tea, beetroot, and bamboo shoots. It crystallises with 3 mols. of water in long colourless needles, sublimes at 210°, softens at 250°, and melts at 360°–365°. It is sparingly soluble in cold, but easily in hot water. Adenine picrolonate, m.p. 2 crystallises from water. The base was synthesised by Fisch by treating trichloropurine (I) with aqueous ammonia, w produced 6-amino-2 : 8-dichloropurine (II), and this on reduct with hydriodic acid yielded adenine (III), thus :



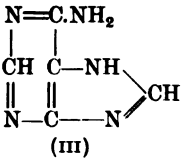
2 : 6 : 8-*Trichloropurine* (I) 6-*Amino*-2 : 8-*dichloropurine* (II)

[1] *Zeits. physiol. Chem.* 1885, **19**, 420 ; 1886, **20**, 326 ; 1904, **41**, 455 ; 191 **66**, 128.

[2] *Ibid.* 1910, **70**, 143. [3] *Berichte*, 1909, **42**, 2469.

[4] *7th Int. Congr. Appl. Chem.* 1909, Sect. V, 331.

[5] *Zeits. physiol. Chem.* 1912, **76**, 145. [6] *Berichte*, 1897, **30**, 2226.



(III)

Adenine (6-*aminopurine*)

A synthesis of adenine has also been effected by Traube by the general method already described (p. 316), using thiocarbamide and malononitrile, the thioadenine formed being oxidised to adenine by hydrogen peroxide.[1]

Vicine, $C_{20}H_{36}O_{15}N_8$, has been obtained together with convicine from various species of vetch, *e.g. Vicia sativa*, *V. Faba*, and *V. Faba minor*.[2] It crystallises in voluminous masses of white needles, becomes anhydrous at 120°, and melts at 180° (*decomp.*); it dissolves in water or methyl alcohol, but is insoluble in dry ethyl alcohol. The sulphate, $B_3.4H_2SO_4$, and the hydrochloride, $B_4.11HCl$, separate in fine white needles from their aqueous solutions on addition of alcohol.

When boiled with potassium hydroxide solution, vicine liberates ammonia, and when fused with potash, hydrocyanic acid is formed. Boiling dilute sulphuric acid hydrolyses vicine, forming a sugar and *divicine*, $C_8H_{14}O_4N_8$. Vicine and its decomposition products all dissolve in acids producing yellow colours, and the solutions after warming give with ferric chloride and ammonia a deep blue colour, changing into violet on addition of barium hydroxide.

Convicine, $C_{20}H_{28}O_{16}N_6.2H_2O$, occurs with vicine in *Vicia* species (*see above*). It forms thin glancing leaflets, dissolves in boiling water, but is insoluble in cold water or alcohol.[3] It gives the murexide reaction, and on heating with dilute sulphuric acid yields alloxanthine, ammonia, and a hexose.[4]

[1] *Annalen*, 1904, **331**, 64.

[2] Ritthausen, *Journ. prakt. Chem.* 1870 [ii], **1**, 336; 1873 [ii], **7**, 374; 1881 [ii], **24**, 202; 1884 [ii], **29**, 359; 1899 [ii], **59**, 480. *Cf.* Schulze and Trier, *Zeits. physiol. Chem.* 1910, **70**, 143.

[3] Ritthausen, *J. prakt. Chem.* 1881 [ii], **24**, 212; 1899 [ii], **59**, 487.

[4] Schulze and Trier, *Zeits. physiol. Chem.* 1910, **70**, 143.

Physiological Action of the Purine Bases

Foodstuffs containing caffeine or theobromine, with smaller quantities of the other naturally occurring xanthine bases, are used in many parts of the world as stimulants. The use of tea, coffee, and cocoa among civilised peoples is well known, but there are a number of other similar products in use by uncivilised peoples. Kola nuts are used in this way by natives throughout West Africa, guarana by natives in the Argentine, and maté by Indians in Brazil, whilst the Arabs use not only coffee but also the flowers of *Catha edulis*, which are believed to contain an alkaloid of this group.

The alkaloids chiefly concerned are caffeine, theobromine, and theophylline, although in recent years a very large number of xanthine derivatives have been prepared synthetically, some of which have been, or are being, used in medicine.

Caffeine stimulates the central nervous system, especially the part associated with psychical functions, and increases the capacity for physical exertion. In large doses it may cause headache, and in specially susceptible people mild delirium. Theophylline resembles caffeine in its action on the central nervous system, but theobromine is less active in this respect. In small amounts caffeine increases the irritability of muscle, as well as its strength and extensibility, and some investigators attribute the increased capacity for work induced by caffeine to this direct action. Theobromine exerts a greater action on muscle than caffeine, and xanthine is still more active.

Caffeine also stimulates the vaso-motor centre in the medulla and the heart, causes a rise in blood-pressure, and accelerates and strengthens the respiration.

The most important physiological action of caffeine and the related bases is, however, that on the kidney, since they cause increased secretion of urine. The mechanism of this action is still a matter of dispute, but it is generally regarded as due to direct action on the renal cells. Theophylline appears to be the most active of the naturally occurring xanthine bases in this respect.

Caffeine is excreted in the urine, partly unchanged, but chiefly as dimethylxanthine, methylxanthine, and xanthine. Theobromine and theophylline are excreted as methylxanthines.[1]

One of the difficulties experienced in the use of these alkaloids in medicine is their insolubility. To overcome this the soluble double salts formed with various sodium salts have been utilised, and several of these are now in use, *e.g.* diuretine (sodium-theobromine-sodium salicylate), agurine (sodium-theobromine-sodium acetate), uropherine (lithium diuretine), uropherine-B (theobromine-lithium benzoate), barutine (barium-theobromine-sodium salicylate), and theocine sodium acetate (sodium-theophylline-sodium acetate).

[1] *Cf.* Levinthal, *Zeits. physiol. Chem.* 1912, **77**, 259.

VIII. ALKALOIDS DERIVED FROM ALIPHATIC AMINES

Arginine, $C_6H_{14}O_2N_4$, occurs frequently in etiolated embryos, and has been obtained from such preparations of *Lupinus* species, *Cryptomeria japonica*, *Pinus Thunbergii*, *Gingko biloba*, &c.,[1] and is also produced by the hydrolysis of proteins of etiolated plants of *Abies pectinata* and *Picea excelsa*. It occurs naturally in the roots of *Brassica Rapa* (rape), *Helianthus tuberosus* (artichoke), and *Beta vulgaris* (beetroot).

It crystallises in stellate aggregates of tablets or thin prisms, decomposes at 207°–207·5°, and is readily soluble in water, sparingly so in alcohol; it forms crystalline salts (hydrochloride, $B.HCl.H_2O$, $[\alpha]_D^{20} + 12{\cdot}5°$ in water, m.p. 209° [*dry*], tablets), and compounds with metallic nitrates, ($B_2.Cu(NO_3)_2.3\frac{1}{2}H_2O$), dark blue needles, m.p. 232°–234° (*dry*, *decomp.*). Dibenzoylarginine, m.p. 217°–218°, forms needles or tablets.

On heating with concentrated sulphuric acid it is converted into *dl*-arginine.[2] From *dl*-arginine, *l*-arginine may be prepared by the action of arginase.[3]

Arginine is hydrolysed by baryta water or by the enzyme arginase, yielding ornithine ($\alpha : \delta$-diaminovaleric acid) and carbamide.[4] On oxidation with barium permanganate, it yields GUANIDINE (iminocarbamide, $HN : C(NH_2)_2$), γ-guanidinobutyric acid, and succinic acid.[5]

On the basis of these and other results, Schulze and Winterstein represent arginine by the following formula:

$$NH_2.C(:NH).NH.CH_2.CH_2.CH_2.CH(NH_2).COOH,$$

[1] Suzuki, *Journ. Chem. Soc. Abstr.* 1900 [ii], 562.
[2] Kutscher, *Zeits. physiol. Chem.* 1901, **32**, 476.
[3] Riesser, *ibid.* 1906, **49**, 210.
[4] Schulze and Winterstein, *ibid.* 1898, **26**, 1.
[5] Kutscher, *ibid.* 1901, **32**, 413.

and this is supported by the fact that it is formed by the action of cyanamide on ornithine,[1] or by condensing benzoylornithine with cyanamide and hydrolysing the *α*-benzoylamino-*α*-guanidino-*n*-valeric acid formed.[2]

Arginine is physiologically inactive in animals.[3]

Betaine, $C_5H_{11}O_2N$ (lycine, oxyneurine), was first obtained by Husemann and Marmé from *Lycium barbarum*, and subsequently from beetroot sap by Scheibler, and since then has been found in many other plants, especially in the Chenopodiaceæ and Amaranthaceæ. It may be prepared by treating beetroot molasses with hydrogen chloride and extracting the filtrate with alcohol. For its detection and estimation in plants, *see* Schulze.[4]

Betaine forms hygroscopic crystals from water or alcohol, m.p. 293° (*dry*), is optically inactive and slightly sweet in taste. The aurichloride, $B.HAuCl_4$, has m.p. 209°. The constitution of betaine follows from Liebrich's synthesis [5] of the substance from chloroacetic acid and trimethylamine, in which betaine hydrochloride is formed :

$$Cl.CH_2COOH \longrightarrow Cl.N(CH_3)_3.CH_2.COOH \longrightarrow \overbrace{(CH_3)_3N.CH_2.CO.O}.$$

The name "betaine" is now used generically for substances containing the anhydride group: $\begin{array}{l} :N\!\!<\!\!\begin{array}{l}CH_2— \\ \\ .CO.O—\end{array} \\ \text{\_\_\_\_\_}\end{array}$ Examples of "betaines" among the alkaloids are trigonelline (p. 16), hypaphorine (p. 15), and strychnine (p. 184).

According to Velich and Stanék [6] betaine behaves as a mild diuretic and is not toxic.[7] Betaine hydrochloride has been used in medicine under the name "acidol."

[1] *Berichte*, 1899, **32**, 3191.
[2] Sörensen, *ibid.* 1910, **43**, 643. *Cf. Zeits. physiol. Chem.* 1911, **76**, 44.
[3] Schulze, *ibid.* 1896, **29**, 352.
[4] *Zeits. physiol. Chem.* 1909, **60**, 155 ; 1910, **67**, 46 ; 1912, **76**, 258 ; and Stanek, *ibid.* 1911, **72**, 402 ; *Zeit. Zuckerind. Böhm.* 1910, **34**, 297.
[5] *Berichte*, 1869, **2**, 12. [6] *Zeit. Zuckerind. Böhm.* 1905, **29**, 205.
[7] *Cf.* Waller and Lowton, *Proc. Roy. Soc.* 1903, **72**, 320, and Kohlrausch *Zeits. Biol.* 1911, **57**, 273.

Choline, $C_5H_{15}O_2N$, is widely distributed in plants either free or in the form of phosphatides, and is a common decomposition product of proteins, lecithin, &c. It is also formed by the alkaline hydrolysis of sinapine (p. 334). Choline is an alkaline syrup which readily absorbs carbon dioxide from the air. It yields a crystalline hydrochloride, a characteristic platinichloride, m.p. 215°–240° (*decomp.*), a cadmichloride, and a periodide, $C_5H_{14}O_2NI.I_8$, which may be used for its detection and estimation.[1]

The constitution of choline follows from its preparation by the action of trimethylamine on ethylene oxide: [2]

$$C_2H_4O + N(CH_3)_3 + H_2O = N(CH_3)_3OH.CH_2.CH_2OH.$$

Choline is toxic in large doses. Its action has been fully investigated by Mott and Halliburton.[3] According to Modrakowski many of the physiological properties ascribed to it are due to impurities in the commercial products.[4]

Damascenine. The seeds of *Nigella damascena* were examined by Schneider in 1890 and found to contain a crystalline alkaloid, which was named damascenine, $C_{10}H_{15}O_3N$.[5] The alkaloid was re-examined by Pommerehne,[6] who assigned to it the formula $C_6H_{11}O_3N$ and stated that by the action of alkalis it was converted into an isomeride, damasceninic acid. Subsequently Keller, accepting Pommerehne's results, named an alkaloid of the formula $C_{10}H_{13}O_3N$, which he obtained from the seeds of *Nigella aristata* (*N. arvensis*), "methyldamascenine," since it could also be obtained by treating silver damasceninate with methyl iodide.[7] Ewins has recently repeated this work, and in addition to confirming Schneider's results has effected a synthesis of damascenine.[8] According to Ewins, Pommerehne's "damascenine" was a mixture of Schneider's damascenine with its hydrolytic product, damas-

[1] Stanék, *Zeits. physiol. Chem.* 1905, **46**, 280; 1906, **47**, 83. *Cf.* Kiesel, *ibid.* 1907, **53**, 215, and Rosenheim, *J. Physiol.* 1905, **33**, 220.

[2] Wurtz, *Annalen Suppl.* **6**, p. 201. [3] *Proc. Roy. Soc.* 1899, **65**, 91.

[4] Pflüger's *Archiv.* 1908, **124**, 601. *Cf.* Pal, *Abstr. Chem. Soc.* 1912 [ii], 75.

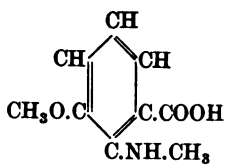
[5] *Pharm. Centr.-h.* 1890, **31**, 173. [6] *Arch. Pharm.* 1900, **238**, 531.

[7] *Ibid.* 1904, **242**, 299; 1908, **246**, 1. [8] *Trans. Chem. Soc.* 1912, **101**, 544.

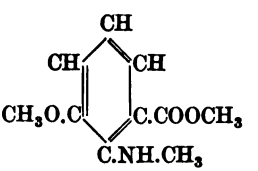
ceninic acid, whilst Keller's methyldamascenine is identical with Schneider's damascenine.

For the preparation of the alkaloid, Ewins extracted the ground seeds with light petroleum and then shook out the latter directly with 5 per cent. hydrochloric acid. From this the alkaloid was recovered by adding sodium carbonate, shaking out with ether, distilling off the solvent, and distilling the residue under reduced pressure. The yield from the seeds was 0·32 per cent.

DAMASCENINE, $C_{10}H_{13}O_3N$, is a crystalline mass, m.p. 24°–26°, b.p. 154°/15 mm. or 270°/750 mm. It is readily soluble in most organic solvents, giving solutions showing a blue fluorescence. The salts crystallise well, and the forms of certain of them have been described.[1] The hydrochloride forms triclinic crystals with $1H_2O$ from 80 per cent. alcohol, m.p. 122° or 156° (*dry*); the nitrate has m.p. 94°–95°; the picrate crystallises in lemon-yellow rhombic plates, m.p. 158°–159°. On hydrolysis with acids or alkalis, damascenine yields methyl alcohol and damasceninic acid, $C_9H_{11}O_3N$. The latter is a monobasic acid, and on treatment with hydriodic acid yields methyl iodide and 2-methylamino-3-hydroxybenzoic acid, whence Keller [2] has assigned to it the following formula, while Ewins [3] has shown that damascenine is the methyl ester of damasceninic acid :



Damasceninic acid (Keller)



Damascenine (Ewins)

Ewins has synthesised both these substances from *m*-methoxybenzoic acid, which on nitration gave 2-nitro-3-methoxybenzoic acid, and this on reduction and treatment with methyl iodide yielded 2-methylamino-3-methoxybenzoic acid identical with damasceninic acid, which on esterification with methyl alcohol furnished damascenine, identical with the natural alkaloid.

[1] Schwantke, *Zeit. Kryst. Min.* 1909, **46**, 73. [2] *Loc. cit.* [3] *Loc. cit.*

Ephedrine. *Ephedra vulgaris* yields two alkaloids, ephedrine and ψ-ephedrine, the first of which was obtained by Nagai[1] and the second by Merck.[2] According to Miller[3] *E. vulgaris* var. *helvetica* contains ψ-ephedrine only. Schmidt has found that these two substances are convertible into each other by heating with hydrochloric acid, an equilibrium mixture of the two being formed, and therefore regards them as geometrical isomerides.[4]

EPHEDRINE, $C_{10}H_{15}ON$, is a colourless crystalline substance, m.p. 40°, b.p. 225° (*decomp.*). The hydrochloride forms colourless needles, m.p. 216°, $[\alpha]_D^{15} - 36{\cdot}66°$ in water; the platinichloride, $(B.HCl)_2PtCl_4$, crystallises in colourless needles, m.p. 186°, and the aurichloride, $B.HAuCl_4$, in yellow needles, m.p. 128°–131°. Ephedrine yields a dibenzoyl derivative, and on treatment with methyl iodide yields methylephedrinemethylammonium hydroxide, which on distillation gives trimethylamine and α-phenylpropylene-αβ-oxide.[5] According to Schmidt and Bümming,[6] ephedrine hydrochloride on distillation in carbon dioxide yields methylamine and propiophenone. On acetylation ephedrine is converted into ψ-ephedrine (*see below*), so that both give the same acetyl derivative.[7] A number of isomerides of ephedrine have been prepared by Fourneau[8] and by Schmidt.[9] The formula of ephedrine is discussed under ψ-ephedrine (*see below*). Ephedrine is poisonous and dilates the pupil of the eye. The hydrochloride has been used in medicine as a mydriatic.

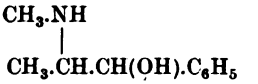
ψ-Ephedrine (iso*ephedrine*), $C_{10}H_{15}ON$, occurs with ephedrine in *Ephedra vulgaris*, and is formed by heating ephedrine with hydrochloric acid.[10] It was first obtained by Merck and was investigated later by Ladenburg and Oelschlägel.[11] It crystallises

[1] *Pharm. Zeit.* 1887, **32**, 700. [2] *Merck's Bericht*, 1893, p. 13.
[3] *Arch. Pharm.* 1902, **240**, 481.
[4] *Ibid.* 1908, **246**, 210. *Cf.* Emde, *ibid.* 1907, **245**, 662.
[5] Rabe, *Berichte*, 1911, **44**, 824. *Cf.* Schmidt, *Arch. Pharm.* 1911, **249**, 305.
[6] *Ibid.* 1909, **247**, 141. [7] Calliess, *Apoth. Zeit.* 1910, **25**, 677.
[8] *J. Pharm. Chim.* 1904 [vi], **20**, 481 ; 1907 [vi], **25**, 593.
[9] *Arch. Pharm.* 1905, **243**, 73 ; 1909, **247**, 141 ; *Apoth. Zeit.* 1911, No. 37.
[10] Flaecher, *Arch. Pharm.* 1904, **242**, 380 ; Schmidt, *ibid.* 1906, **244**, 239.
[11] *Berichte*, 1889, **22**, 1823.

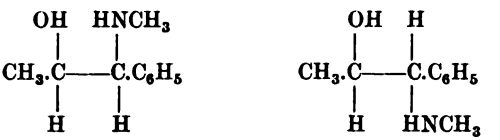
from ether and melts at 114°–115°. The hydrochloride, B.HCl, forms colourless needles, m.p. 176°, and the aurichloride golden-yellow needles.

The alkaloid is poisonous, dilates the pupil of the eye when taken internally, but is said not to exert any mydriatic action when applied to the pupil itself.[1]

When oxidised by permanganate, benzoic acid is the only product, whilst nitric acid forms a nitrosoamine and benzoyl chloride a dibenzoyl derivative, m.p. 119°–120°. These observations led Ladenburg and Oelschlägel to assign to ψ-ephedrine the following formula :



Emde [2] has suggested that ephedrine and *pseudo*ephedrine are optical isomerides having the formula $CH_3.CHOH.CHPh.NHCH_3$, the relationship between the two being the same as that between *l*-arabonic and *l*-ribonic acids, thus :



More recently, however, Rabe [3] has reverted to Ladenburg and Oelschlägel's formula, and regards the two substances as optically isomeric β-methylamino-α-phenylpropane-α-ols.

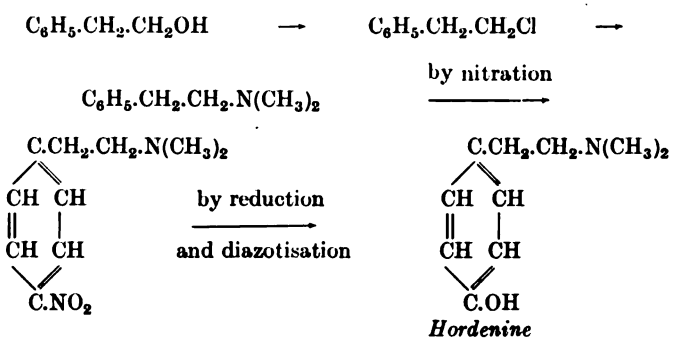
The name ephedrine was also applied to a substance, $C_{13}H_{19}ON$, isolated by Spehr [4] from *Ephedra monostachya*. This crystallises in monoclinic prisms, melts at 112°, and has practically no physiological action.

Hordenine, $C_{10}H_{15}ON$, was isolated from barley malt germs (*Hordeum sativum*) by Léger,[5] who subsequently examined it in detail and assigned to it the constitutional formula given on p. 332.

[1] Ladenburg and Oelschlägel, *loc. cit.* [2] *Loc. cit.*
[3] *Loc. cit.* [4] *Abstr. Chem. Soc.* 1892, 893.
[5] *Compt. rend.* 1906, **142**, 108 ; **143**, 234, 916 ; 1907, **144**, 208, 488.

Torquati [1] has pointed out that hordenine does not occur in barley until the latter germinates.

Hordenine forms colourless, bulky, orthorhombic prisms, melts at 117·8°, boils at 173°–174°/11mm., sublimes at 140°–150°, is optically inactive, and is readily soluble in alcohol, chloroform, or ether, but sparingly so in benzene. It is alkaline in reaction and liberates ammonia from its salts. It behaves as a monoacidic, tertiary base, and yields well-crystallised salts and a crystalline methiodide (m.p. 229°–230°). The oxygen atom is present as a phenolic hydroxyl group. On "exhaustive methylation" hordenine yields trimethylamine and *p*-vinylanisole. Acetylhordenine on oxidation furnishes *p*-acetoxybenzoic acid. On the basis of these results Léger suggested that hordenine is *p*-hydroxyphenylethyldimethylamine,[2] and this was confirmed by the synthesis of hordenine effected by Barger [3] and later by Rosenmund.[4] The former used as a starting-point phenylethyl alcohol, which was converted into hordenine by the following series of changes:



Hordenine

Hordenine is therefore closely related to *p*-hydroxyphenylethylamine (p. 386) found in ergot.

According to Camus [5] hordenine is only slightly toxic, but in large doses causes death by arrest of respiration. The alkaloid is hæmolytic.

[1] *Abstr. Chem. Soc.* 1911 [ii], 523.
[2] *Cf.* Gaebel, *Arch. Pharm.* 1906, **244**, 435.
[3] *Trans. Chem. Soc.* 1909, **95**, 2193. [4] *Berichte*, 1910, **43**, 306.
[5] *Compt. rend.* 1906, **142**, 110, 237, 350.

Muscarine, $C_5H_{15}O_3N$, was isolated by Schmiedeberg and Koppe [1] from " fly agaric " (*Amanita muscaria*) and has since been found in other poisonous fungi.

It forms tasteless, hygroscopic crystals, is readily soluble in alcohol or water, but nearly insoluble in ether or chloroform, and is alkaline in reaction. The platinichloride, $(C_5H_{14}O_2NCl)_2.PtCl_4.2H_2O$, forms small octahedra, m.p. 223°–224°, soluble in alcohol, but sparingly soluble in water.

The constitution of muscarine is still uncertain, though it is generally believed to be related to choline in the following way :

$$(CH_3)_3N(OH).CH_2.CH_2OH \longrightarrow (CH_3)_3N(OH).CH_2.CH(OH)_2,$$

which represents it as the " hydrate " of the aldehyde corresponding to choline. A substance isomeric with muscarine and indistinguishable from it except physiologically is formed when choline platinichloride is oxidised with nitric acid.[2] Natural muscarine and muscarine from choline are both toxic, but the latter causes paralysis of the intermuscular nerve terminations, and myosis in the pupils of the eyes of birds, whereas the former produces neither of these effects.[3] Honda has stated recently that the muscarine of toadstools has the same physiological action as choline-muscarine.[4]

*iso*MUSCARINE, $(CH_3)_3N(OH).CHOH.CH_2OH$, prepared synthetically by Bode,[5] is toxic, but does not resemble muscarine in physiological action.[6]

ANHYDROMUSCARINE, $(CH_3)_3N(OH).CH_2.CHO$, was obtained by Berlinerblau [7] and later by Fischer [8] by the action of trimethylamine on chloroacetal. This substance differs in composition from muscarine by $1H_2O$ and, like it, causes increased activity of the secretory glands, but differs in having no marked action on the frog's heart or on the pupil of the eye.

[1] *Jahresb.* 1870, p. 875.
[2] Schmiedeberg and Harnack, *Chem. Centr.* 1876, p. 558.
[3] Nothnagel, *Berichte*, 1893, **26**, 801 ; *Arch. Pharm.* 1894, **232**, 261.
[4] *Arch. exp. Path. Pharm.* 1911, **65**, 444.
[5] *Annalen*, 1892, **267**, 268.
[6] Schmidt, *ibid.* p. 249.
[7] *Berichte*, 1884, **17**, 1139.
[8] *Ibid.* 1893, **26**, 464.

Muscarine closely resembles pilocarpine (p. 309) in physiological action, causing especially increased activity of the secretory glands, and like pilocarpine is antagonistic to atropine. It has a very marked action on the heart, as little as 0·00003 grm. being sufficient to arrest the frog's heart.

It differs from pilocarpine mainly in its more marked action on intestinal muscle; thus whilst pilocarpine only occasionally causes nausea and vomiting, these symptoms are always produced by muscarine. The latter is also far more toxic than pilocarpine.

Sinapine, $C_{16}H_{25}O_6N$, was isolated in the form of its thiocyanate from black mustard seeds (*Brassica nigra*) by Henry and Garot[1] by precipitating a concentrated alcoholic extract of the oil-free seeds with potassium thiocyanate in alcohol, a method still employed for the isolation of the alkaloid. Will and Laubenheimer[2] first called attention to the fact that sinapine occurs in white mustard seed in the form of the alkaloidal glucoside, SINALBINE, $C_{30}H_{42}O_{15}N_2S_2$. The latter on hydrolysis by the enzyme myrosin, also present in the seed, furnishes dextrose, *p*-hydroxybenzylthiocarbimide, and sinapine sulphate.[3] Sinapine, owing to the ease with which it decomposes, is unknown in the free state. The thiocyanate is recrystallised from water until pure, and can be converted into the acid sulphate by treatment with sulphuric acid.

Sinapine acid sulphate, $C_{16}H_{24}O_5N.HSO_4.3H_2O$, crystallises from alcohol in leaflets, m.p. 127° (188° *dry*). The thiocyanate, $C_{16}H_{24}O_5N.SCN.H_2O$, forms pale yellow needles, m.p. 178°.

When the thiocyanate is warmed with alkalis there is formed choline (*see* p. 328) and sinapic acid, $C_{11}H_{12}O_5$;[4] the acid was investigated by Remsen and Coale,[5] and by Gadamer.[6] It crystallises in prisms, m.p. 191°–192°, contains two methoxyl groups, furnishes a monoacetyl derivative and contains a carboxyl group. When treated with methyl iodide in presence of alkalis, it yields methyl

[1] *Journ. Pharm.* 1825, **20**, 63. [2] *Annalen*, 1879, **199**, 162.

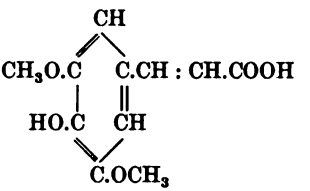
[3] Gadamer, *Arch. Pharm.* 1897, **235**, 44; 1897, **235**, 570; *Berichte*, 1897, **30**, 2322, 2327, 2328, 2330.

[4] von Babo and Hirschbrunn, *Annalen*, 1852, **84**, 10.

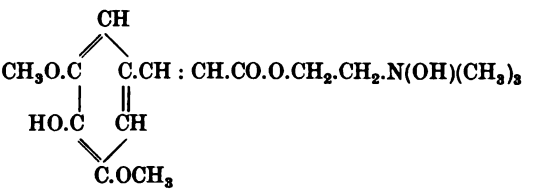
[5] *Amer. Chem. Journ.* 1884, **6**, 52. [6] *Loc. cit.*

methylsinapate $C_6H_4(OMe)_3.CO_2Me$, which by partial hydrolysis with alcoholic potash forms methylsinapic acid, and from the latter there is formed by oxidation trimethylgallic acid. Acetylsinapic acid on oxidation by permanganate yields syringic acid (3 : 5-dimethoxy-4-hydroxybenzoic acid).

Gadamer[1] has proposed the following formulæ for sinapic acid and sinapine, the latter being the choline ester of sinapic acid :



Sinapic acid (Gadamer)



Sinapine (Gadamer)

For other bases of this group occurring in plants, *see under* solanaceous alkaloids (p. 48), anhalonium alkaloids (p. 364), and ergot (p. 383).

[1] *Loc. cit.*

IX. ALKALOIDS OF UNKNOWN CONSTITUTION

ALKALOIDS OF *ACHILLEA* SPECIES

Achilleine, $C_{20}H_{38}O_{15}N_2$, was first obtained from common yarrow (*Achillea Millefolium*) by Zanon [1] and afterwards from the related plant *A. moschata* by von Planta.[2] It is a brown, amorphous, hygroscopic substance, soluble in water and possessing a peculiar odour and bitter taste; when boiled with dilute sulphuric acid there are formed a reducing sugar, ammonia, and an amorphous bitter alkaloid, *achilletine*, $C_{11}H_{17}O_4N$.

A second alkaloidal glucoside, *moschatine*, $C_{21}H_{27}O_7N$, was obtained by von Planta [3] from *A. moschata*; it also is ill-defined and of doubtful purity.

THE ACONITE ALKALOIDS

The genus *Aconitum* includes a large number of species; the alkaloids of comparatively few of these have been examined. The best known species is the common monkshood or wolf's bane, *Aconitum Napellus*, the toxic properties of which appear to have been known from very early times; preparations of aconite roots are stated to have been used as arrow poisons by the Chinese,[4] and probably also by the aborigines of ancient Gaul.[5] The drug was first employed in medicine in the thirteenth century, and was introduced into regular practice in Vienna about 1762.

Aconitum Napellus is widely distributed in the mountainous districts of Europe and the Pacific coast of North America. In

[1] *Annalen*, 1846, **58**, 21. [2] *Ibid.* 1870, **155**, 153. [3] *Loc. cit.*
[4] Smith, *Nat. Med. and Nat. Hist. of China*, 1871.
[5] *Pharmacographia*, p. 8.

Great Britain its natural occurrence is limited to a few districts in the West of England and South Wales, although it has been cultivated to some extent for use in medicine. Among other European species are *A. variegatum*, *A. Cammarum*, and *A. paniculatum*, all of which have tuberous roots similar to those of *Aconitum Napellus*.

In addition to the foregoing species two other plants, *Aconitum Lycoctonum* (*A. vulparia*)[1] and *Aconitum septentrionale*, which are both common in the mountainous districts of Europe, are known to contain poisonous alkaloids, but there is as yet no evidence to show that their constituents are of the type characteristic of the better known aconite alkaloids.

In India an interesting group of aconites occurs, which was examined botanically in 1905 by Stapf.[2] It includes *A. chasmanthum*, *A. spicatum*, *A. deinorrhizum*, and *A. Balfourii*, all of which are known to be poisonous, and *A. heterophyllum* and *A. palmatum*, which are not toxic. All these Indian species have been examined by Dunstan and his collaborators. The "bikh" or "bish" aconite root, which has been imported to Europe from India at various times under the name "Nepaul aconite," has been assumed recently to be the root of *A. spicatum*[3] or of *A. laciniatum*, but the "Nepaul aconite" of European commerce has always yielded the alkaloid pseud*aconitine*, and so far as is known at present this alkaloid is only obtained from the roots of *A. deinorrhizum* and *A. Balfourii*.[4]

The source of the Japanese aconite, which is occasionally imported into Europe, is as yet uncertain. This material yields the characteristic and well-defined alkaloid jap*aconitine*. According to Makoshi[5] two sorts of aconite roots are in use in Japan: the

[1] Carr has suggested on the authority of Stapf that the *A. Lycoctonum* of some chemical authors is really *A. vulparia* (Allen's *Organic Analysis*, 4th ed. vol. vi, p. 255).

[2] *Annals of the Royal Botanic Garden, Calcutta*, 1905, **10**, Part 2.

[3] Stapf, *loc. cit.*; Watt, *Agric. Ledger, India*, 1902, No. 3.

[4] For a full discussion of the alkaloids of the Indian aconites, see the *Bulletin of the Imperial Institute*, 1906, **4**, 32. [5] *Arch. Pharm.* 1909, **247**, 243.

one known as "bushi," grown in Hokkaido (Jeso), is from *A. Fischeri* and yields *jes*aconitine, whilst the other is from a variety of *A. Fischeri* grown in Hondo and yields *jap*aconitine. It is the latter which reaches Europe as Japanese aconite. According to Holmes it is the product of *A. uncinatum* var. *japonicum*.

Those aconite alkaloids which have been fully examined are now known to belong to three well-defined groups, viz. (1) aconitines, which are highly poisonous; (2) decomposition products of the aconitines, which are scarcely toxic in the ordinary sense; and (3) the atisines, which are not toxic. The principal members of these groups are as follows:

ACONITINES:

Aconitine, acetylbenzoylaconine, from *A. Napellus*.

*bikh*Aconitine, acetylveratroyl*bikh*aconine, from *A. spicatum*.

*ind*Aconitine, acetylbenzoyl*pseud*aconine, from *A. chasmanthum*.

*jap*Aconitine, acetylbenzoyl*jap*aconine, from Japanese aconite roots (Hondo sort).

*pseud*Aconitine, acetylveratroyl*pseud*aconine, from *A. deinorrhizum* and *A. Balfourii*.

The alkaloids *jes*aconitine, *lapp*aconitine, and *lyc*aconitine may also belong to the group of "aconitines," but this cannot be asserted definitely until they have been further examined.

DECOMPOSITION PRODUCTS OF THE "ACONITINES":

(1) *Acylaconines*:

Benzaconine (benzoylaconine), from Aconitine.

Veratroyl*bikh*aconine, from *bikh*Aconitine.

*ind*Benzaconine (benzoyl*pseud*aconine), from *ind*Aconitine.

*jap*Benzaconine, from *jap*Aconitine.

Veratroyl*pseud*aconine, from *pseud*Aconitine.

(2) *Aconines*:

Aconine, from Aconitine.

*bikh*Aconine, from *bikh*Aconitine.

*pseud*Aconine, from *ind*Aconitine and *pseud*Aconitine.

*jap*Aconine, from *jap*Aconitine.

ATISINES :

Atisine, from *A. heterophyllum.*

*palm*Atisine, from *A. palmatum.*

The "aconitines" are diacyl esters of polyhydroxyamino-alcohols, the "aconines," and their structure, as known at present, is shown in the following extended formulæ :

Aconitine : Acetylbenzoylaconine

$$C_{21}H_{27}O_3N(OAc)(OBz)(OCH_3)_4$$

Bikhaconitine : Acetylveratroylbikhaconine

$$C_{21}H_{27}ON(OAc)(OVe)(OCH_3)_4$$

Indaconitine : Acetylbenzoylpseudaconine

$$C_{21}H_{27}O_2N(OAc)(OBz)(OCH_3)_4$$

Japaconitine : Acetylbenzoyljapaconine

$$C_{21}H_{29}O_3N(OAc)(OBz)(OCH_3)_4$$

Pseudaconitine : Acetylveratroylpseudaconine

$$C_{21}H_{27}O_2N(OAc)(OVe)(OCH_3)_4$$

Ac = *acetyl*; Bz = *benzoyl*; Ve = *veratroyl.*

It appears therefore that the "aconitines" may all be regarded as derived from a parent base, $C_{21}H_{31}$ or $_{36}N$.[1]

ALKALOIDS OF *ACONITUM NAPELLUS*

The presence of alkaloidal constituents in the roots of *Aconitum Napellus* was first indicated by Geiger and Hesse,[2] and later an amorphous alkaloid was isolated by von Planta.[3] Crystallised aconitine was not obtained until 1860, when it was prepared by Groves.[4] The alkaloid was further investigated by Wright and collaborators,[5] who prepared several of its salts and examined its hydrolytic products. More recently the alkaloid has been investigated in England by Dunstan and his collaborators, and in Germany by Freund and his pupils.

[1] Dunstan and Henry, *Trans. Chem. Soc.* 1905, **87**, 1655.

[2] *Annalen*, 1833, **7**, 276. [3] *Ibid.* 1850, **74**, 257.

[4] *Pharm. Journ.* 1860 [ii], **8**, 121.

[5] *Journ. Chem. Soc.* 1875, p. 1265; 1877, **31**, 143; 1878, **33**, 151, 318; 1879, **35**, 387.

Preparation. Aconitine is best prepared by extracting the finely ground roots of *Aconitum Napellus* with a mixture of amyl alcohol (1 part) with wood spirit (3 parts). From this liquid the wood spirit is distilled under reduced pressure and the total alkaloids removed from their solution in amyl alcohol by agitation with dilute (1 per cent.) sulphuric acid. This acid solution, after the removal of non-basic impurities by shaking with ether, is made slightly alkaline by the addition of ammonia solution, and the aconitine, together with small quantities of benzaconine, extracted by shaking with ether, the aconine and the greater portion of the benzaconine remaining dissolved in the aqueous layer. The ethereal solution is washed once with water, and then on evaporation aconitine crystallises out, and is freed from a small amount of associated resinous impurity by conversion into its crystalline hydrobromide, which is recrystallised until of constant melting-point, and from this the alkaloid is regenerated and crystallised by solution in alcohol and addition of ether, in which it is sparingly soluble.

Properties. Wright and Luff[1] first assigned a formula, $C_{33}H_{43}O_{12}N$, to aconitine, and this was adopted subsequently with negligible modifications by Jürgens[2] and by Dunstan and his co-workers.[3] The source of the alkaloid used by Wright and by Dunstan was *Aconitum Napellus* root cultivated in England. In 1894 Freund and Beck[4] questioned the accuracy of the formula up to that time assigned to aconitine, and working with commercial German aconitine suggested the formula $C_{34}H_{47}O_{11}N$, which was subsequently modified by Schulze to $C_{31}H_{45}O_{11}N$.[5] Schulze's formula for aconitine extracted from German aconite roots was accepted by Dunstan in 1905,[6] who then pointed out that this aconitine of German origin is not identical with that obtained from *Aconitum Napellus* roots grown in England, as the following table of constants for the two alkaloids and their derivatives shows :

[1] *Loc. cit.* [2] *Inaug. Diss.* Dorpat, 1885.
[3] *Trans. Chem. Soc.* 1891, **59**, 271 ; 1892, **61**, 385.
[4] *Berichte*, 1894, **27**, 433.
[5] *Apoth. Zeit.* 1904, **18**, 783 ; 1905, **20**, 368.
[6] *Trans. Chem. Soc.* 1905, **87**, 1653.

Alkaloid from English *Aconitum Napellus*	Alkaloid from German *Aconitum Napellus*
Aconitine.	*Aconitine.*
Composition $C_{33}H_{45}O_{12}N$.	Composition $C_{34}H_{45}O_{11}N$.
Melting-point 188·5°.	Melting-point 197°–198°.
Specific rotation $[\alpha]_D$ + 10·47° to + 11·1° (in alcohol).	Specific rotation $[\alpha]_D$ + 14·36° to + 14·96° (in chloroform).
Aconitine hydrobromide.	*Aconitine hydrobromide.*
Melting-point 163°.	Melting-point 200°–207°.
Aconitine aurichloride.	*Aconitine aurichloride.*
Melting-points :	Melting-points :
α-form 135·5°.	α-form 136°.
β-form 152·0°.	β-form 149°–152°.
γ-form 176·0°.	No γ-form obtainable.
Benzaconine hydrochloride.	*Benzaconine hydrochloride.*
Melting-point 268°.	Two varieties.
	Melting-points :
	α-form = 217°.
	β-form = 268°–270°.
Benzaconine hydrobromide.	*Benzaconine hydrobromide.*
Melting-point 282°.	Melting-point 273°–274°.

Since then Schulze has asserted[1] that the two alkaloids must be identical since his aconitine possesses the same crystallographic characters as were ascribed by Tutton[2] to Dunstan's aconitine, but identity in crystalline form does not necessarily imply chemical identity in the group of "aconitines," since indaconitine[3] has the same crystalline form as aconitine, but is certainly not identical with that alkaloid. Since the aconitine of commerce of the present day is of German origin it is convenient that the name aconitine should be reserved for that alkaloid, and the following data, mostly recorded by Schulze,[4] refer to that substance.

Aconitine, $C_{34}H_{45}O_{11}N$, m.p. 197°–198°, crystallises in prisms belonging to the rhombic system (a : b : c = 0·54492 : 1 : 0·38917).[5] It is readily soluble in chloroform or benzene, less so in ether or dry alcohol, and almost insoluble in water or light petroleum. The alkaloid is dextrorotatory, $[\alpha]_D$ + 14·61° in chloroform. The salts

[1] *Arch. Pharm.* 1906, **244**, 169. [2] *Trans. Chem. Soc.* 1891, **59**, 233.
[3] Dunstan and Andrews, *ibid.* 1905, **87**, 1622.
[4] *Arch. Pharm.* 1906, **244**, 136, 165 ; 1908, **246**, 281.
[5] *Trans. Chem. Soc.* 1891, **59**, 288 ; *Berichte*, 1894, **27**, 722 ; *Arch. Pharm.* 1906, **244**, 169.

crystallise well and are lævorotatory: the hydrobromide, B.HBr, crystallises from water in hexagonal tablets with $2\frac{1}{2}H_2O$ (it sinters at 160° and melts at 200°), or from alcohol and ether in minute needles with $\frac{1}{2}H_2O$, m.p. 206°–207°; this salt has $[\alpha]_D$ — 30° 48′ in water; the hydriodide, m.p. 226°, is sparingly soluble in water; the hydrochloride has m.p. 149° and $[\alpha]_D$ — 30·9° in water; the aurichloride, $B.HCl.AuCl_3.3H_2O$, m.p. 136·5° or 152° (*dry*), crystallises in golden-yellow needles.

Aconitine contains four methoxyl groups and a methyl group linked to a nitrogen atom: on treatment with acetyl chloride at atmospheric temperature it yields a triacetyl derivative, m.p. 207°–208°, crystallising from alcohol in colourless needles.

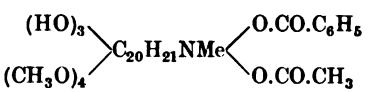
When a salt of aconitine is heated in aqueous solution under pressure it undergoes hydrolysis in two stages, yielding first acetic acid and a new base, *benzoylaconine* (picraconitine, isaconitine, benzaconine), which also occurs in aconite roots, and eventually benzoic acid and *aconine*: the latter also occurs as such in the plant. These changes may be represented thus:

$$\underset{\textit{Aconitine}}{C_{34}H_{45}O_{11}N} + H_2O = \underset{\textit{Acetic acid}}{CH_3.COOH} + \underset{\textit{Benzoylaconine}}{C_{32}H_{43}O_{10}N}$$

$$\underset{\textit{Benzoylaconine}}{C_{32}H_{43}O_{10}N} + H_2O = \underset{\textit{Benzoic acid}}{C_6H_5.COOH} + \underset{\textit{Aconine}}{C_{25}H_{39}O_9N}$$

When water is replaced by methyl alcohol, acetic acid is split off and methylbenzoylaconine, m.p. 210°–211°,[1] is formed.

Aconitine may be represented by the following extended formula (*see also* p. 449):



Aconitine

Benzoylaconine (*Benzaconine*), $C_{32}H_{43}O_{10}N$, m.p. 130°, is amorphous, but yields crystalline salts. Like aconitine it is dextrorotatory, $[\alpha]_D$ + 5° 37′, but furnishes lævorotatory salts; the hydrobromide, m.p. 273°, crystallises from dilute hydrobromic

[1] *Cf.* Dunstan, Tickle and Jackson, *Proc. Chem. Soc.* 1896, p. 159.

acid in thick colourless prisms ;[1] the hydriodide has m.p. 204°–205° ; the hydrochloride occurs in two forms, m.p. 217° and m.p. 270°.[2] The aurichloride is amorphous, m.p. 125-135°.

On acetylation benzoylaconine yields a tetracetyl derivative, m.p. 207°–208°, which Schulze states is identical with triacetylaconitine.

ACONINE, $C_{25}H_{39}O_9N$, m.p. 132°, the final basic product of aconitine hydrolysis, has not been obtained crystalline : it is readily dissolved by water and is hygroscopic, as are also its salts. The alkaloid is dextrorotatory, $[\alpha]_D + 23°$ in water, but yields lævorotatory salts. The hydrobromide, $B.HBr.1\frac{1}{2}H_2O$, m.p. 225° (*dry*), and the hydrochloride, $B.HCl.2H_2O$, m.p. 175°–176° $[\alpha]_D - 7{\cdot}7°$ in water, are both crystalline, but the aurichloride is amorphous. Tetracetylaconine, m.p. 231°–232°, is crystalline. Aconine contains four methoxyl groups and a methyl linked to nitrogen. On oxidation with alkaline permanganate, it yields acetaldehyde and an amorphous base, but with chromic acid it furnishes methylamine and two new amorphous bases, $(OH)_4.C_{20}H_{19}O(OMe)_3.NMe$ (hydrochloride, m.p. 213° $[\alpha]_D^{20} + 54{\cdot}37°$, slender, colourless needles), and $C_{19}H_{20}O_4(OMe)_3.NMe.COOH$ (hydrochloride, m.p. above 300°, short, colourless prisms). (*See also* p. 449.)

When heated at its melting-point aconitine loses one molecule of acetic acid and gives rise to a new alkaloid, *pyraconitine*, m.p. 167·5°, colourless, slender needles, which is optically inactive, but yields crystalline lævorotatory salts. Pyraconitine is very readily hydrolysed by alkalis, yielding benzoic acid and *pyraconine*, which is lævorotatory and amorphous, but yields a crystalline, lævorotatory hydrochloride, m.p. 154°, $[\alpha]_D - 102°$ in water.[3]

Aconitine is most readily detected by the tingling sensation produced when a drop of a very dilute solution is applied to the tip of the tongue. This test must be used with caution owing to the highly toxic character of the alkaloid. It furnishes with permanganate in presence of a little acetic acid an unstable precipitate

[1] Schulze, *loc. cit.* [2] Freund and Beck, *loc. cit.*
[3] Dunstan and Carr, *Trans. Chem. Soc.* 1894, **65**, 176.

of rosettes of purple needles.[1] These reactions are also given by the other "aconitines," and for the identification of any individual "aconitine" the preparation of the alkaloid or one of its crystalline derivatives and the determination of its melting-point and other typical constants are desirable.

ESTIMATION. Various methods have been proposed for the estimation of aconitine in aconite root, but these yield aconitine mixed with more or less benzaconine and other alkaloids also present in the roots. The United States Pharmacopœia (8th Rev.) gives the following method: Ten grammes of aconite root in No. 40 powder are placed in a 200 c.c. Erlenmeyer flask with 75 c.c. of a mixture of alcohol (7 volumes) and water (3 volumes). The flask is securely closed and kept with occasional agitation during four hours. A cylindrical glass percolator 25 mm. in diameter is then closed at the lower end with a plug of cotton-wool, and the contents of the flask completely transferred to it. When all the liquid has passed through and been collected, percolation is continued with the diluted alcohol until 150 c.c. of percolate has been collected. This is transferred to a shallow evaporating dish and evaporated to dryness at a temperature not exceeding 60°. To the residue 5 c.c. of $N/10$ sulphuric acid and 25 c.c. of water are added, and when the extract has dissolved as far as possible the liquid is filtered into a separator and the dish washed with 25 c.c. of water and the washings also filtered into the separator. To the latter 25 c.c. ether and 2 c.c. ammonia solution (sp. gr. 0·958 at 25°) are added, and the whole thoroughly shaken during one minute and set aside to separate. The lower layer is drawn off and the ether filtered into a beaker. The extraction of the alkaline liquor is repeated three times, using 15, 10, and 10 c.c. of ether. The combined filtered ether solutions are evaporated to dryness, and the residue dissolved in 3 c.c. $N/10$ sulphuric acid. The number (n) of c.c. of $N/50$ potassium hydroxide needed to neutralise the excess of acid, in presence of cochineal as indicator, is noted. The following formula gives the percentage of aconitine present $(3 - n/5) \times 0{\cdot}64$. The quantity found

[1] Dunstan and Carr, *Pharm. Journ.* 1896, **56**, 122.

should not be less than 0·5 per cent. According to Stevens, who describes a process very similar to the foregoing,[1] it gives results of the same order as (1) those obtained by noting the dilution necessary to inhibit the causation of a tingling sensation when a drop of an aconite preparation is applied to the tip of the tongue (Squibb's test); (2) those afforded by the determination of the toxicity of aconite preparations towards frogs. Dunstan and Ince have, however, pointed out that from crude aconite extracts, rendered alkaline by ammonia, ether extracts other alkaloids as well as aconitine,[2] and this is confirmed by Schulze. Dunstan and Tickle have shown that whilst the amount of aconitine may be determined by noting the quantity of acetic acid formed when the alkaloid is heated at its melting-point, this process is not applicable to galenical preparations of aconite or to total alkaloid extracted from them, since some other substance yielding an acid distillate is present.[3]

Physiological Action of Aconitine and its Basic Decomposition Products

The physiological action of these alkaloids has been investigated by Cash and Dunstan, with results which have brought out an interesting relationship between the constitution of these bases and the physiological effects they produce.

Aconitine is highly toxic: it at first stimulates the medullary centres slowing the heart; acceleration follows, auricles and ventricles taking up an independent rhythm. The alkaloid at first stimulates and finally depresses the respiratory centre, and in mammals produces death by central respiratory failure. The motor and reflex nervous systems are at first stimulated, but eventually depressed. The alkaloid induces lowering of internal temperature. The lethal dose per kilogramme of body weight is—for rabbits 0·000139 grm., for guinea-pigs 0·00012 grm., and for frogs (*Rana temporaria*) 0·000586 (March) to 0·0014 (July) grm.[4]

[1] *Pharm. Arch.* 1903, **6**, 49. [2] *Trans. Chem. Soc.* 1891, **59**, 271.
[3] *Pharm. Journ.* 1896 [iv], **56**, 121. [4] *Phil. Trans.* 1898, **190**, 239.

Benzoylaconine. The toxicity of this alkaloid is slight as compared with that of aconitine. The main physiological action is somewhat antagonistic to that of the parent alkaloid. Benzoylaconine slows the action of the heart, and especially of the ventricles it depresses the respiratory centres from the first, but its effect on respiration and internal temperature is on the whole similar to, but far less marked than, that of aconitine. The lethal dose for frogs is 0·284 grm. per kilogramme of body weight.[1]

Pyraconitine induces slowing of the action of the heart, depresses the activity of the respiratory centres, and is from five to six times as toxic as benzoylaconine towards frogs.[2]

Methylbenzoylaconine causes slowing of the heart, and in large doses failure in sequence. The cardiac vagus is depressed in action, and its inhibitory function is ultimately suspended. Motor nerves are greatly affected by doses which are distinctly below the lethal for cold-blooded animals, the action being curare-like in character. The toxicity of aconitine is from 80 to 100 times greater than that of methylbenzoylaconine, whilst the latter is from three to four times more toxic (towards rabbits) than benzoylaconine.

Aconine behaves as a cardiac tonic and is antagonistic to aconitine in a much greater degree than is benzoylaconine. It exerts a curare-like effect on the motor nerve endings of muscles. The lethal dose for frogs is 1·055 to 1·75 grm. per kilogramme of body weight.[1]

These results show that the powerful toxicity of aconitine is correlated with the presence of the acetyl group; thus benzoylaconine in its action on the heart is antagonistic to aconitine, though in its influence on the respiration and temperature it still retains traces of the depressant action of the parent alkaloid. Pyraconitine, produced by the action of heat on aconitine resulting in the loss of a molecule of acetic acid, differs from benzoylaconine by the elements of water. It resembles benzoylaconine generally in its physiological action, though it is rather more toxic. Methylbenzoylaconine is aconitine in which the acetyl group is replaced

[1] *Phil. Trans.* 1898, **190**, 239. [2] *Ibid.* 1902, **195**, 97.

by methyl. Though methylbenzoylaconine is more toxic than benzoylaconine, it is a very feeble poison when compared with aconitine. The introduction of the methyl group induces a curare-like action. The removal of the benzoyl group from benzoylaconine gives rise to aconine and still further reduces the toxicity, and aconine in a much greater degree than benzoylaconine is antagonistic to aconitine, so much so that the administration of aconine is successful in averting in small animals the effect of a lethal dose of aconitine. Perhaps the most characteristic feature of the physiological action of aconine is the curare-like effect on the motor nerve endings of the muscles. Aconine is not poisonous in the usual sense, very large doses being required to produce death, even in frogs.

ALKALOIDS OF JAPANESE ACONITES

The Japanese aconite roots of European commerce are usually regarded as identical with those known as "kusauzu" in Japan, and are generally stated to be derived from *Aconitum Fischeri*, though their exact botanical origin is by no means settled. Makoshi states[1] that at least two kinds of aconite roots are known as "kusauzu" in Japan, the one occurring in Hondo, and the other found in China and the island of Hokkaido (Jeso) in Japan. The former is used in medicine, and the latter was formerly employed as an arrow poison. The same author finds that the Hondo "kusauzu" roots contain japaconitine, and the Hokkaido "kusauzu" or "bushi" roots contain a different alkaloid, jesaconitine. Makoshi quotes Miyabe as stating that the Hokkaido roots are derived from typical *Aconitum Fischeri*, and the Hondo roots from a variety of *A. Fischeri*. In this connection it may be mentioned that *A. chasmanthum*, Stapf, of India, was formerly regarded as a variety of *Aconitum Napellus*, and in the same way it seems likely that the Hondo plant may prove on further examination to be a species distinct from *A. Fischeri*, and Makoshi's observation that

[1] *Arch. Pharm.* 1909, **247**, 243.

the alkaloids from the Hondo and Hokkaido roots are different is useful evidence in favour of this supposition. According to Holmes the Japanese aconite of European commerce is probably derived from *Aconitum uncinatum* var. *japonicum*.

Japaconitine, $C_{34}H_{49}O_{11}N$. As explained above, the source of this alkaloid is Japanese aconite roots of European commerce, probably identical with Hondo "kusauzu" roots and derived from *A. uncinatum* var. *japonicum*. Crystalline japaconitine was first obtained by Paul and Kingzett,[1] and was subsequently investigated by Wright, Luff, and Menke,[2] who assigned to it the formula $C_{66}H_{88}O_{21}N_2$ and regarded it as the sesqui-apo-derivative of a hypothetical base of the formula $C_{33}H_{47}O_{12}N$. They prepared crystalline salts of the alkaloid and observed its hydrolysis into benzoic acid and amorphous japaconine. Later observers, Mandelin,[3] Lübbe,[4] and Freund and Beck,[5] concluded that the alkaloid of Japanese aconite was identical with aconitine obtained from *Aconitum Napellus*. Dunstan and Read, after an exhaustive examination of the alkaloid, its salts and principal derivatives, have shown that japaconitine is a distinct alkaloid very closely allied to, but not identical with, aconitine, and this conclusion has been confirmed by Makoshi.[6] Pope [7] and Schwantke [8] have shown that japaconitine is crystallographically distinct from aconitine.

Japaconitine may be prepared by the method described under aconitine (p. 340); it forms colourless rosettes of needles and melts at 204·5° (*corr.*), is soluble in chloroform, hot ether, or hot alcohol, but insoluble in light petroleum or water. Its solutions are dextrorotatory, $[\alpha]_D + 20{\cdot}26°$ in chloroform or $+ 23{\cdot}6°$ in alcohol. The salts crystallise from alcohol on addition of ether; their solutions are lævorotatory; the hydrochloride, $B.HCl.3H_2O$, separates from water in rosettes of hexagonal plates, m.p. 149°–150°, $[\alpha]_D - 23{\cdot}8°$ in water; the nitrate, $B.HNO_3$, minute rosettes,

[1] *Pharm. Journ. and Trans.* 1877 [iii], **8**, 173.
[2] *Trans. Chem. Soc.* 1879, **35**, 387.
[3] *Arch. Pharm.* 1885, **23**, 162.
[4] *Chem. Central.* 1890 [ii], 148.
[5] *Berichte*, 1894, **27**, 723.
[6] *Loc. cit.*
[7] *Trans. Chem. Soc.* 1900, **77**, 49
[8] *Arch. Pharm.* 1909, **247**, 242.

m.p. 173°–177°, and the thiocyanate, B.HCNS, lustrous needles, m.p. 190°–192°. The aurichloride, $B.HAuCl_4$, occurs in two forms : the *α*-form, which is the more stable, separates by the addition of ether or water to solutions in alcohol, in golden-yellow rosettes, m.p. 231°; and the *β*-form, obtained by spontaneous evaporation of solutions in chloroform, crystallises in yellow prisms, m.p. 154°–160°. Japaconitine and its salts, like aconitine, cause, even in very dilute solution, an intense tingling when applied to the tip of the tongue.

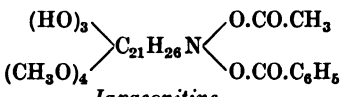
Japaconitine contains four methoxyl groups; it combines with methyl iodide, forming a methiodide, m.p. 224°–225°, which on treatment with dilute potash produces methyljapaconitine, $C_{34}H_{48}O_{11}NCH_3$; this crystallises from ether in needles, m.p. 206°. Acetyl chloride in the cold converts japaconitine into triacetyljapaconitine, crystallising in rosettes, m.p. 166° (Dunstan and Read), 188° (Makoshi). Japaconitine on hydrolysis furnishes at first one molecular proportion of acetic acid and *japbenzaconine* (benzoyljapaconine), $C_{32}H_{47}O_{10}N$; the latter is to some extent further hydrolysed, producing benzoic acid and *japaconine*, $C_{25}H_{43}O_9N$, in equimolecular quantities.

JAPBENZACONINE (benzoyljapaconine), $C_{32}H_{47}O_{10}N$, crystallises from ether by addition of light petroleum in minute rosettes, m.p. 183°; it is dextrorotatory in solution, $[\alpha]_D + 40{\cdot}16°$ in alcohol. The salts crystallise well and are lævorotatory; the hydrochloride, $B.HCl.H_2O$, forms small rosettes, m.p. 253°; the aurichloride, $B.HAuCl_4$, crystallises from dry alcohol and then melts at 219°; when crystallised from alcohol by addition of light petroleum, the aurichloride is converted into aurichlorjapbenzaconine, $C_{32}H_{46}O_{10}N.AuCl_2$, which crystallises in colourless octahedra, m.p. 178°. Tetracetyljapbenzaconine, m.p. 231°–232°, forms compact transparent crystals (Makoshi).

JAPACONINE, $C_{25}H_{43}O_9N$, best obtained by hydrolysing japbenzaconine with alcoholic soda, is a colourless, hygroscopic powder, m.p. 99°–100°, insoluble in ether or light petroleum, but soluble in water, alcohol, or chloroform; its solutions are dextrorotatory,

$[\alpha]_D + 10{\cdot}8°$ in water. The salts crystallise with difficulty, the hydrobromide in triangular plates, m.p. 221°.

In view of the facts recorded above, japaconitine may be represented by the following extended formula :



Japaconitine

PYROJAPACONITINE, $C_{32}H_{45}O_9N$, is formed when japaconitine is heated at its melting-point, a molecule of acetic acid being split off. It crystallises in needles, m.p. 167°–168° ; its solutions are lævorotatory, $[\alpha]_D - 65{\cdot}8°$ in alcohol. The hydrobromide, $B.HBr.2H_2O$, crystallises from water in colourless needles, m.p. 241°, $[\alpha]_D - 102{\cdot}5°$ in water ; the aurichloride, $B\,HAuCl_4$, is crystalline, m.p. 160°–161°, from chloroform.

When pyrojapaconitine is warmed in alkaline solution it undergoes hydrolysis into benzoic acid and *pyrojapaconine*, $C_{25}H_{41}O_8N$. The latter is amorphous, melts at 123°–128°, and has specific rotation $[\alpha]_D - 73{\cdot}9°$. No crystalline salts have been obtained.

Japaconitine is highly toxic and produces on the heart, respiratory and nervous systems physiological effects similar to, but as a rule slightly greater than, those induced by aconitine (p. 345). Taking the activity of aconitine as equal to unity, that of japaconitine is approximately equal to 1·125°.[1] Cash and Dunstan suggest that, administered in smaller doses corresponding with its greater activity, japaconitine could replace aconitine in therapeutics.

Jesaconitine, $C_{40}H_{51}O_{12}N$, was obtained by Makoshi[2] from the roots of a species of aconite, which Miyabe regards as *A. Fischeri*, found in the island of Hokkaido (Jeso) in Japan (p. 347). It is amorphous, and on hydrolysis furnishes benzoic and anisic acids and aconine, the latter identical with that from aconitine, so that it is regarded as benzoylanisoylaconine. It furnishes a triacetyl

[1] Cash and Dunstan, *Phil. Trans.* 1902, **195**, 39.
[2] *Arch. Pharm.* 1909, **247**, 251.

derivative, m.p. 213°–215°. Its physiological action resembles that of aconitine in general, but shows certain differences, and it is even more poisonous.

ALKALOID OF *ACONITUM DEINORRHIZUM*

Pseudaconitine, $C_{36}H_{51}O_{12}N$, occurs in *Aconitum deinorrhizum*, Stapf, and *A. Balfourii*, Stapf,[1] and is obtainable from "Nepaul aconite roots," which occasionally appear in European commerce. Pseudaconitine was first isolated by Wright and Luff,[2] and has since that time been further examined by Dunstan and Carr,[3] and by Freund and Niederhofheim.[4] It may be prepared by the method described under aconitine. The alkaloid crystallises from chloroform, on adding ether and light petroleum, in colourless rhombs, m.p. 211°–212°. It is readily soluble in alcohol or chloroform, less so in ether, and slightly soluble in water; its solutions are dextrorotatory, $[\alpha]_D$ + 18° 36′ in alcohol. The salts crystallise well and are lævorotatory in solution; the hydrobromide, $B.HBr.2H_2O$, forms rosettes of colourless cubes, m.p. 191°, $[\alpha]_D$ — 19·5° in water; the hydriodide, B.HI, minute needles, m.p. 215°, and the nitrate, $B.HNO_3.H_2O$, needles, m.p. 192°; the aurichloride, $B.HAuCl_4$, crystallises in golden-yellow needles, m.p. 235°–236°. Pseudaconitine, like aconitine, causes an intense tingling when even a very dilute solution is applied to the tip of the tongue. It also yields a crystalline permanganate which is more stable and somewhat more soluble in water than that of aconitine (*see* p. 343). Pseudaconitine contains six methoxyl groups. When hydrolysed by heating neutral solutions of its salts in water at 135° it undergoes partial hydrolysis into acetic acid and VERATROYLPSEUDACONINE, $C_{34}H_{49}O_{11}N.H_2O$. This base crystallises from ether in large irregular crystals, melts at 199°, and is soluble in alcohol, ether, or chloroform, but almost insoluble in water or petroleum. The alkaloid, unlike the parent base, is lævorotatory in solution,

[1] *Bull. Imp. Inst.* 1906, **4**, 37. [2] *Journ. Chem. Soc.* 1878, **33**, 151.
[3] *Proc. Chem. Soc.* 1895, p. 154; *Trans. Chem. Soc.* 1897, **71**, 350.
[4] *Berichte*, 1896, **29**, 852.

$[\alpha]_D$ — 38·15° in alcohol. The salts crystallise well; the hydrobromide, B.HBr.$3H_2O$, separates from its solutions in alcohol on addition of ether, in large prisms; the nitrate, B.HNO_3, crystallises in rosettes of rhombic prisms, sinters at 222°, and melts completely at 232°. The aurichloride, B.$HAuCl_4$, is amorphous. When veratroylpseudaconine is allowed to stand with alcoholic sodium hydroxide it is hydrolysed, forming *pseudaconine* and veratric acid:

$$\underset{\textit{Veratroylpseudaconine}}{C_{34}H_{49}O_{11}N} + H_2O = \underset{\textit{Veratric acid}}{C_6H_3(OCH_3)_2.COOH} + \underset{\textit{Pseudaconine}}{C_{25}H_{41}O_8N}.$$

Pseudaconine is also formed by the hydrolysis of indaconitine (p. 354).

Pseudaconine, $C_{25}H_{41}O_8N$, is an amorphous, hygroscopic base, readily soluble in water, chloroform, alcohol, or acetone, and nearly insoluble in ether. It readily combines with alcohol (1 mol.), forming a well-crystallised compound, m.p. 94°–95°, which can be utilised for its isolation in a pure state. It is dextrorotatory, $[\alpha]_D$ + 39·11° in water. The salts, owing to their deliquescent nature, are difficult to obtain crystalline, but the aurichloride, B.$HAuCl_4$, has been obtained in needles, m.p. 125°–126°.[1]

When pseudaconitine is heated at its melting-point it loses a molecule of acetic acid, forming *pyropseudaconitine*:

$$\underset{\textit{Pseudaconitine}}{C_{36}H_{51}O_{12}N} = \underset{\textit{Acetic acid}}{CH_3.COOH} + \underset{\textit{Pyropseudaconitine}}{C_{34}H_{47}O_{10}N}.$$

Pyropseudaconitine is a colourless varnish, insoluble in water, but readily soluble in ether, chloroform, or alcohol. The hydriodide forms colourless prisms.

Pseudaconitine is intensely poisonous and closely resembles aconitine in physiological action, but is much more toxic; if the activity of aconitine is taken as equal to unity, that of pseudaconitine would be from 2·2 to 2·5.[2] Cash and Dunstan suggest that pseudaconitine might replace aconitine in therapeutics, provided

[1] Dunstan and Andrews, *Trans. Chem. Soc.* 1905, **87**, 1620.
[2] Cash and Dunstan, *Phil. Trans.* 1902, **195**, 39.

it is administered in the smaller doses, which would correspond with its greater activity.

ALKALOID OF *ACONITUM CHASMANTHUM*, STAPF

The roots of this Indian species, which is known in India as "Mohri," were examined by Dunstan and Andrews[1] and found to contain the crystalline alkaloid indaconitine. The alkaloid was obtained by a slightly modified form of the process described under aconitine (*see* p. 340).

Indaconitine, $C_{34}H_{47}O_{10}N$, crystallises in rosettes of colourless needles or in hexagonal prisms from ether, the latter form being very similar to, and possibly isomorphous with, aconitine. It has m.p. 202°–203°, and $[\alpha]_D$ + 18° 17′ in alcohol. The hydrobromide separates from water in hexagonal prisms, m.p. 183°–187° (*dry*), $[\alpha]_D$ — 17° 16′, or from alcohol by addition of ether in crystals, m.p. 217°–218°; the aurichloride, $B.HCl.AuCl_4$, crystallises from hot alcohol in rosettes of yellow needles, sinters at 142°, and melts at 147°–152°; it exists in one form only, but crystallises from chloroform on addition of ether with 1 mol. of chloroform. Like aconitine, indaconitine causes an intense tingling when even a very dilute solution is applied to the tip of the tongue, and gives a crystalline precipitate with permanganate, but the crystals are smaller. It contains four methoxyl groups. When indaconitine sulphate in aqueous solution is heated in a sealed tube it undergoes hydrolysis, yielding 1 mol. each of acetic acid and BENZOYLPSEUDACONINE (indbenzaconine). The latter is a colourless varnish, m.p. 130°–133°, $[\alpha]_D$ + 33° 35′, yielding well-crystallised lævorotatory salts; the hydrobromide, $C_{32}H_{45}O_9N.HBr.2H_2O$, m.p. 247° (*dry*), crystallises in rosettes; the hydrochloride forms needles or octahedra, m.p. 242°–244° (*dry*), $[\alpha]_D$ — 8·0° in water, and the aurichloride crystallises from alcohol in orange-coloured rosettes, m.p. 180°–182°, but when recrystallised from alcohol by addition of light petroleum is partly converted into aurichlorindbenzaconine, m.p.

[1] *Trans. Chem. Soc.* 1905, **87**, 1620.

234°–235°, which forms minute colourless needles, and is unstable in the light.

When indaconitine is allowed to stand at atmospheric temperature with alcoholic soda it is hydrolysed, forming 1 mol. each of acetic acid, benzoic acid, and PSEUDACONINE, $C_{25}H_{41}O_8N$, the latter being identical with the final basic product of the hydrolysis of pseudaconitine (*see* p. 352).

When indaconitine is heated at its melting-point it loses 1 mol. of acetic acid and furnishes a new base, *α-pyroindaconitine*, $C_{32}H_{43}O_8N$, which is amorphous, but yields a crystalline hydrobromide, m.p. 194°–198° (*dry*), which is dextrorotatory like the free base; the aurichloride is amorphous. Indaconitine hydrochloride, heated at 165°–170° for a few minutes, yields the isomeric *β-pyroindaconitine*, which is also amorphous, but gives a crystalline hydrobromide (small needles, m.p. 248°–250°, $[\alpha]_D$ + 27° 37′).

Indaconitine and its salts are highly poisonous and in general exert a physiological action differing only in degree from that of aconitine (*see* p. 345). The poisonous dose is similar to that for aconitine. As is the case with the aconitines as a class, the toxicity disappears with the removal of the acetyl group and benzoylpseudaconine (indbenzaconine), like benzaconine, is scarcely poisonous. The physiological action of pseudaconine from indaconitine resembles that of aconine (p. 346) and of pseudaconine from pseudaconitine (p. 352).[1]

ALKALOID OF *ACONITUM SPICATUM*, STAPF

This species is one of those known in India as "bikh" or "bish," and it has been suggested that it yields the "Nepaul aconite" of European commerce, though this is unlikely in view of the fact that "Nepaul aconite" contains pseudaconitine, which is quite distinct from the bikhaconitine found in *A. spicatum* roots. The roots of this species were examined by Dunstan and Andrews.[2]

[1] Cash and Dunstan, *Proc. Roy. Soc.* 1905, B, **76**, 468.
[2] *Trans. Chem. Soc.* 1905, **87**, 1636.

Bikhaconitine, $C_{36}H_{51}O_{11}N.H_2O$, may be obtained from *A. spicatum* roots by the process described under aconitine (p. 340). It crystallises less easily than the " aconitines " as a class, but may be obtained from ether in button-shaped masses, m.p. 118°–123°, or, better, with $1H_2O$ from alcohol, on addition of water, in colourless granules, m.p. 113°–116° (*dry*). It is readily soluble in alcohol, ether, or chloroform, but almost insoluble in water or light petroleum. It is dextrorotatory, $[\alpha]_D^{20} + 12{\cdot}21°$, in alcohol. The salts crystallise well; the hydrobromide, $B.HBr.5H_2O$, m.p. 173°–175° (*dry*), $[\alpha]_D^{20} - 12{\cdot}42°$; the hydrochloride, $B.HCl.5H_2O$, m.p. 159°–161° (*dry*), $[\alpha]_D^{20} - 8{\cdot}86°$, may be crystallised from alcohol on adding ether. The aurichloride, $B.HCl.AuCl_3$, m.p. 232°–233°, separates from chloroform on addition of light petroleum in canary-yellow needles. Bikhaconitine and its salts, even in very dilute solutions, excite the intense tingling sensation characteristic of the aconitines when applied to the tip of the tongue.

Bikhaconitine contains six methoxyl groups, of which two are in the veratroyl radical (*see below*).

When an aqueous solution of bikhaconitine sulphate is heated at 130°, hydrolysis takes place with the formation of 1 mol. each of acetic acid and a new base, VERATROYLBIKHACONINE, $C_{34}H_{49}O_{10}N$, m.p. 120°–125°, $[\alpha]_D^{20} + 29{\cdot}9°$, which is amorphous and is best obtained pure by regeneration from the recrystallised aurichloride, $B.HCl.AuCl_3$, which separates from alcohol in clusters of orange-yellow prisms containing $2C_2H_5OH$ or $5H_2O$, m.p. 145°–148° (*dry*). The hydriodide, m.p. 189°–190° (*dry*), forms rosettes of needles from water. The other haloid salts are amorphous.

By the action of alcoholic soda on veratroylbikhaconine at atmospheric temperature, 1 mol. each of veratric acid and BIKHACONINE are formed. Bikhaconine, $C_{25}H_{41}O_7N$, is amorphous, $[\alpha]_D^{22} + 33{\cdot}85°$, and differs from its analogues aconine (p. 343), japaconine (p. 349), and pseudaconine (p. 352) in being soluble in ether and in yielding readily crystallisable salts; the hydrobromide, B.HBr, m.p. 145°–150° (*dry*), forms tetragonal prisms; the nitrate, $B.HNO_3.2H_2O$, m.p. 125°–128°, $[\alpha]_D^{20} + 15{\cdot}38°$, separates from

alcohol or water in transparent tetragonal prisms with acicular or pyramidal ends; the aurichloride, $B.HCl.AuCl_3.3H_2O$, m.p. 129°–132° or 187°–188° (*dry*), forms glistening rhombic plates on adding light petroleum to its solution in chloroform or alcohol.

When heated at 180° bikhaconitine loses 1 mol. of acetic acid and forms PYROBIKHACONITINE, $C_{34}H_{47}O_9N$, a colourless varnish yielding only amorphous salts; the aurichloride is yellow and melts indefinitely at 115°–123°.

Bikhaconitine resembles the "aconitines" generally in physiological action, but agrees most closely with pseudaconitine (p. 352), and in toxicity lies between japaconitine and pseudaconitine, the last-mentioned being the most toxic of the three. Bikhaconine closely resembles aconine, its physiological action being essentially curare-like in character.[1]

ALKALOIDS OF *ACONITUM SEPTENTRIONALE*[2]

The roots of this species were examined by Rosendahl in 1896,[3] and the following three alkaloids isolated:

Lappaconitine, $C_{34}H_{48}O_8N_2$, crystallises in large, hexagonal prisms, m.p. 205°, is dextrorotatory, and sparingly soluble in ether, in which it forms a solution showing a reddish-green fluorescence. The alkaloid is toxic and produces paralysis of the respiration and the heart.

Cynoctonine, $C_{36}H_{55}O_{13}N_2$, is amorphous and dextrorotatory. It causes convulsions when injected hypodermically.

Septentrionaline, $C_{31}H_{48}O_9N_2$, is amorphous and dextrorotatory. It produces local anæsthesia and resembles curarine in physiological action when injected subcutaneously, but like cynoctonine is not toxic when swallowed.

[1] Cash and Dunstan, *Proc. Roy. Soc.* 1905, B, **76**, 468.

[2] On the authority of Stapf, Carr has suggested that the roots used by Rosendahl were those of *A. Lycoctonum* (Allen's *Organic Analysis*, 4th ed. vol. vi, p. 255).

[3] *Journ. Pharm. Chim.* 1896 [iv], **4**, 262.

ALKALOIDS OF *ACONITUM LYCOCTONUM*[1]

From the roots of this species Hübschmann isolated the amorphous alkaloids acolyctine and lycoctonine.[2] Subsequently Dragendorff and Spohn showed[3] that Hübschmann's alkaloids were probably decomposition products of *lycaconitine*, $C_{27}H_{34}O_6N_2.2H_2O$, which they isolated along with *myoctonine*, $C_{27}H_{30}O_8N_2.5H_2O$, from the roots of *A. Lycoctonum*. LYCACONITINE is bitter, amorphous, and dextrorotatory, $[\alpha]_D + 31{\cdot}5°$ in alcohol, has m.p. 111°–114°, and is readily soluble in alcohol or chloroform. Water at 100° hydrolyses it into *lycaconine*, $C_{33}H_{56}O_8N_4$, *lycoctonic acid*, $C_{17}H_{18}O_7N_2$, *acolyctine* (?), and a dihydroxybenzoic acid. With alkalis *lycoctonine* and *lycoctonic acid* are formed. MYOCTONINE, $C_{27}H_{30}O_8N_2.5H_2O$, m.p. 143°–144°, is amorphous. Both alkaloids are toxic, causing convulsions, paralysis of the motor nerve endings, and failure of the heart.

ALKALOID OF *ACONITUM HETEROPHYLLUM*

Atisine, $C_{22}H_{31}O_2N$. The roots of the Indian plant *Aconitum heterophyllum* are employed in Indian native medicine as a mild tonic under the name Atis root. It was first investigated in 1873 by Broughton,[4] who isolated from it the alkaloid atisine, to which he ascribed the formula $C_{46}H_{74}O_5N_2$. Atisine was subsequently investigated by Wasowicz,[5] who showed that it occurred in atis root associated with aconitic acid. He prepared several crystalline salts and suggested for the alkaloid the formula $C_{46}H_{74}O_4N_2$. The formula $C_{22}H_{31}O_2N$, now assigned to it, was proposed by Wright[6] and was subsequently confirmed by Jowett,[7] who more fully investigated the properties of the alkaloid and its salts.

Atisine is a colourless varnish of indefinite melting-point,

[1] *A. vulparia* (?); *see* footnote on p. 337. [2] *Jahresberichte*, 1866, p. 483.
[3] *Pharm. Zeit. Russland*, 1884, **23**, 313.
[4] *Blue Book. Cinchona Cultivation in East India*, 1877, p. 133.
[5] *Arch. Pharm.* 1879, **214**, 193. [6] *Yearbook of Pharmacy*, 1879, 422.
[7] *Trans. Chem. Soc.* 1896, **69**, 1578.

slightly soluble in water and readily so in alcohol, ether, or chloroform; it is lævorotatory, $[\alpha]_D$ — 19·6° in water. The salts crystallise well; the hydrochloride, B.HCl, forms thin rectangular prisms, m.p. 296°, and is dextrorotatory, $[\alpha]_D$ + 18·46°; the hydrobromide, B.HBr, has m.p. 273° and $[\alpha]_D$ + 24·3° in water; the hydriodide, B.HI, crystallises in brilliant rectangular plates, m.p. 279°, $[\alpha]_D$ + 27·4°, and is slightly soluble in cold water. The aurichloride, B.$HAuCl_4$, is amorphous, but the platinichloride is a yellowish-brown crystalline powder.

When atisine is heated with alkalis or acids it does not suffer hydrolysis, but is converted into an amorphous hydrate, B.H_2O.

Atisine is not poisonous. Its physiological action has been investigated by Cash and shown to be somewhat similar to that of aconine (p. 346).

ALKALOID OF *ACONITUM PALMATUM*

The roots of this Indian species contain a colourless crystalline alkaloid, PALMATISINE, which resembles atisine from *A. heterophyllum* in being bitter and non-poisonous.[1]

ALKALOIDS OF *ADLUMIA CIRRHOSA*

This plant was examined by Schlotterbeck[2] and found to contain about 1 per cent. of protopine (*see* p. 381) in its roots. The whole plant was subsequently examined by the same author,[3] who found, in addition to protopine, β-homochelidonine (p. 380) and three new alkaloids, of which two were named *adlumine* and *adlumidine*.

Adlumine, $HO.C_{37}H_{34}O_9N(OCH_3)_2$, m.p. 188°, crystallises in colourless, orthorhombic crystals, and has $[\alpha]_D$ + 39·88°.

Adlumidine, $C_{30}H_{29}O_9N$, forms small square plates and has m.p. 234°.

The third alkaloid, which has not been named, is present in

[1] *Bull. Imp. Inst.* 1906, **4**, 39.
[2] *Amer. Chem. Journ.* 1900, **24**, 249.
[3] *Pharm. Archiv.* 1903, **6**, 17.

very small quantity: it is crystalline and melts at 176°–177°. These alkaloids appear to be present as tartrates and citrates.

ALKALOIDS OF ALSTONIA SPECIES

Alstonine, $C_{21}H_{20}O_4N_2.3\frac{1}{2}H_2O$ (Chlorogenine), is an amorphous base isolated by Palm from *Alstonia constricta* bark, used in Australia as a febrifuge. It was obtained later by Hesse [1] together with the amorphous alkaloids *porphyrine*, $C_{21}H_{25}O_2N_3$, and *porphyrosine*, and the crystalline base *alstonidine* (needles, m.p. 181°).

The bark of *Alstonia scholaris* (Dita bark), occurring in the Philippines and used as a febrifuge, was examined in 1875 by Gorup-Besanez,[2] who isolated from it a crystalline alkaloid. The bark was examined by Jobst and Hesse [3] in the same year and yielded to them the alkaloids *ditamine*, *echitamine*, and *echitenine*, of which the second was subsequently identified with Merck and Harnack's ditaine (*see below*). Hesse subsequently found the same three alkaloids in *Alstonia spectabilis* bark and assigned formulæ to them.[4]

Ditamine, $C_{16}H_{19}O_2N$, is an amorphous powder which melts at 75°; its solutions are bitter and strongly alkaline in reaction.

Echitamine, $C_{22}H_{28}O_4N_2.H_2O$ (Ditaine), was obtained as a crystalline tetrahydrate by spontaneous evaporation of its alcoholic solution. This at 80° loses $3H_2O$, giving a crystalline monohydrate, m.p. 206°, which on drying at 105° yields the anhydrous base as a varnish. The monohydrate is soluble in ether or chloroform when freshly precipitated, but almost insoluble when crystallised; it is insoluble in benzene; its alcoholic solution is lævorotatory, $[\alpha]_D$ — 28·8°. The platinichloride, $(B.HCl)_2.PtCl_4.3H_2O$, is amorphous. The alkaloid dissolves in concentrated sulphuric acid with a purple-red colour, and gives with concentrated nitric acid a fugitive red passing into intense green. The base paralyses the

[1] *Annalen*, 1880, **205**, 360.
[2] *Ibid.* 1875, **176**, 326.
[3] *Ibid.* 1875, **178**, 49.
[4] *Ibid.* 1880, **203**, 147, 162.

motor nerves in warm-blooded animals and reduces the blood-pressure.[1]

Echitenine, $C_{20}H_{27}O_4N$, a brown, amorphous, bitter substance melting above 120°, forms anhydrous amorphous salts and gives colour reactions with nitric and sulphuric acids similar to those of echitamine.

Alstonamine occurs only in the bark of *Alstonia spectabilis*. It is crystalline, but its composition is unknown.

ALKALOIDS OF *ANAGYRIS FŒTIDA*

Anagyrine, $C_{15}H_{22}ON_2$, was obtained together with cytisine (p. 396) from the seeds of *Anagyris fœtida* by Partheil and Spasski,[2] and was subsequently investigated by Klostermann [3] and by Litterscheid.[4] The former prepared it by the addition of lead acetate solution to the water-soluble portion of an alcoholic extract of the seeds. The precipitate was decomposed by hydrogen sulphide and the alkaloid separated from cytisine by means of the mercuric chloride compound, from which anagyrine can be regenerated in the usual manner. Cytisine may also be separated by conversion into the insoluble phenylthiocarbamide. From the filtrate anagyrine may be recovered by adding alkali and shaking out with chloroform.[4]

It is an amorphous varnish-like substance. The hydrochloride, $B.HCl.H_2O$, crystallises in rhombic plates and has $[\alpha]_D$ — 142° 28′; the hydriodide, $B.HI.H_2O$, forms stellar aggregates of yellow needles, and the platinichloride, $B.2HCl.PtCl_4.1\frac{1}{2}H_2O$, forms ruby-red needles, m.p. above 235°. The methiodide, $B.CH_3I$, forms colourless needles.

Anagyrine contains no hydroxyl group. When oxidised with permanganate a crystalline oxidation product, $C_{15}H_{20}O_2N_2$, m.p. 195°, is formed.

The base is ditertiary and has the composition and properties

[1] Harnack, *Berichte*, 1878, **11**, 2004; 1880, **13**, 648; Hesse, *ibid.* 1880, **13**, 1841.
[2] *Apoth. Zeit.* 1895, **10**, 903.
[3] *Arch. Pharm.* 1900, **238**, 227.
[4] *Ibid.* 1900, **238**, 191.

of a butylcytisine, but Goessmann [1] has recently thrown doubt on the validity of the formula $C_{15}H_{22}ON_2$, usually assigned to anagyrine.

In cold-blooded animals anagyrine exerts a curare-like action, and in warm-blooded species induces depression of respiration. Its physiological action is unlike that of cytisine.

ALKALOIDS OF *ANAMIRTA PANICULATA*

Menispermine, $C_{18}H_{24}O_2N_2$, was obtained by Pelletier and Courbé,[2] together with a second alkaloid, paramenispermine, from the pericarp of the fruits of the Indian fish poison, *Anamirta paniculata*. It crystallises in rectangular prisms, m.p. 120°, and is readily soluble in alcohol or ether. The sulphate is crystalline.

Paramenispermine also forms rectangular prisms, m.p. 250°; it is soluble in alcohol and very sparingly so in water or ether.

Both alkaloids are bitter and physiologically inactive.

ALKALOIDS OF ANHALONIUM SPECIES

A number of plants belonging to the genus *Anhalonium* (*Mammillaria*) are used by Mexican Indians to produce intoxication in the course of certain religious ceremonies. The plants are known by the name "pellote." The best known product of this kind is the flowering heads of *Anhalonium Lewinii*, which have been imported into Europe for use in medicine under the name "mescal buttons." The following alkaloids of this group are known: [3]

Anhalamine, $C_{11}H_{15}O_3N$, in *A. Lewinii*.

Anhaline, $C_{10}H_{17}O_3N$, in *A. fissuratum*.

Anhalonidine, $C_{12}H_{15}O_3N$, in *A. Lewinii*.

Anhalonine, $C_{12}H_{15}O_3N$, in *A. Lewinii* and *A. Jourdanianum*.

Lophophorine, $C_{13}H_{17}O_3N$, in *A. Lewinii*.

[1] *Arch. Pharm.* 1906, **244**, 20. [2] *Annalen*, 1834, **10**, 198.

[3] *Cf.* Lewin, *Arch. f. exp. Path.* 1888, **24**, 401; 1894, **34**, 374. Heffter, *ibid.* 1894, **34**, 82; 1898, **40**, 385; *Berichte*, 1894, **27**, 2975; 1896, **29**, 216; 1898, **31**, 1193. Ewell, *Journ. Amer. Chem. Soc.* 1896, **18**, 624. Also other references quoted later.

Mezcaline, $C_{11}H_{17}O_3N$, in *A. Lewinii*.

Pellotine, $C_{13}H_{19}O_3N$, in *A. Lewinii* and *A. Williamsii*.

The alkaloids present in " mescal buttons " may be isolated by the following process:[1] The heads are ground and percolated with alcohol until exhausted. The percolate is concentrated to a small bulk, set aside to facilitate the separation of resin, and the clear extract poured off. To this, ammonia solution is added in excess, and the alkaline liquid shaken with chloroform until alkaloids are no longer extracted. The chloroform solution is extracted with dilute sulphuric acid, from which the alkaloids readily soluble in ether, viz. anhalonine, lophophorine, and pellotine, are removed by adding ammonia and shaking with ether. The remaining alkaloids, anhalamine, anhalonidine, and mezcaline, are then extracted with chloroform. The mixed ether-soluble alkaloids are converted into the mixed hydrochlorides, which on recrystallisation from dry alcohol separate in the order anhalonine, pellotine, lophophorine. The second group of alkaloids, viz. those sparingly soluble in ether, are converted into the sulphates; these on solution in hot water deposit mezcaline sulphate on cooling. The mother liquors are treated with ammonia and shaken out with chloroform, when anhalamine remains undissolved. The alkaloids passing into solution are mezcaline and anhalonidine, which are separated by conversion into the hydrochlorides and treatment of these with hot alcohol, in which anhalonidine hydrochloride is insoluble, whilst the mezcaline salt dissolves. According to Heffter,[2] mescal buttons contain mezcaline 6·3 per cent., anhalonidine 5·3 per cent., anhalonine 3 per cent., and lophophorine 0·5 per cent.

Anhalamine, $C_{11}H_{15}O_3N$, microscopic needles, m.p. 185·5°, $[\alpha]_D$ 0°, dissolves in boiling chloroform or benzene. The hydrochloride, $B.HCl.2H_2O$, forms lustrous leaflets from water, and the sulphate, $B_2.H_2SO_4$, colourless prisms. The base contains two methoxyl groups and probably one hydroxyl group, since both a dibenzoyl derivative, m.p. 128°–129°, and a monobenzoyl derivative, m.p. 167·5°, are formed with benzoyl chloride, the latter, but not the

[1] Kauder, *Arch. Pharm.* 1899, **237**, 190. [2] *Berichte*, 1896, **29**, 216.

former, being soluble in alkalis. The formula $OH.C_9H_7(OCH_3)_2:NH$ has been provisionally assigned by Heffter to the alkaloid.[1]

Anhaline, $C_{10}H_{17}O_3N$, obtained by extracting *A. fissuratum* with ammoniacal alcohol, crystallises in prisms, m.p. 115°, and dissolves readily in alcohol, ether, or light petroleum. The salts crystallise well; the aurichloride and platinichloride are amorphous, and soluble in water, but insoluble in alcohol. With nitric acid a yellow solution is produced, which on the addition of potash changes to orange-red. The base causes paralysis of the central nervous system in frogs.[2]

Anhalonidine, $C_{12}H_{15}O_3N$, crystallises in small octahedra, m.p. 154°, $[\alpha]_D$ 0°, and dissolves readily in chloroform, alcohol, or water, but is insoluble in light petroleum and nearly so in dry ether. The aqueous solution is strongly alkaline, and liberates ammonia from its salts. The hydrochloride, B.HCl, crystallises in prisms, but the platinum and gold salts are amorphous. The alkaloid contains two methoxyl groups. Benzoylanhalonidine crystallises in lustrous plates, m.p. 189°. With methyl iodide the alkaloid forms methylanhalonidine hydriodide (yellow prisms, m.p. 125°–130°). Heffter[2] represents the alkaloid by the following provisional formula, $OH.C_{10}H_7.(OCH_3)_2:NH$.

Anhalonine, $C_{12}H_{15}O_3N$, crystallises from light petroleum in long needles which melt at 85°. It is soluble in water, alcohol, or ether; the solutions are lævorotatory. The hydrochloride, B.HCl, forms colourless prisms; the platinichloride, $(B.HCl)_2.PtCl_4$, golden-yellow needles. Anhalonine contains one methoxyl group. It is a secondary base, forms a nitroso derivative, and reacts with methyl iodide, forming a *N*-methylanhalonine, which in turn gives a methiodide, $C_{12}H_{14}O_3N(CH_3).CH_3I$, m.p. 210°.[2]

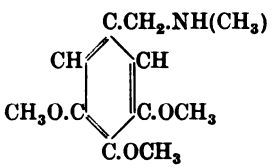
Lophophorine, $C_{13}H_{17}O_3N$, has only been obtained as a colourless syrup, insoluble in water, but readily soluble in organic solvents. The hydrochloride, B.HCl, crystallises in small colourless needles. The base contains one methoxyl group. It is

[1] *Berichte*, 1901, **34**, 3004.
[2] Heffter, *ibid.* 1894, **27**, 2976.

isomeric, but not identical with methylanhalonine and methylanhalonidine.

Mezcaline, $C_{11}H_{17}O_3N$, is a colourless alkaline oil, which rapidly absorbs carbon dioxide from the air, forming a crystalline carbonate. It is soluble in chloroform, water, benzene, or alcohol, but insoluble in dry ether or light petroleum. The sulphate, $B_2.H_2SO_4.2H_2O$, forms brilliant prisms, the hydrochloride colourless crystals, and the platinichloride, $(B.HCl)_2.PtCl_4$, bright yellow needles. The alkaloid contains three methoxyl groups and a methyl linked to nitrogen. The methiodide, $B.CH_3I$, crystallises in colourless prisms, m.p. 169°, and on shaking with chloroform furnishes methylmezcaline ; the methiodide of the latter crystallises in pale yellow plates, m.p. 220°. Benzoylmezcaline forms lustrous needles, m.p. 120°.

On oxidation the parent alkaloid furnishes 3 : 4 : 5-trimethoxybenzoic acid and a small amount of a neutral nitrogenous substance. From this evidence Heffter[1] assigned to the alkaloid the constitution



but subsequently showed that the synthesised product of this formula was not identical with mezcaline.[2]

Mezcaline gives a lemon-yellow coloration with sulphuric acid, passing into violet on warming or on adding a small fragment of sucrose or sodium nitrate. A similar reaction is also given by all the alkaloids of this group.

Pellotine, $C_{13}H_{19}O_3N$, occurs in *A. Williamsii* (*Echinocactus Williamsii*) to the extent of 3·5 per cent.[3] It was found in *A. Lewinii* by Kauder,[4] but this may have been due to the presence of

[1] *Berichte*, 1901, **34**, 3004.
[2] Heffter and Capellmann, *Berichte*, 1905, **38**, 3634.
[3] Heffter, *ibid.* 1894, **27**, 2975 ; 1901, **34**, 3004. [4] *Loc. cit.*

A. Williamsii heads in the plant material used.[1] It crystallises from alcohol in transparent tablets, m.p. 110°. The hydrochloride, B.HCl, forms rhombic prisms. The alkaloid is a tertiary base and contains two methoxyl groups, a methyl group joined to nitrogen, and a phenolic hydroxyl group. The methiodide, $B.CH_3I.H_2O$, crystallises in small prisms, m.p. 198°. When distilled with soda-lime, trimethylamine is formed. From these reactions the formula $C_{10}H_9(OCH_3)_2(OH)(NCH_3)$ has been assigned to this alkaloid.

Physiological Action of Anhalonium Alkaloids

Dixon has shown[2] that the physiological action of anhalonidine, anhalonine, lophophorine, and mezcaline is qualitatively the same. They cause an increased flow of saliva, occasionally vomiting, and in large doses diarrhœa. The action of the heart is slowed and there is a fall in blood-pressure. With toxic doses respiration becomes quicker and shallower, and death results from failure of the respiratory centre. In animals there is at first increased reflex activity, then paralysis, which is central in origin.

In man there is a preliminary stage of excitement, resembling that produced by alcohol. A number of subjective sensations are also experienced; a feeling of "dual existence" and increased sensitiveness to colours and to music are noticed, and a kaleidoscopic play of colours is seen. The alkaloids are excreted in the urine and there is some diuresis. Lophophorine is the most powerful of the alkaloids, but mezcaline is most active in producing colour vision.

The following additional observations are mainly due to Lewin[3] and Heffter:[4] The physiological action of anhalamine has not been investigated. Anhaline exercises a paralysing action on the central nervous system. Anhalonine is highly toxic, producing reflex irritability in small doses and reflex tetanus in large doses: the lethal dose of the hydrochloride for rabbits is 0·16 to 0·2 grm. per kilogramme of body weight. The quaternary ammonium

[1] Heffter, *loc. cit.*
[2] *Journ. Physiol.* 1899, **25**, 69.
[3] *Loc. cit.*
[4] *Loc. cit.*

derivatives of anhalonidine show the characteristic physiological action of such products and produce paralysis of the motor nerve endings in frogs, but this is not the case with the corresponding anhalonine derivatives. Lophophorine is the most toxic of this group of alkaloids, 0·0011 grm. per kilogramme of body weight being the lethal dose for frogs. Pellotine is slightly narcotic, and has been used in medicine as a hypnotic in doses of one-third to two-thirds of a grain.

ALKALOID OF *ARACHIS HYPOGÆA*

Arachine, $C_5H_{14}ON_2$, occurs along with choline and betaine in the earth-nut (pea-nut, ground nut) (*Arachis hypogœa*). It is a yellowish-green syrup, readily soluble in alcohol or water, less so in chloroform, and insoluble in ether. The platinichloride, m.p. 216°, and the aurichloride are both crystalline. The alkaloid produces transient narcosis in frogs and rabbits with partial paralysis.[1]

ALKALOID OF *ARARIBA RUBRA*

Aribine, $C_{23}H_{20}N_4.8H_2O$, was obtained by Rieth and Wöhler [2] from the bark of *Arariba* (*Sickingia*) *rubra*, formerly used as a red dye for wool. It crystallises in anhydrous octahedra from ether by rapid cooling, or with $8H_2O$ in prisms by spontaneous evaporation from solution in wet ether. The anhydrous base melts at 229°, volatilises at higher temperatures, is slightly soluble in water, but readily in alcohol or ether. It is bitter to the taste. The hydrochloride, B.2HCl, forms prisms, and the platinichloride, $B.2HCl.PtCl_4$, bright yellow needles. The alkaloid combines with two molecules of ethyl iodide.

ALKALOIDS OF *ARGEMONE MEXICANA*

This plant contains berberine (p. 285) and protopine (p. 381). The alkaloid " argemonine " is impure protopine.[3]

[1] Mooser, *Landw. Versuchs-Stat.* 1904, **60**, 321; *Chem. Soc. Abstr.* 1905 [i], 79.
[2] *Annalen*, 1861, **120**, 247.
[3] Schlotterbeck, *Pharm. Rev.* 1901, **19**, 458.

ALKALOIDS OF ARISTOLOCHIA SPECIES

A considerable number of species of *Aristolochia* have been used in medicine in various parts of the world; at the present time the stems and roots of *Aristolochia indica* and *A. bracteata* are so used in India, and under the name of serpentary the rhizomes and roots of *A. Serpentaria*, Lam., and *A. reticulata*, Nutt, are so employed in the United Kingdom and the United States. These are all now used as bitter tonics, but all four have in the past enjoyed an unfounded reputation as remedies for snake bites. They all contain bitter substances, and Hesse suggested[1] that the bitter substance isolated by Chevallier from *A. reticulata* may contain some aristolochine (*see below*), but it is not yet certain that any of these species contain alkaloids.[2] In *A. longa* Hesse[3] was unable to find any alkaloidal constituents.

The three species which have been fully investigated are *A. Clematitis* and *A. rotunda*, occurring in S. America, especially Brazil, and *A. argentina*, from the Argentine Republic. These three have all been used in medicine in the countries in which they are found, and the first two in Europe, as tonics.

Aristolochine (*Aristolochic acid*, Hesse), $C_{32}H_{22}O_{13}N_2$ or $C_{17}H_{11}O_7N$, was isolated by Pohl[4] from the seeds of *Aristolochia Clematitis* and the roots of *Aristolochia rotunda*. It forms orange-yellow needles, decomposes at 215°, is soluble in ether, alcohol, boiling water, or alkaline solutions, and dissolves in concentrated sulphuric acid with a dark green colour. The alkaloid is highly poisonous, especially when injected intravenously, causing dilatation of the blood-vessels in the intestinal tract, resulting in a fall in blood-pressure and sometimes hæmorrhage. In action it resembles aloin, but is more powerful.

[1] *Pharm. Journ.* 1891-92, **51**, 551.

[2] *Cf.* Dymock, Warden and Hooper, *Pharmacographia indica*, 1893, vol. iii, p. 163.

[3] *Loc. cit.*

[4] *Arch. f. exp. Path.* 1891, **29**, 282. *Cf.* Hesse, *Arch. Pharm.* 1895, **233**, 684.

From the root of the allied species *Aristolochia argentina* Hesse [1] has obtained the following series of alkaloids :

Aristinic acid, $C_{18}H_{13}O_7N$, crystallises from hot acetic acid in greenish-yellow leaflets or needles, m.p. 275° (*decomp.*). The potassium salt, $C_{18}H_{12}O_7NK.2H_2O$, separates from potassium hydroxide solution in reddish needles; the methyl ester forms yellow needles, m.p. 250°.

Aristidinic acid, $C_{18}H_{13}O_7N$, is isomeric with the foregoing : it forms greenish-yellow needles, m.p. 260° (*approx.*), and contains one methoxyl group.

Aristolic acid, $C_{15}H_{11}O_7N$, forms orange-red needles, m.p. 260°–270°, and like the two foregoing alkaloids gives a green solution with concentrated sulphuric acid.

From the same source Hesse obtained [1] an amorphous alkaloid which he called "aristolochine," and which was different from Pohl's aristolochine. The latter he proposed should be named aristolochic acid, and suggested that it was probably a lower homologue of aristinic or aristolic acid.

ALKALOID OF *ARTEMISIA ABROTANUM*

Abrotine, $C_{21}H_{22}ON_2$, obtained by Giacosa [2] rom the root of *Artemisia Abrotanum*, is a crystalline substance, sparingly soluble in hot water. The sulphate and platinichloride have been prepared ; the former is crystalline. The alkaloid is stated to have antiseptic properties, but does not inhibit fermentation.

ALKALOIDS OF ASPIDOSPERMA SPECIES

The two species of this genus which have been examined are *Aspidosperma Quebracho*, Schlecht, from Argentina, and an unidentified species from Central America, which yields the so-called "Payta" bark. *A. Quebracho* is sometimes confused with the quebracho of the Argentine, which yields the quebracho wood of

[1] *Pharm. Journ.* 1891-92, **51**, 551 ; *Arch. Pharm.* 1895, **233**, 684.
[2] *Jahresberichte*, 1883, p. 1356.

commerce largely used for making the extract of the same name used in tanning, and derived from a different species, *Quebrachia* (*Loxopterygium*) *Lorentzii*, Griseb (p. 429). The latter bears the local name "quebracho colorado," and the former is called "quebracho blanco."

Quebracho blanco bark (*A. Quebracho*)

The bark is used in South America as a substitute for cinchona in the treatment of fevers and malaria. It was examined by Fraude,[1] who isolated from it the alkaloid aspidospermine, and later by Hesse,[2] who isolated several other bases. The bark from young trees contains 1·4 per cent., and that from old trees 0·3 per cent. of alkaloids.

Aspidosamine, $C_{22}H_{28}O_2N_2$. This amorphous isomeride of aspidospermatine (*see below*) was obtained by Hesse.[2] It is bitter, but differs somewhat in physical properties from its isomeride, and gives a brown coloration with ferric chloride, a reddish coloration with perchloric acid, and blue with sulphuric acid, becoming darker on adding potassium dichromate.

Aspidospermatine, $C_{22}H_{28}O_2N_2$, was obtained by Hesse;[2] it is crystalline, bitter, strongly basic, melts at 162°, and is readily soluble in alcohol, ether, or chloroform. The solutions are lævorotatory, $[\alpha]_D$ — 73·3° in alcohol. The salts are mostly amorphous. It is coloured red by perchloric acid.

Aspidospermine, $C_{22}H_{30}ON_2$, crystallises in colourless prisms or needles, m.p. 205°–206°. It is bitter, readily soluble in benzene or chloroform, but less so in alcohol, ether, or light petroleum. The solutions are lævorotatory; in alcohol $[\alpha]_D$ — 100·2°, in chloroform — 83·6°. Salts are formed with difficulty owing to the weakly basic character of the alkaloid; the platinichloride, $[B.HCl]_2.PtCl_4$, is a crystalline precipitate. The sulphate has been used in medicine as a tonic and febrifuge and antispasmodic. The base, when warmed with perchloric acid containing chlorine, gives a

[1] *Berichte*, 1878, **11**, 2189; 1879, **12**, 1560.
[2] *Annalen*, 1882, **211**, 249.

magenta-red coloration, and with sulphuric acid and potassium dichromate a brown colour slowly passing into green.

Hypoquebrachine, $C_{21}H_{26}O_2N_2$, is a varnish, m.p. 80°, soluble in alcohol, ether, or choroform. It is bitter to the taste, strongly alkaline in reaction, and forms amorphous salts. In sulphuric acid it forms a colourless solution, which gradually becomes bluish-violet. Perchloric acid in water colours it magenta-red on warming.

Quebrachamine is crystalline and melts at 142°, but its composition has not been determined.

Quebrachine, $C_{21}H_{26}O_3N_2$, crystallises in colourless needles, m.p. 214°–216° (*decomp.*). It is bitter, alkaline in reaction, soluble in chloroform or boiling alcohol, and the solutions are dextrorotatory; in chloroform $[\alpha]_D + 18{\cdot}6°$, and in alcohol $+ 65°$. The salts are crystalline; the hydrochloride forms flattened needles. The colour reactions resemble those of hypoquebrachine.

The physiological action of the quebracho alkaloids was investigated by Penzoldt,[1] who found that in frogs aspidospermatine, aspidospermine, hypoquebrachine, and quebrachamine act on the central nervous system, producing paralysis of the motor nerves, whilst aspidosamine and quebrachine produce the same effect in a curare-like manner.

Payta Bark (*Aspidosperma* sp.)

This material contains two alkaloids.[2]

Paytamine, $C_{21}H_{24}ON_2$, occurs in the bark in minute amount. The alkaloid and its salts are amorphous, and according to Hesse [2] it is formed by isomerisation of paytine, from which it is distinguished by not being precipitated by potassium iodide solution.

Paytine, $C_{21}H_{24}ON_2.H_2O$, was isolated by Hesse. It crystallises from alcohol with $1H_2O$, melts at 156°, dissolves in most organic solvents, but sparingly in water; the solutions are lævorotatory, alkaline in reaction, and possess a bitter taste. The hydrochloride, B.HCl, crystallises from hot water in prisms; with

[1] *Annalen*, 1882, **211**, 271.
[2] Hesse, *Annalen*, 1870, **154**, 287; 1873, **166**, 272; 1882, **211**, 280.

platinic chloride it furnishes a precipitate, which on warming becomes brownish red, then blue, and finally deep indigo in colour. Perchloric acid gives a magenta-red colour on warming.

ALKALOID OF *ATHEROSPERMA MOSCHATUM*

Atherospermine, $C_{30}H_{40}O_5N_2$ (?), was obtained by Zeyer[1] from the bark of *Atherosperma moschatum*, Lab., which is used in Australia for making a kind of herb tea.

It is an amorphous, bitter powder, m.p. 128°, soluble in alcohol or chloroform, sparingly so in ether, and insoluble in water. When heated it gives off trimethylamine (?). The alkaloid is alkaline in reaction and forms amorphous salts ; it dissolves in sulphuric acid, forming a colourless solution, which becomes green on the addition of a crystal of potassium dichromate.

ALKALOIDS OF *BUPHANE DISTICHA*

From the outer layers of the bulbs of this South African plant Tutin[2] isolated buphanine, narcissine (*see* p. 414), and two unnamed alkaloids.

Buphanine is amorphous and strongly basic, but has not been characterised. It resembles scopolamine in physiological action, but is weaker. On treatment with alcoholic potash it is converted into BUPHANITINE, $C_{23}H_{24}O_6N_2$, which crystallises from alcohol in colourless prisms, containing 1 mol. of the solvent, which is lost at 130°, and the substance then melts at 240°. It is readily soluble in chloroform and moderately so in alcohol or boiling water. The hydrochloride, B.HCl, forms colourless needles, m.p. 265°–268° (*decomp.*), and the methiodide, $B.CH_3I$, prisms, m.p. 278° (*decomp.*). Buphanitine is physiologically inactive.

The other two alkaloids have not been characterised, but one is soluble in water and more basic than the other, and exerts a

[1] *Jahresberichte*, 1861, 769.

[2] *Trans. Chem. Soc.* 1911, **99**, 1240. *Cf. Arch. exp. Path. Pharm.* 1912, **68**. 333 ; **69**, 314.

physiological action similar to those of colchicine and narcissine. The less basic alkaloid is a convulsant poison.

ALKALOIDS OF BOXWOOD [1] (*BUXUS SEMPERVIRENS*)

The alkaloid buxine was isolated from the bark and leaves of the boxwood plant by Fauré,[2] and subsequently asserted by Walz [3] to be identical with bebeerine (*see* p. 414), a suggestion confirmed by Flückiger.[4] Scholtz has shown, however, that buxine cannot be crystallised from methyl alcohol, and is consequently not identical with bebeerine.[5] In these circumstances it is impossible to assign any formula to buxine or to describe it. The same applies to the ill-defined alkaloids parabuxine, buxinidine, and parabuxinidine (crystalline), which Barbaglia obtained from this source,[6] or to the supposed sepeerine (*see* p. 414), which Walz [7] prepared from the box plant.

Boxwood bark has been used as a febrifuge.

ALKALOIDS OF CALUMBA ROOT (*JATEORHIZA COLUMBA*)

Calumba root has been stated to contain berberine, but this has been disproved (*see* p. 286). The root has been examined by Günzel [8] and by Feist,[9] who have shown that it contains the following three alkaloids. The formulæ of the alkaloids are still doubtful, as the latter have not been obtained in a free state and they appear to form salts by loss of $1H_2O$.

Columbamine, $C_{21}H_{21}O_5N$. The hydriodide, B.HI, is yellow and has m.p. 224°; the hydrochloride, $B.HCl.2\frac{1}{2}H_2O$, forms yellow needles, m.p. 194°, or $B.HCl.4H_2O$, brown prisms, m.p. 184°; the nitrate, $B.HNO_3.2\frac{1}{2}H_2O$, crystallises in lemon-yellow needles,

[1] For West African boxwood, *see* p. 447.
[2] *Jahresberichte Berz.* 1830, **11**, 245. [3] *Jahresberichte*, 1860, p. 548.
[4] *Pharm. Journ.* 1869-70 [ii], **11**, 192. [5] *Arch. Pharm.* 1898, **236**, 530.
[6] *Gazzetta*, 1883, **13**, 249; *Berichte*, 1884, **17**, 2655.
[7] *Jahresberichte*, 1859, p. 565.
[8] *Arch. Pharm.* 1906, **244**, 257. [9] *Ibid.* 1907, **245**, 586.

m.p. 232°; the aurichloride forms slender needles, m.p. 220°. On warming with potash solution the nitrate yields columbamine anhydride in violet-black prisms, m.p. 190° (*decomp.*).

The alkaloid contains one hydroxyl group and four methoxyl groups. It is yellow, but on reduction yields a colourless tetrahydro derivative. The methyl ether on oxidation furnishes corydaldine (p. 267) and a trimethoxy-*o*-phthalic acid. These reactions indicate that columbamine is very closely related to berberine and corydaline.

Jateorrhizine, $C_{20}H_{19}O_5N$. The hydriodide, $B.HI.H_2O$, forms reddish-yellow needles, m.p. 208°–210°, the hydrochloride, $B.HCl.H_2O$, copper-coloured needles, m.p. 206°, from alcohol, and the nitrate, glistening yellow plates, m.p. 225° (*decomp.*). On reduction the nitrate yields tetrahydrojateorrhizine, $C_{20}H_{23}O_5N$, colourless needles, m.p. 206°. Jateorrhizine contains three methoxyl and two hydroxyl groups, and on methylation gives columbamine methyl ether, so that columbamine appears to be a methyl ether of jateorrhizine.

Palmatine, $C_{21}H_{21}O_6N$. The hydriodide, B.HI, m.p. 238°–240°, and the nitrate, $B.HNO_3.1\frac{1}{2}H_2O$, form slender yellow needles. On reduction tetrahydropalmatine, colourless leaflets, m.p. 145°, is obtained. Palmatine contains four methoxyl groups.

In medicine calumba root is used as a simple bitter, probably mainly on account of its non-nitrogenous bitter constituents, columbin, &c.

ALKALOIDS OF *CALYCANTHUS GLAUCUS*

From the seeds of this plant, Eccles,[1] and later Wiley, obtained the alkaloid calycanthine, and this has been further examined, along with its isomeride *iso*calycanthine, which also occurs in the seeds, by Gordin.[2]

Calycanthine, $C_{11}H_{14}N_2.\frac{1}{2}H_2O$, crystallises in orthorhombic bipyramids, m.p. 216°–218°, or 243°–244° (*dry*), has a bitter taste, is

[1] *Proc. Amer. Pharm. Assoc.* 1888, **84**, 382.

[2] *Journ. Amer. Chem. Soc.* 1905, **27**, 144, 1418; 1909, **31**, 1305; 1911, **33**, 1626.

slightly alkaline to litmus, and readily soluble in ether or chloroform. The salts crystallise well. The alkaloid gives a nitrosoamine, m.p. 175°–176 (*decomp.*), and contains a $N.CH_3$ group. It resembles strychnine in physiological action.

***iso*Calycanthine,** $C_{11}H_{14}N_2.\frac{1}{2}H_2O$, forms orthorhombic crystals, m.p. 212°–214°, or 235°–236° (*dry*), yields a nitrosoamine, m.p. 106°–107° (*decomp.*), and with methyl iodide gives a mixture of the hydriodide with a quaternary iodide, $C_{24}H_{28}ON_3I.H_2O$; the latter forms colourless needles, m.p. 213°–214°. It is suggested that this substance is formed by condensation of two molecules of the alkaloid accompanied by atmospheric oxidation.

ALKALOID OF *CARICA PAPAYA*

Carpaïne, $C_{14}H_{25}O_2N$, was obtained by Greshoff[1] from the fruit and seeds, but especially the leaves, of the papaw tree (*Carica Papaya*), and was afterwards investigated by Merck,[2] who assigned to it the formula $C_{14}H_{27}O_2N$, and later by van Rijn,[3] who prepared a number of its salts and showed that the alkaloid was a secondary base and that it contained a hydroxyl group, but no methoxyl. Carpaïne has been investigated recently by Barger, who has made some progress in the determination of its constitution.[4]

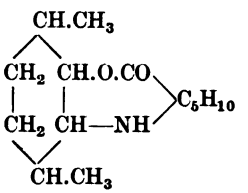
The alkaloid crystallises in monoclinic prisms, m.p. 121°, b.p. 215°–235° *in vacuo*, is insoluble in water, but soluble in most organic solvents; it is optically active, $[\alpha]_D + 21°\ 55'$ in alcohol. The hydrochloride, B.HCl, crystallises from water in needles; the aurichloride, $B.HAuCl_4.5H_2O$, from alcohol in yellow needles, m.p. 205° (*dry*).

Methylcarpaïne, obtained by the action of methyl iodide on the base, forms colourless prisms, m.p. 71°. Nitrosocarpaïne crystallises from alcohol in small prisms, m.p. 144°–145°. The alkaloid

[1] *Meded. 's Lands Plantentuin*, 1890, No. 7, p. 5.
[2] *Merck's Report*, 1891, p. 30.
[3] *Arch. Pharm.* 1893, **231**, 184; 1897, **235**, 332.
[4] *Trans. Chem. Soc.* 1910, **97**, 466.

contains a hydroxyl group, but the acyl derivatives obtained are amorphous.

Barger has found that when carpaïne is heated with 10 per cent. hydrochloric acid at 130°–140°, or with sodium ethoxide, it is converted into carpamic acid, $C_{14}H_{27}O_3N$, by addition of one molecule of water. The acid forms long needles, m.p. 224°, from alcohol, on addition of acetone. On oxidation with permanganate in acetone, carpaïne furnishes ammonia and a nitrogenous acid. The latter yields a methyl ester, which on hydrolysis gives ammonia and an acid, $C_8H_{14}O_4$ (possibly $a\delta$-dimethyladipic acid), which is also produced by the direct oxidation of carpaïne by nitric acid. On the basis of the results so far obtained, Barger suggests the following formula as possibly representing carpaïne :



Carpaïne

No structure can yet be suggested for the group C_5H_{10}.

Carpaïne has an intensely bitter taste. According to Plugge the alkaloid depresses the action of the heart and adversely affects respiration, whilst von Oefele recommends its application by subcutaneous injection as a substitute for digitalis in cardiac diseases.

ALKALOIDS OF *CASIMIROA EDULIS*

From the seeds of this Mexican plant Bickern isolated an alkaloidal glucoside, "casimirine," $C_{30}H_{32}O_5N_2$.[1] The seeds were re-examined by Power and Callan,[2] who were unable to confirm the existence of "casimirine," but obtained instead the crystalline alkaloids casimiroine and casimiroedine.

Casimiroine, $C_{24}H_{20}O_3N_2$, crystallises from alcohol in rosettes of needles, m.p. 196°–197°, $[a]_D$ 0°, and gives an aurichloride, $B.HAuCl_4$,

[1] *Arch. Pharm.* 1903, **241**, 166. [2] *Trans. Chem. Soc.* 1911, **99**, 1993.

orange-yellow needles, m.p. 195°–196°, and a picrate, m.p. 165°. The alkaloid gives a green coloration with sulphuric acid, which becomes orange on adding a trace of nitric acid.

Casimiroine contains two methoxyl groups, and on hydrolysis by boiling alcoholic potash yields a new base, CASIMIROITINE, $C_{23}H_{22}O_7N_2$, which crystallises from alcohol in hair-like needles, m.p. 171°, and appears to be formed by the absorption of a molecule of water by casimiroine, and the subsequent loss of a molecule of carbon dioxide.

Casimiroedine, $C_{17}H_{24}O_5N_2$, crystallises from alcohol in warty masses of small needles, m.p. 222°–223°, $[\alpha]_D$ — 36·5° in dilute hydrochloric acid, and gives an aurichloride, $B.HAuCl_4.2H_2O$, bright yellow microscopic needles, m.p. 90° (*approx.*) or 145°–148° (*dry, decomp.*), which is dissociated by water, but can be recrystallised from dilute hydrochloric acid.

Casimiroine and casimiroedine are physiologically inactive.

ALKALOIDS OF *CHEIRANTHUS CHEIRI* (WALLFLOWER)

In 1898 Reeb obtained from the leaves and seeds of the wallflower two substances, which he named cheiranthin and cheirinine. The former was described as a glucoside, having a physiological action akin to that of digitalis, whilst cheirinine was given the formula $C_{18}H_{35}O_{17}N_3$, and was stated to resemble quinine in physiological action.[1] In 1908 Wagner [2] obtained from the seeds the alkaloid CHEIROLINE, $C_9H_{16}O_7N_2S_2$, crystallising in colourless prisms, m.p. 46°–48°, which, like Reeb's cheirinine, resembles quinine in physiological action, and when warmed with mercuric oxide and water yields cheirole, $C_9H_{20}O_9N_2$, colourless needles, m.p. 172·5°.

In the same year Schneider [3] asserted that Wagner's cheiroline should be represented by the formula $C_9H_{16}O_5N_2S_3$, which he

[1] *Arch. exp. Path. Pharm.* 1898, **41**, 302 ; 1899, **43**, 83.
[2] *Chem. Zeit.* 1908, **32**, 76. [3] *Berichte*, 1908, **41**, 4466.

subsequently altered to $C_5H_9O_2NS_2$.[1] According to Schneider, cheiroline is neutral and optically inactive. When heated with aqueous sodium hydroxide it liberates hydrogen sulphide and carbon dioxide and forms a new base, $C_4H_{11}O_2NS$, which is obtained as a deliquescent crystalline mass. This yields a crystalline quaternary methiodide, $C_7H_{18}O_2NSI$, m.p. 183°, whence it seems to be a primary amine. Cheiroline appears to exist in wallflower seed as a glucoside. Wagner has also obtained cheiroline from the seeds of *Erysimum nanum compactum aureum* (*cf.* p. 446).

ALKALOIDS OF *CHELIDONIUM MAJUS*, *BOCCONIA CORDATA*, AND *SANGUINARIA CANADENSIS*

The roots of each of these three papaveraceous plants contain a number of alkaloids, which are common to all three, so that the three plants may be conveniently taken together.

Chelidonium majus (the common celandine). From the roots of this plant the following alkaloids have been isolated: chelerythrine, chelidonine, α-, β-, and γ-homochelidonines, protopine, sanguinarine, and berberine.[2]

Bocconia cordata (*Macleya cordata*) roots contain chelerythrine, β-homochelidonine, protopine, and traces of sanguinarine.[3]

Sanguinaria canadensis roots contain chelerythrine, β- and γ-homochelidonines, protopine, and sanguinarine.

Preparation. Schmidt and Selle extracted the dry powdered root of *Chelidonium majus* with alcohol acidified with acetic acid, and distilled off the alcohol after adding water. The resinous precipitate was filtered off and the filtrate made alkaline with ammonia

[1] *Berichte*, 1909, **42**, 3416.

[2] Godefroy, *Journ. Pharm.* 1824, **10**, 635; Probst, *Annalen*, 1839, **29**, 123; Will, *ibid.* 1840, **35**, 113; Eykman, *Rec. Trav. Chim.* 1884, **3**, 182; Schmidt and Selle, *Arch. Pharm.* 1890, **228**, 96, 441; Wintgen, *ibid.* 1901, 239, 443; Schmidt, *ibid.* 1901, **239**, 395; and Schlotterbeck, *Amer. Journ. Pharm.* 1902, **74**, 584.

[3] Hopfgärtner, *Monats.* 1898, **19**, 179; Murrill and Schlotterbeck, *Pharm. Journ.* 1900 [iv], **11**, 34; and Schlotterbeck and Blome, *Pharm. Rev.* 1905, **23**, 310.

and shaken out with chloroform. The residue left on distilling off this solvent was treated with cold dilute alcoholic hydrochloric acid, which left protopine and chelidonine hydrochlorides undissolved. Water was added to the filtrate, the alcohol distilled off and excess of ammonia solution added, when chelerythrine and *a*-homochelidonine were precipitated, leaving β-homochelidonine in solution, from which it may be extracted by chloroform.

A somewhat similar process was used by Fischer [1] for the separation of the alkaloids of *Sanguinaria canadensis*.

Chelerythrine, $C_{21}H_{17}O_4N$, was first obtained by Probst [2] from the root of *Chelidonium majus*, and later by the same author from *Sanguinaria canadensis* and *Glaucium luteum*.[3] Battandier subsequently obtained it from *Eschscholzia californica* and *Bocconia frutescens*,[4] and Murrill and Schlotterbeck from *Bocconia cordata*.[5] Chelerythrine was probably first obtained in a pure state by König and Tietz.[6] The best source of the alkaloid is the root of *Sanguinaria canadensis*.

It crystallises from alcohol in colourless rhombohedra, m.p. 203°–204°, containing one molecule of alcohol, is readily soluble in chloroform, sparingly so in alcohol or ether. The alkaloid absorbs carbon dioxide from the air, becoming yellow. The solutions fluoresce blue when the alkaloid is contaminated with its oxidation product, which is formed by mere exposure of chelerythrine in solution to the air. The salts are intensely yellow, though the alkaloid itself is colourless. The hydrochloride, $B.HCl.5H_2O$, forms citron-yellow needles, and the sulphate, $B.H_2SO_4.2H_2O$, golden-yellow needles, sparingly soluble in water; the platinichloride, $B_2.H_2PtCl_6$, forms golden-yellow needles, and the aurichloride, $B.HAuCl_4$, long, silky, brown needles, m.p. 233° (*decomp.*). The

[1] *Arch. Pharm.* 1901, **239**, 410.

[2] *Annalen*, 1839, **29**, 120. *Cf.* Wintgen, *Arch. Pharm.* 1901, **239**, 448.

[3] *Ibid.* 1839, **31**, 250. *Cf.* Fischer, *Arch. Pharm.* 1901, **239**, 410, 429.

[4] *Bull. Soc. chim.* 1896 [iii], **15**, 541. *Cf.* Fischer, *Arch. Pharm.* 1901, **239**, 421, and Brindejonc, *Bull. Soc. chim.* 1911 [iv], **9**, 97.

[5] *Pharm. Journ.* 1900 [iv], **11**, 34.

[6] *Arch. Pharm.* 1893, **231**, 145, 161.

alkaloid contains two methoxyl groups, and according to Tietz[1] is the methyl ether of sanguinarine. Sulphuric acid dissolves chelerythrine with the formation of a greenish solution, which slowly becomes dirty yellow. Sulphovanadic acid gives a violet red tint changing to dark red.

Chelidonine, $C_{20}H_{19}O_5N.H_2O$, also occurs in *Stylophorum diphyllum.*[2] It is separated from protopine, with which it occurs in the first separation (*see* p. 377) by regenerating the two alkaloids from the hydrochlorides by ammonia solution and digesting with ether, in which chelidonine is much less soluble than protopine. It is purified by solution in a little dilute sulphuric acid and precipitation with strong hydrochloric acid as the hydrochloride. From this it is regenerated and crystallised from acetic acid.

Chelidonine crystallises in monoclinic tablets, m.p. 135°–136°, $[a]_D$ + 115° 24′ in alcohol, is readily soluble in alcohol or ether, but insoluble in water; the hydrochloride, B.HCl, and the nitrate, $B.HNO_3$, are crystalline and sparingly soluble in water.

Chelidonine is probably a tertiary amine since it gives an ethiodide (crystalline); it contains no methoxyl, but one hydroxyl group is present. The acetyl derivative melts at 161°.

The alkaloid gives with strong sulphuric acid and tincture of guaiacum a deep crimson colour.

α-Homochelidonine, $C_{21}H_{21}O_5N$, has only been found in *Chelidonium majus.* It can be separated from the chelerythrine, with which it occurs in the first separation (*see* p. 377), by digestion with ether, in which chelerythrine is more soluble.

The alkaloid crystallises from acetic ether in prisms, m.p. 182°, dissolves readily in chloroform or alcohol, but with difficulty in ether; the aurichloride, $B.HAuCl_4$, forms reddish-yellow needles, but the hydrochloride, platinichloride, and other salts are amorphous. The alkaloid contains two methoxyl groups.

[1] *Loc. cit.*

[2] Selle, *loc. cit.*; Schlotterbeck and Watkins, *Pharm. Rev.* 1901, **19**, 453; *Pharm. Arch.* 1903, **6**, 141.

β-Homochelidonine, $C_{21}H_{23}O_5N$, occurs also in *Sanguinaria canadensis*,[1] *Eschscholzia californica*,[2] *Adlumia cirrhosa*,[3] and *Bocconia cord*[illegible] It [illegible] prisms, m.p. acetic ether, B.HCl.1½H_2O water; the nit line; the plati aurichloride, B a tertiary base dissolves in sul carmine-red. According to S physical isomeri (p. 379). Fisch interconvertible

γ-Homochel alkaloid is *Sang* extent in the root isomeride of β-h large colourless t can be mechanical isomeride.

It is best p *canadensis*, with a extract and pourin alkaline with amm guinarine, cheleryt chelidonines remai [illegible]

[1] König and Tietz, *Arch. Pharm.* 1893, **231**, 145; Fischer, *ibid.* 1901, **239**, 409. [2] Fischer, *ibid.* 1901, **239**, 421.

[3] Schlotterbeck and Watkins, *Pharm. Arch.* 1903, **6**, 17.

[4] Hopfgärtner, *Monats.* 1898, **19**, 179; Murrill and Schlotterbeck, *Pharm. Journ.* 1900 [iv], **11**, 34; Schlotterbeck and Blome, *Pharm. Rev.* 1905, **23**, 310. [5] *Loc. cit.* [6] *Cf.* Wintgen, *loc. cit.*

[7] König and Tietz, *loc. cit.*; Fischer, *loc. cit.*

[8] Wintgen, *loc. cit.*

together with a little protopine by concentrating the filtrate, adding more ammonia and shaking out with chloroform.

Sanguinarine, $C_{20}H_{15}O_4N.1H_2O$ or $1C_2H_5OH$, the principal alkaloid of *Sanguinaria canadensis* (blood-root), was obtained from this source by Dana,[4] and has since been found in *Bocconia cordata*, *Chelidonium majus*, and *Stylophorum diphyllum* (*see* p. 435).

[1] Fischer, *loc. cit.*
[2] Schmidt, *Arch. Pharm.* 1901, **239**, 395; Gadamer, *ibid.* 1911, **249**, 224.
[3] *Ibid.* 1912, **250**, 590. [4] *Mag. Pharm.* 1829, **23**, 125.

β-Homochelidonine, $C_{21}H_{23}O_5N$, occurs also in *Sanguinaria canadensis*,[1] *Eschscholzia californica*,[2] *Adlumia cirrhosa*,[3] and *Bocconia cordata*.[4] It crystallises from acetic ether in monoclinic prisms, m.p. 159°–160°, and is readily soluble in chloroform or acetic ether, less so in alcohol or ether. The hydrochloride, $B.HCl.1\frac{1}{2}H_2O$, forms colourless needles and is readily soluble in water; the nitrate, hydrobromide, and hydriodide are also crystalline; the platinichloride, $B.H_2PtCl_6.2\frac{1}{2}H_2O$, is amorphous, but the aurichloride, $B.HAuCl_4$, m.p. 187°, forms blood-red crystals. It is a tertiary base and yields a methiodide, m.p. 185°. The alkaloid dissolves in sulphuric acid, forming a yellow solution changing to carmine-red. β-Homochelidonine contains two methoxyl groups. According to Schmidt, β- and γ-homochelidonines (*see below*) are physical isomerides and dihydro derivatives of α-homochelidonine (p. 379). Fischer states[5] that β- and γ-homochelidonines are interconvertible and yield the same aurichloride.[6]

γ-Homochelidonine, $C_{21}H_{23}O_5N$. The principal source of this alkaloid is *Sanguinaria canadensis*,[7] but it also occurs to a small extent in the root of *Chelidonium majus*.[8] The alkaloid is a physical isomeride of β-homochelidonine, and separates with the latter, in large colourless tablets, m.p. 169° (*dry*), from acetic ether, which can be mechanically separated from the small prisms of the associated isomeride.

It is best prepared by extracting blood-root, *Sanguinaria canadensis*, with alcohol containing acetic acid, concentrating the extract and pouring it into water. The filtrate from this is made alkaline with ammonia solution. The precipitate contains sanguinarine, chelerythrine, and protopine, whilst β- and γ-homochelidonines remain in the filtrate and may be extracted

[1] König and Tietz, *Arch. Pharm.* 1893, **231**, 145; Fischer, *ibid.* 1901, **239**, 409. [2] Fischer, *ibid.* 1901, **239**, 421.

[3] Schlotterbeck and Watkins, *Pharm. Arch.* 1903, **6**, 17.

[4] Hopfgärtner, *Monats.* 1898, **19**, 179; Murrill and Schlotterbeck, *Pharm. Journ.* 1900 [iv], **11**, 34; Schlotterbeck and Blome, *Pharm. Rev.* 1905, **23**, 310. [5] *Loc. cit.* [6] *Cf.* Wintgen, *loc. cit.*

[7] König and Tietz, *loc. cit.*; Fischer, *loc. cit.*

[8] Wintgen, *loc. cit.*

together with a little protopine by concentrating the filtrate, adding more ammonia and shaking out with chloroform.

It crystallises with 1 mol. of alcohol or acetic ether. The alkaloid yields mostly amorphous salts, but the aurichloride, $B.HAuCl_4$, forms blood-red warty crystals, m.p. 187°, and is identical with β-homochelidonine aurichloride.[1] The salts are amorphous; the methiodide, $B.CH_3I.2\frac{1}{2}H_2O$, forms bright yellow prisms; the alkaloid contains two methoxyl groups.

Protopine (*Macleyine*), $C_{20}H_{19}O_5N$. This alkaloid was first isolated by Hesse from opium, but has since been found in a great variety of papaveraceous plants,[2] including the following: *Chelidonium majus*, *Stylophorum diphyllum*, *Sanguinaria canadensis*, *Eschscholzia californica*, *Glaucium luteum*, *Bocconia cordata* and *frutescens*, *Argemone mexicana*, *Adlumia cirrhosa*, *Dicentra* spp., *Corydalis Vernyi*, *C. ambigua*, *C. tuberosa*, and *Fumaria officinalis*.

The crude alkaloid (p. 378) is purified by conversion into the sulphate, reprecipitation by ammonia, and crystallisation from chloroform, by addition of a little alcohol. It forms monoclinic crystals, m.p. 208°, dissolves readily in chloroform, less so in alcohol, acetone or ammonia solution. The hydrochloride, B.HCl, forms slightly soluble prisms; the platinichloride and aurichloride are amorphous. The base dissolves in strong sulphuric acid, forming a blue-violet solution changing to green; sulphovanadic acid gives a reddish-violet colour changing to deep blue. Protopine, according to Danckwortt,[3] contains two dioxymethylene groups and a non-reactive carbonyl group. He provisionally represents it as 2 : methyl-6 : 7-dioxymethylene-1-*ortho*methylpiperonoyl-1 : 2 : 3 : 4-tetrahydro*iso*quinoline.

Sanguinarine, $C_{20}H_{15}O_4N.1H_2O$ or $1C_2H_5OH$, the principal alkaloid of *Sanguinaria canadensis* (blood-root), was obtained from this source by Dana,[4] and has since been found in *Bocconia cordata*, *Chelidonium majus*, and *Stylophorum diphyllum* (*see* p. 435).

[1] Fischer, *loc. cit.*
[2] Schmidt, *Arch. Pharm.* 1901, **239**, 395; Gadamer, *ibid.* 1911, **249**, 224.
[3] *Ibid.* 1912, **250**, 590. [4] *Mag. Pharm.* 1829, **23**, 125.

The separation of sanguinarine from the chelerythrine and protopine with which it is precipitated (p. 377) is difficult, and for details the original papers should be consulted, especially König and Tietz,[1] Fischer,[2] and Kozniewski.[3]

Sanguinarine crystallises from acetic ether or alcohol in *colourless* groups of needles, m.p. 212° (from alcohol), and dissolves in the usual organic solvents, forming solutions that are fluorescent. It slowly reddens in the air, due to the formation of the carbonate. The salts are *deep red* in colour; the hydrochloride, $B.HCl.5H_2O$, and the nitrate, $B.HNO_3.H_2O$, form red needles, but the gold and platinum salts are amorphous. The base contains one methoxyl group. With sulphovanadic acid a dark red solution passing into violet is obtained.

Physiological Action

Chelerythrine is poisonous. It paralyses the central nervous system without any initial increase in irritability, resembles protopine in its muscular action, and like sanguinarine first irritates and then paralyses the sensory nerve terminations.

Chelidonine and *α-homochelidonine* resemble morphine in their effects on the central nervous system, but are only slightly toxic. Like protopine, they paralyse the sensory nerve endings in the skin and cornea.

β-Homochelidonine closely resembles protopine in action.

Protopine resembles cryptopine in action (*see* p. 257). These two alkaloids differ markedly from the alkaloids with which they occur in opium. In frogs they produce narcosis like that due to morphine, but without any increase in reflex irritability. If striated muscle is poisoned by these alkaloids and subjected to a tetanising series of electric shocks, tetanus does not occur, but a series of rapid contractions and relaxations is produced. In mammals, restlessness and convulsions occur. Both alkaloids paralyse the sensory nerve endings on local application.

[1] *Arch. Pharm.* 1893, **231**, 145, 161.
[2] *Ibid.* 1901, **239**, 409.
[3] *Bull. Acad. Sci. Crac.* 1910, p. 235.

Sanguinarine causes tetanus and excitement, and therefore occupies a place between codeine and thebaine in the opium group of alkaloids (p. 256). It resembles protopine in its action on muscle, and at first irritates and then paralyses the sensory nerve endings in the skin, when applied locally.

None of these alkaloids is used as such in medicine, but the latex of *Chelidonium majus* and extracts of the plant were formerly employed, and galenical preparations of *Sanguinaria canadensis* root are official in the United States Pharmacopœia. Sanguinaria preparations appear to be used principally as expectorants and emetics.

ALKALOID OF *CHLOROXYLON SWIETENIA*

From the wood of this tree, which forms the East Indian satinwood of commerce, Auld isolated the crystalline alkaloid chloroxylonine.[1]

Chloroxylonine, $C_{22}H_{23}O_7N$, crystallises from ethyl alcohol in colourless prisms, m.p. 182°–183°, $[\alpha]_D^{18}$ — 9° 18′ in chloroform or dilute acids. It behaves as a weak, monoacidic base and yields well-crystallised salts. The hydrochloride, B.HCl, forms faintly green rosettes of long needles, m.p. 95°, the hydrobromide, B.HBr, prismatic needles, m.p. 125°, and the aurichloride, $B.HAuCl_4$, reddish-yellow needles, m.p. 70°. Chloroxylonine contains four methoxyl groups, but no hydroxyl.

Cash finds that chloroxylonine is a powerful irritant, causing dermatitis when applied to the skin.[2]

ALKALOIDS OF *CLAVICEPS PURPUREA* (ERGOT)

Ergot consists of the mycelia of *Claviceps purpurea*, a fungus which occurs on cereal crops, but especially on rye. This material has long been used in medicine and was first investigated by Wenzell in 1865, who prepared from it two basic products which he named ergotine and ecboline.[3] A crystalline alkaloid, ergotinine, was

[1] *Trans. Chem. Soc.* 1909, **95**, 964. [2] *Brit. Med. Journ.* Oct. 7, 1911.
[3] *Amer. Journ. Pharm.* 1864, **36**, 193.

obtained from ergot for the first time by Tanret, who also isolated from the mother liquors of this alkaloid an amorphous base which he named "amorphous ergotinine."[1] Tanret's crystalline ergotinine is probably identical with the "picrosclerotine" of Dragendorff and Podwyssozki,[2] and with Jacobi's "secaline."[3] Kobert[4] showed that crystallised ergotinine was practically physiologically inactive, whilst the amorphous alkaloid, which he called cornutine, was highly active. This amorphous alkaloid has been obtained in an impure condition by various investigators, but was obtained pure for the first time by Barger and Carr,[5] who named it ergotoxine. It was prepared almost simultaneously by Kraft,[6] who called it hydroergotinine, since it is converted into ergotinine by loss of water. It seems clear that Tanret's "amorphous ergotinine," Kobert's "cornutine," and Jacobi's sphacelotoxine were all products whose activity depended on the presence of some ergotoxine.

Since 1906 a large number of other well-defined products, chiefly amino-acids, have been isolated from ergot, including betaine and choline, putrescine, and cadaverine, which are not markedly active physiologically. The more important of these new constituents are described below. No completely satisfactory method of estimating the physiological activity of ergot or of medicinal preparations of ergot has yet been devised.

For the isolation of ergotoxine and ergotinine Barger and Carr recommend the following method:[7] The ground ergot is extracted with alcohol, the solvent distilled off, and the residue washed with light petroleum to remove oil. The purified residue is dissolved in ethyl acetate and shaken out with successive quantities of citric acid solution until all the alkaloid has been removed. To the citric acid solution sodium bromide is added, which precipitates a mixture of ergotoxine and ergotinine hydrobromides. When such a mixture is shaken with dilute caustic soda and ether, the ergotinine

[1] *Compt. rend.* 1875, **81**, 896; 1878, **86**, 888.
[2] *Arch. exp. Path. Pharm.* 1876, **6**, 153.
[3] *Ibid.* 1897, **39**, 104.
[4] *Ibid.* 1884, **18**, 316.
[5] *Chem. News*, 1906, **94**, 89.
[6] *Arch. Pharm.* 1906, **244**, 336.
[7] *Trans. Chem. Soc.* 1907, **91**, 337.

is dissolved by the ether first and after separation in this way may be crystallised from alcohol. Ergotoxine remains in the mother liquors and is obtained by neutralising these, then making alkaline with sodium carbonate and extracting with ether. The residue left on evaporating off the ether is dissolved in 80 per cent. alcohol and a slight excess of phosphoric acid in alcohol added, when ergotoxine phosphate crystallises out after a few days and can be recrystallised from alcohol.

Ergotoxine, $C_{35}H_{41}O_6N_5$ (*Hydroergotinine*), is a bulky white powder, m.p. 162°–164°, soluble in cold alcohol, sparingly so in ether. The specific rotation of specimens prepared by Barger and Carr in several ways varied from + 0·6° to + 40·6° in alcohol.

Ergotoxine is precipitated by the usual alkaloidal reagents and is particularly sensitive to Mayer's reagent and to iodine solution, which give precipitates with one part in two million and one million respectively. Ergotoxine forms well-crystallised salts, and these are best prepared by adding an alcoholic solution of the appropriate acid to a dilute solution of ergotoxine in ether; the salts with inorganic acids are sparingly soluble in water. The phosphate, $B.H_3PO_4.H_2O$, forms groups of needles, m.p. 186°–187° (*decomp.*), and is soluble in 14 parts of boiling or 313 parts of cold 90 per cent. alcohol; with cold water it gives a colloidal solution which on addition of *N*-hydrochloric acid forms a jelly: the hydrochloride, B.HCl, forms minute, diamond-shaped plates, m.p. 205°; the neutral oxalate, $B_2.H_2C_2O_4$, forms rectangular elongated plates, m.p. 179°, and the acid oxalate, $B.H_2C_2O_4$, minute prisms, m.p. 179° (*decomp.*). Kraft[1] observed that when ergotoxine is boiled with methyl alcohol it is converted into ergotinine, $C_{35}H_{39}O_5N_5$, and Barger and Carr have found that the same change occurs when ergotoxine is treated with acetic anhydride and is due to the loss of one molecule of water:

$$\underset{\textit{Ergotoxine}}{C_{35}H_{41}O_6N_5} - H_2O = \underset{\textit{Ergotinine}}{C_{35}H_{39}O_5N_5}$$

[1] *Loc. cit.*

Barger and Ewins [1] have shown that ergotoxine contains a carboxyl group, so that ergotinine is probably the corresponding lactone. Both ergotoxine and ergotinine, when heated dry, yield *iso*butyrylformamide, $(CH_3)_2CH.CO.CO.NH_2$.

Ergotinine, $C_{35}H_{39}O_5N_5$, prepared as described already, crystallises from dry alcohol in long needles, m.p. 229° (placed in a bath at 210°), $[\alpha]_D$ + 338° in alcohol, + 396° in chloroform, is readily soluble in acetone or chloroform, less so in alcohol (1 in 292 at 18° or 1 in 52 boiling), and sparingly in ether. The salts are all amorphous. Ergotinine is distinctly less sensitive to alkaloidal precipitants than ergotoxine, but Mayer's reagent gives a cloudiness with 1 part in 1,000,000, and iodine solution with 1 part in 200,000. The relationship of ergotinine to ergotoxine has been discussed above. Kraft [2] has observed that ergotinine is partly converted into ergotoxine when allowed to stand in dilute acetic acid. Barger and Ewins [3] have found that when ergotinine in alcohol is heated with phosphoric acid it is converted into ethyl ergotoxine phosphate. Both ergotinine and ergotoxine dissolved in ether give with sulphuric acid a transient orange colour changing to blue, whilst a solution in sulphuric acid gives with dry ferric chloride an orange tint changing to crimson, green, and blue.

Aminosecalesulphonic acid, $NH_2.C_{15}H_{27}O_{15}.SO_3H$ (Kobert's ergotic acid), was obtained by Kraft [2] together with betaine and choline. According to Vahlen [4] aminosecalesulphonic acid is physiologically inert.

Clavine. This supposed new physiologically active constituent of ergot, obtained by Vahlen,[5] was shown by Barger and Dale [6] to be a mixture of leucine and aspartic acid and to be physiologically inert.[7]

***p*-Hydroxyphenylethylamine** was isolated by Barger [8] from a concentrated aqueous extract of ergot by making this alkaline with

[1] *Trans. Chem. Soc.* 1910, **97**, 284. [2] *Loc. cit.* [3] *Loc. cit.*
[4] *Arch. exp. Path. Pharm.* 1908, **60**, 42.
[5] *Ibid.* 1906, **55**, 136.
[6] *Bio-chem. Journ.* 1907, **2**, 240. [7] *Cf.* Vahlen, *loc. cit.* and 1908, **60**, 42.
[8] *Trans. Chem. Soc.* 1909, **95**, 1125.

sodium carbonate solution and extracting with amyl alcohol, concentrating the amyl alcohol solution, and extracting the phenolic amine with dilute caustic soda solution. This was neutralised by hydrochloric acid, evaporated to dryness, and the residue extracted with alcohol. From this solution impurities were precipitated by mercuric chloride, and after removal of excess of mercury by hydrogen sulphide the solution was concentrated, made slightly alkaline with caustic soda, and shaken out with ether, which removed no physiologically active substance. The solution was then neutralised by acid, made alkaline with sodium carbonate, and again shaken with ether, which extracted *p*-hydroxyphenylethylamine, identified by means of its dibenzoyl derivative, m.p. 167°. Barger and Dale have shown that *p*-hydroxyphenylethylamine causes a rapid increase in blood-pressure and accounts in part for this effect produced by aqueous extracts of ergot.[1] The substance has been synthesised by Barger[2] by the reduction of *p*-hydroxyphenylacetonitrile, first prepared by Pschorr, Wolfes and Buckow,[3] with sodium in alcohol.

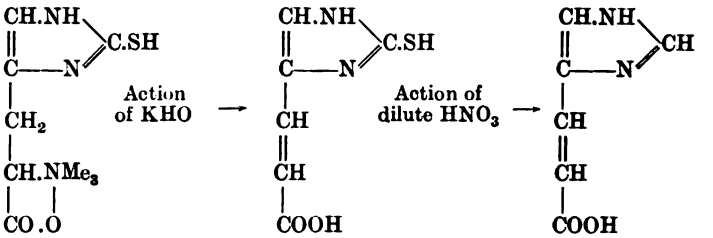
***iso*Amylamine.** Barger and Dale[2] have also found this amine in aqueous extracts of ergot.

Ergothioneine, $C_9H_{15}O_2N_3S.2H_2O$, was found to the extent of 0·1 per cent. in ergot by Tanret.[4] It crystallises in colourless lamellæ, m.p. 290° (*decomp.*), $[\alpha]_D + 110°$, and is soluble in 8·6 parts of water at 20°, but insoluble in ether or dry alcohol. The substance is feebly basic, but forms well-defined salts, and gives precipitates with Mayer's reagent and mercuric chloride, but not with picric or tannic acids. The hydrochloride, $B.HCl.2H_2O$, m.p. 250° (*dry*), $[\alpha]_D + 88·5°$, and the sulphate, $B_2.H_2SO_4.2H_2O$, $[\alpha]_D + 87·4°$, are crystalline, as is also the mercurichloride, $B.HgCl_2.HCl$.

Ergothioneine has been further examined by Barger and Ewins,[5] who found that it is decomposed quantitatively into trimethylamine and β-2-thiolglyoxaline-4-acrylic acid, $C_6H_6O_2N_2S$; the latter on boiling with dilute nitric acid loses sulphur and gives

[1] *Proc. Physiol. Soc.* May 15, 1909. [2] *Loc. cit.* [3] *Berichte*, 1910, **33**, 171.
[4] *Compt. rend.* 1909, **149**, 222. [5] *Trans. Chem. Soc.* 1911, **99**, 2336.

rise to β-glyoxaline-4- (or 5-) acrylic acid. The sulphur in ergothioneine reacts in every way like that in thiolglyoxalines; thus it is oxidised by ferric chloride or bromine water to sulphuric acid with the formation of β-glyoxaline-4- (or 5-) propiobetaine. On these grounds Barger and Ewins have assigned the following formulæ to ergothioneine and its derivatives:



Ergothioneine — *β-2-Thiolglyoxaline-4-acrylic acid* — *β-Glyoxaline-4- (or 5-) acrylic acid*

4- (or 5-) **β-Aminoethylglyoxaline,** $C_5H_9N_3$, was obtained by Barger and Dale [1] and simultaneously by Kutscher [2] from ergot extract. The substance is present in very minute amount and was isolated as the dipicrate, dark yellow rhombic plates, m.p. 234°–235° (*decomp.*), identical with the synthetic substance first prepared by Windaus and Vogt,[3] and more recently by Pyman.[4]

Agmatine, $C_5H_{14}N_4$, was obtained by Engeland and Kutscher [5] from ergot. It had previously been prepared by Kössel [6] from herring spawn and was subsequently synthesised by him [7] by the action of cyanoamide in aqueous solution on tetramethylenediamine, whence it is regarded as aminobutyleneguanidine, which brings it into close relationship with arginine (p. 326).

$NH_2.C(NH).NH.CH_2.CH_2.CH_2.CH_2.NH_2$
Agmatine

$NH_2.C(NH).NH.CH_2.CH_2.CH_2.CH(NH_2).COOH$
Arginine

[1] *Trans. Chem. Soc.* 1910, **97**, 2592.
[2] *Zeits. Physiol.* 1910, **24**, 163.
[3] *Berichte*, 1907, **40**, 3691.
[4] *Trans. Chem. Soc.* 1911, **99**, 668.
[5] *Zeits. Physiol* 1910, **24**, 479.
[6] *Zeits. Physiol. Chem.* 1910, **68**, 257.
[7] *Ibid.* 1910, **68**, 170.

Physiological Action of Ergot Alkaloids

Of the various bases isolated from ergot, ergotoxine, *p*-hydroxyphenylethylamine, 4- (or 5-) β-aminoethylglyoxaline, and agmatine are physiologically active.

Ergotoxine causes all the effects that are characteristic of ergot,[1] viz. contraction of the uterus, rise of blood-pressure, and gangrene of the cock's comb.[2] *p*-Hydroxyphenylethylamine causes uterine contraction and rise of blood-pressure; 4- (or 5-) β-aminoethylglyoxaline is very active physiologically; it causes contraction of the isolated uterus of the non-pregnant cat, and induces a very rapid rise in blood-pressure.[3] Agmatine produces effects similar to those shown by the last-named substance,[4] but is less active. Ergotinine and ergothioneine are practically inert. *iso*Amylamine is active, but the amount present in ergot is too small to be of physiological significance.

ALKALOIDS OF *COLCHICUM AUTUMNALE*

Colchicine, $C_{22}H_{25}O_6N$, is contained in the seeds and corms of the autumn crocus, *Colchicum autumnale*, in which it was first observed by Pelletier and Caventou.[5] According to Albo[6] it occurs in numerous other species of *Colchicum* and *Merendera*. It was subsequently investigated by various chemists, and especially by Zeisel,[7] who assigned to it the formula now in general use.

Colchicine is prepared by treating a concentrated alcoholic extract of the seeds with water, filtering from resin and oil, and shaking out the aqueous solution with chloroform; by repetition of this treatment, viz. solution of the residue in water and extraction with chloroform, the crystalline chloroform additive product of the base is eventually obtained in a pure state, and from this the amorphous alkaloid is regenerated by a current of steam.

[1] *Cf.* Dale, *Journ. Physiol.* 1906, **34**, 163.
[2] Barger and Dale, *Bio-chem. Journ.* 1907, **2**, 240.
[3] *Cf.* Dale and Laidlaw, *Journ. Physiol.* 1911, **41**, 318; 1911, **43**, 182.
[4] Engeland and Kutscher, *loc. cit.* [5] *Ann. Chim. Phys.* 1820 [ii], **14**, 82.
[6] *Arch. Sci. phys. nat.* 1901 [iv], **12**, 227.
[7] *Monatshefte*, 1883, **4**, 162; 1886, **7**, 557; 1888, **9**, 1, 865.

For the estimation of colchicine in the corms and seeds, the United States Pharmacopœia (8th Rev.) gives the following processes:

Corms. To 10 grm. in No. 60 powder, 100 c.c. of a mixture of ether (77 c.c.), chloroform (25 c.c.), alcohol (8 c.c.), ammonia water (sp. gr. 0·958 at 25°, 3 c.c.) are added and shaken frequently during twelve hours. Fifty cubic centimetres of the filtrate (= 5 grm. of the drug) are evaporated nearly to dryness at a low temperature; the residue is dissolved in 10 c.c. of ether, 5 c.c. of water are added, the mixture stirred, the ether evaporated, and the aqueous solution filtered into a separating funnel. Any insoluble matter is kept in the dish, and the treatment with ether and water repeated. Finally the filter and dish are washed with a little water and the combined aqueous filtrate (†) extracted four times, using 15, 10, 10, and 10 c.c. of chloroform (*). The combined chloroform solution is evaporated to dryness on the water-bath, the residue dissolved in alcohol, the latter evaporated, and the residue dissolved in 5 c.c. of ether, 5 c.c. of water added, the mixture stirred, the ether evaporated, the aqueous solution filtered, and the dish and filter washed with 5 c.c. of water. The combined aqueous filtrate is extracted four times with chloroform, using 15, 10, 10, and 10 c.c. The chloroformic solutions are collected in a tared flask, evaporated to dryness, and the residue dissolved twice in succession in a little alcohol and the latter evaporated off each time. The residue is then dried at 100° and weighed. The corms should contain not less than 0·35 per cent. of colchicine as determined by this method.

Seeds. The process is identical with that for the corms up to the point marked (*) in the preceding paragraph. The combined chloroformic solutions are collected in a tared flask, the solvent distilled off, the residue dissolved twice in succession in alcohol, the latter being evaporated off each time. The residue is then dried at 100° and weighed. The seeds should contain not less than 0·45 per cent. of colchicine as determined by this process. For a simpler process, *see* Prescott and Gordin.[1]

[1] *Apoth. Zeit.* 1900, **15**, 521.

Galenical Preparations. For the *extract*, *fluid extract*, and *tincture*, the process prescribed is the same as that for the corms, the alkaloid being liberated by ammonia and the process taken up at the point marked (†) (p. 390).

Colchicine is a yellow varnish, m.p. 143°–147° (*dry*), miscible in all proportions with cold water, aqueous alcohol, or chloroform, less soluble in warm water (12 per cent. at 82°) or absolute alcohol. Its solutions are lævorotatory; the aqueous solution has a bitter taste. It unites with chloroform to form a crystalline compound, $B.2CHCl_3$.

The alkaloid dissolves in sulphuric acid, forming a yellow solution, which becomes green, violet, and finally red on addition of a drop of nitric acid. Platinic chloride gives no precipitate, but gold chloride affords an amorphous precipitate which crystallises on standing. With ferric chloride, colchicine in hydrochloric acid solution gives a green coloration, and Fabinyi [1] has proposed this as a colorimetric method of estimation.

When treated with hydrochloric acid, colchicine furnishes methyl alcohol, acetic acid, and trimethylcolchicinic acid (I); the latter by the further action of hydrochloric acid produces three molecular proportions of methyl chloride, leaving colchicinic acid (II), thus:

I. $C_{22}H_{25}O_6N + 2H_2O = C_{19}H_{21}O_5N + CH_3.COOH + CH_3OH.$
II. $C_{19}H_{21}O_5N + 3HCl = C_{16}H_{15}O_5N + 3CH_3Cl.$

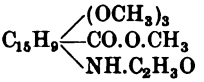
With alcoholic ammonia, methyl alcohol is split off and an amide is formed thus:

$$C_{22}H_{25}O_6N + NH_3 = CH_3OH + C_{21}H_{24}O_5N_2.$$

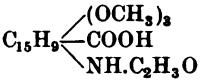
On hydrolysis by alkalis this amide yields colchiceine (p. 393).

When heated with hydriodic acid, colchicine furnishes methyl iodide and colchiceine. The following formulæ, suggested by Zeisel, which represent colchicine as the methyl ester of colchiceine, explain these reactions:

[1] *Abstr. Chem. Soc.* 1912 [ii], 503.

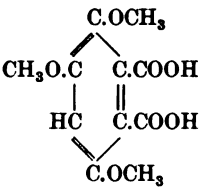


Colchicine

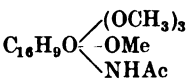


Colchiceine

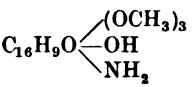
Windaus has shown recently[1] that on oxidation with alkaline permanganate colchicine yields trimethoxy-*o*-phthalic acid.



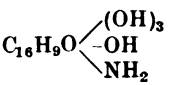
Trimethylcolchicinic acid, which, according to Windaus, differs from colchicine as shown by the following formulæ :



Colchicine

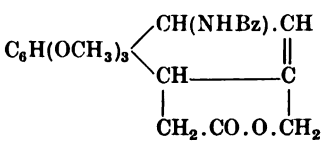


Trimethylcolchicinic acid

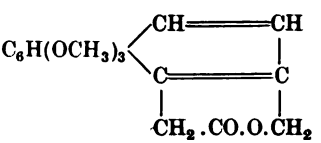


Colchicinic acid

yields a dibenzoyl derivative, $(CH_3O)_3.C_{16}H_9O(OBz).NHBz$, which on treatment with 25 per cent. potassium hydroxide solution yields N-benzoyltrimethylcolchicinic acid, which, unlike the dibenzoate, is coloured dark green by ferric chloride solution. This on oxidation by potassium permanganate yields N-benzoylcolchide (I). The latter when heated at 250° under reduced pressure yields benzamide and trimethoxyhomonaphthide (II), and on further oxidation gives the trimethoxy-*o*-phthalic acid referred to above.



(I)

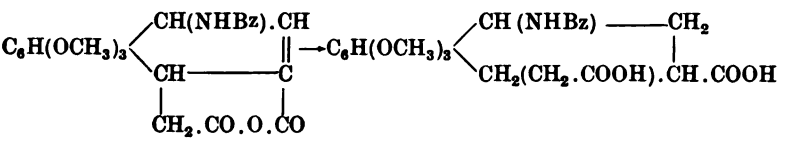


(II)

N-Benzoyltrimethylcolchicinic acid also yields on oxidation some

[1] *Sitzungsber. Heidelb. Akad. Wiss.* 1910, p. 1 ; 1911, p. 1.

N-benzoylcolchinic anhydride. This on reduction with zinc dust and acetic acid yields a tetrahydronaphthalene derivative, having the following formula :



N-Benzoylcolchinic anhydride

On the basis of these results Windaus regards colchicine as having the following formula, which represents it as the *enol* methyl ether of colchiceine (*see below*) :

$C_6H(OCH_3)_3 : C_{10}H_8O(OCH_3).NH.COCH_3$
Colchicine (Windaus)

Colchiceine, $C_{21}H_{23}O_6N.\frac{1}{2}H_2O$, was stated by Oberlin[1] to occur along with colchicine in the corms and seeds of the autumn crocus. According to Zeisel it probably does not occur in the plant, but is formed by decomposition of colchicine during extraction.

Colchiceine is best prepared by heating colchicine with dilute sulphuric acid, when one molecule each of methyl alcohol and colchiceine are formed. It crystallises in colourless needles, m.p. 172° (*dry*), is readily soluble in alcohol or chloroform, and sparingly so in water, is lævorotatory and neutral in reaction. Mineral acids dissolve it, forming yellow solutions, and it is also soluble in alkaline liquids. The base gives a dark green coloration with ferric chloride. Its relation to colchicine is shown by its mode of formation therefrom, and by the fact that it yields colchicine on methylation with sodium methoxide and methyl iodide. It may therefore be represented by the following formula :

$C_6H(OCH_3)_3 : C_{10}H_8O(OH).NH.COCH_3$
Colchiceine

[1] *Monats.* 1888, **9**, 870.

Physiological Action

Colchicine and colchiceine appear to exert much the same physiological action, but the former has been more thoroughly investigated. It is a slow poison, no symptoms being shown for several hours after its administration, due to its slow absorption into the central nervous system. It excites the nerve endings in plain muscle, but has no action on that in the heart or in the glands. It causes marked leucocytosis and induces increased activity of the bone-marrow. It causes acute intestinal pain with nausea and diarrhœa, and in mammals poisoned with colchicine the alimentary canal shows all the symptoms of acute gastro-enteritis, but in man the abdominal disorder is somewhat less marked. Death is due to vaso-motor paralysis. The lethal dose is about 0·0012 grm. per kilogramme of body weight.

Colchicum is used in medicine chiefly as a remedy in gout and rheumatism, and colchicine itself, mostly as the salicylate, has been used in this way.

ALKALOIDS OF *CORYNANTHE JOHIMBE*

The bark of this tree, indigenous to Kamerun in West Africa, where it has some repute as an aphrodisiac among the natives, was examined by Spiegel [1] and found to contain two alkaloids, yohimbine and yohimbinine. According to Siedler [2] two other alkaloids are also present.

For the preparation of the alkaloids Thoms [3] extracted the bark with alcohol containing hydrochloric acid, concentrated the liquors almost to dryness, dissolved the residue in water as far as possible, made the solution alkaline with soda and extracted with ether. The residue left on distilling off the ether was dissolved in dilute sulphuric acid and the solution shaken in succession with ether and chloroform. From this purified solution caustic soda solution

[1] *Chem. Zeit.* 1896, **20**, 970; 1897, **21**, 833; 1899, **23**, 59, 81.
[2] *Abstr. Chem. Soc.* 1903 [i], 195. [3] *Ibid.* 1898 [i], 455.

precipitated the alkaloids as a white powder, which was purified by repetition of this treatment and finally obtained in granular condition by stirring with light petroleum. It was then separated into its two components by crystallisation from hot benzene, in which yohimbine is less soluble than yohimbinine.

Yohimbine, $C_{22}H_{30}O_4N_2$, crystallises from dilute alcohol in colourless needles, m.p. 234°, $[\alpha]_D + 50{\cdot}9°$, is readily soluble in alcohol or chloroform, but sparingly so in ether. It forms salts with the loss of $1H_2O$; the hydrochloride, $C_{22}H_{28}O_3N_2.HCl$, is crystalline, m.p. 295°–300° (*decomp.*), $[\alpha]_D^{20} + 105°$; the nitrate forms colourless prisms, m.p. 276°; the thiocyanate separates from hot water in rectangular crystals, m.p. 233°–234° (Siedler). Yohimbine behaves as a tertiary base and gives a methiodide. It contains one methoxyl group and yields a monoacetyl derivative, m.p. 133°. When heated at 120°–130° or when evaporated to dryness in dry alcohol it loses $1H_2O$ and is converted into anhydroyohimbine, $C_{22}H_{28}O_3N_2$.

When yohimbine is heated with concentrated potash solution it is converted into potassium yohimboate (potassium yohimbine), $C_{20}H_{25}O_4N_2K$, from which yohimboaic acid, $C_{20}H_{26}O_4N_2$ (noryohimbine), is obtained on treatment with acetic acid; it crystallises from water in lustrous prisms, m.p. 257°–260° (*decomp.*). On treatment with diazomethane in excess it regenerates yohimbine which appears to be methyl N-methylyohimboate.[1] Quite recently Fourneau and Fiore [2] have asserted that yohimbine is isomeric with corynanthine (*see* p. 424) and has the formula $C_{21}H_{26}O_3N_2$.

Yohimbine is poisonous; it exerts a local anæsthetic action similar to that caused by cocaine, but is not mydriatic. The alkaloid is said to act as an aphrodisiac and has been so used in veterinary medicine.

Yohimbinine, $C_{35}H_{45}O_6N_3$, contained in the same plant, is a nearly colourless crystalline substance, m.p. 135°, soluble in chloroform or alcohol with a green fluorescence, but has not yet been obtained in a pure state. It is physiologically inactive.

[1] Spiegel and collaborators, *Berichte*, 1903, **36**, 169; 1904, **37**, 1759; 1905, 2825.

[2] *Bull. Soc. chim.* 1911 [iv], **9**, 1037.

ALKALOID OF *CYTISUS LABURNUM*

The seeds of *Cytisus Laburnum* (*Laburnum vulgare*) and of a large number of other leguminous plants contain cytisine, which was first recognised as an alkaloidal poison by Scott-Gray.[1] The alkaloid was isolated in a pure state by Husemann and Marmé,[2] and subsequently examined by Partheil,[3] Buchka and Magelhaes,[4] and van de Moer.[5] In addition to laburnum it is now known to occur in the following plants, usually in the seeds: *Ulex europæus*,[6] *Baptisia* spp., *Sophora* spp., *Genista* spp. (*cf.* p. 429, *under* Retamine), *Anagyris fœtida* (*see* p. 360), *Euchresta* spp.[7] The amount present varies from 1·03 per cent. in *Ulex europæus* seeds to 1·87 per cent. in those of *Genista monosperma*.

Cytisine (*Ulexine*, *Baptitoxine*, *Sophorine*), $C_{11}H_{14}ON_2$. The alkaloid is usually prepared by percolating powdered laburnum seeds with alcohol acidified with acetic acid, distilling off most of the solvent, and decanting the liquid from deposited resin and fat. The colouring matter is then removed by addition of lead acetate; to the filtered liquid alkali is added in slight excess, and the liberated alkaloid shaken out with chloroform, the crude residue being subsequently repeatedly crystallised from absolute alcohol or purified by distillation *in vacuo*.

Cytisine forms large colourless rhombic crystals, m.p. 153°, b.p. 218° at a pressure of 2 mm., is soluble in water, alcohol, or chloroform, but insoluble in ether or in petroleum; the solutions are strongly alkaline and optically active, $[\alpha]_D^{17}$ — 119° 57′ in water, or — 127° 40′ at 12° (Rauwerda). Cytisine is a diacidic base and forms well-crystallised salts; the monohydrochloride, $B.HCl.H_2O$, forms colourless prisms, and the dihydrochloride, $B.2HCl.3H_2O$, yellow needles; the aurichloride, $B.HCl.AuCl_3$, reddish-brown

[1] *Edinb. Med. Journ.* 1862, **7**, 908, 1025.
[2] *Zeits. für Chemie*, 1865, **1**, 161; **5**, 679.
[3] *Arch. Pharm.* 1892, **230**, 1; *Berichte*, 1890, **23**, 3202; 1891, **24**, 635.
[4] *Ibid.* 1891, **24**, 253, 674. [5] *Rec. Trav. Chim.* 1891, **10**, 47.
[6] Gerrard and Symons, *Pharm. Journ.* 1889-90 [iii], **20**, 1017.
[7] *See especially* Plugge, *Rec. Trav. Chim.* 1894, **13**, 486; 1896, **15**, 187, with Rauwerda, *Arch. Pharm.* 1896, **234**, 685.

needles, m.p. 220°, is sparingly soluble in warm water; the nitrate, $B.HNO_3.H_2O$, forms needles or leaflets, $[\alpha]_D$ — 81° 29′.

In aqueous solution cytisine gives a blood-red colour with ferric chloride, which is discharged by hydrogen peroxide, a blue colour being eventually developed; nitrobenzene containing nitrothiophene produces a reddish-violet coloration.

Cytisine reacts with methyl iodide to form in turn methylcytisine, rhombic needles, m.p. 134°, $[\alpha]_D$ — 234° 10′ in water, dimethylcytisine (amorphous) and dimethylcytisine methiodide (amorphous, deliquescent). The last of these when heated decomposes into trimethylamine, formaldehyde, and an amorphous base, $C_{10}H_{13}O_2N$, which yields amorphous salts (Partheil). Cytisine yields crystalline monoacetyl (m.p. 208°) and monobenzoyl (m.p. 116°) derivatives. These reactions indicate that the alkaloid contains both a secondary and a tertiary nitrogen atom.[1]

When cytisine is oxidised with hydrogen peroxide, the imino group is converted into an N.OH group, and a crystalline alkaloid, hydroxycytisine,[2] $C_{11}H_{13}ON : N.OH$, is produced. By the action of nitric acid, cytisine is converted into nitronitrosocytisine, and this on treatment with alcoholic hydrochloric acid yields nitrocytisine, rhombic prisms, m.p. 185°–188°. When heated with phosphorus and hydriodic acid cytisine yields ammonia and cytisoline, $C_{11}H_{11}ON$, which crystallises from alcohol in needles, m.p. 199°, is oxidised by chromic acid to cytisolinic acid, $C_{11}H_9O_3N$, and is reduced by sodium in alcohol to α-cytisolidine, $C_{11}H_{15}N$, a coniine-like base, giving a platinichloride, m.p. 216°. The isomeric β-cytisolidine, which is produced along with cytisoline in the initial reduction, gives a platinichloride, m.p. 207°.[3]

On reduction electrolytically cytisine yields tetrahydrodeoxycytisine, $C_{11}H_{20}N_2$, a strongly alkaline oil, b.p. 270°, which gives a crystalline hydrochloride, B.2HCl, m.p. 282°, $[\alpha]_D$ — 10° 15′. This yields a nitroso derivative, and by treatment with methyl iodide yields first a methyl and then a dimethyl derivative. The latter

[1] *Cf.* Maass, *Berichte*, 1908, **41**, 1635.
[2] Freund and Friedmann, *Berichte*, 1901, **34**, 605.
[3] Freund, *ibid.* 1904, **37**, 16.

forms a dimethiodide, NMeI : $C_{11}H_{18}.NMe_3I$, which on heating with aqueous potassium hydroxide yields trimethylamine and a viscid oil, b.p. 255°–265°.[1]

Cytisine is a powerful poison causing nausea, convulsions, and death by asphyxiation. In small doses the hydrobromide has been suggested as a diuretic. Its physiological action has been studied recently by Dale and Laidlaw,[2] who find that it closely resembles nicotine in action.

ALKALOIDS OF *DAUCUS CAROTA*

Carrot leaves contain, according to Pictet and Court,[3] pyrrolidine and an alkaloid, DAUCINE, $C_{11}H_{18}N_2$. The latter is a colourless oily liquid, b.p. 240°–250°, $[\alpha]_D$ + 7·74° in ether, having an odour like that of nicotine, but which does not give the pyrrole reaction.

Carrot seeds contain a base which differs from daucine in affording the pyrrole reaction and in giving an insoluble aurichloride, m.p. 172°–175° (*decomp.*).

ALKALOIDS OF *DELPHINIUM CONSOLIDA*

From the seeds of this species Keller[4] has isolated three alkaloids by extracting, with a mixture of chloroform and ether, the water-soluble portion of the matter dissolved from the seeds by 95 per cent. alcohol, containing 0·5 per cent. of hydrochloric acid.

The most important alkaloid can be obtained by converting the crude total alkaloids into hydrochlorides, dissolving in water, regenerating with ammonia, and extracting with ether, from which it separates in hexagonal prisms, m.p. 195°–197°. It is strongly alkaline in solution and highly toxic.

The other two alkaloids are obtained from the residual liquors by adding sodium hydroxide solution and extracting first with ether and then with chloroform.

[1] Freund and Horkheimer, *Berichte*, 1906, **39**, 814.
[2] *Journ. Pharm. exp. Ther.* 1912, **3**, 205. [3] *Bull. Soc. chim.* 1907 [iv], **1**, 1001.
[4] *Arch. Pharm.* 1910, **248**, 468.

ALKALOIDS OF *DELPHINIUM STAPHISAGRIA*

Delphinine, $C_{31}H_{49}O_7N$, was obtained in 1819 by Brandes from the seeds of *Delphinium Staphisagria*, and has since been examined by Kara-Stojanow,[1] who assigned to it the foregoing formula. It is obtained by extracting brown staphisagria seeds with alcohol, washing the alcoholic extract with light petroleum to remove oil, and shaking out this purified liquid with ether after the addition of excess of sodium bicarbonate. The ether solution contains delphinine, delphisine, and delphinoidine, which may be separated by fractional crystallisation, delphinine coming out first. From the alkaline liquid chloroform extracts a mixture of bases formerly known as "staphisagrine."

Delphinine crystallises in rhombs, begins to decompose at 120° and melts at 191·8°; it is soluble in the usual organic solvents, but not in water. According to Keller,[2] commercial delphinine is a mixture of two crystalline alkaloids. It is intensely poisonous, resembling aconitine in its action and affecting especially the respiration and circulation by paralysing the nerves of the respiratory system. The lethal dose for dogs is 0·0015 grm. per kilogramme of body weight.

Delphisine. This isomeride of delphinine closely resembles it in physical properties. It melts at 189°. The lethal dose for dogs is 0·0007 grm. per kilogramme of body weight.

Delphinoidine, $C_{25}H_{42}O_4N$ (?), is an amorphous base slightly soluble in water and organic solvents, and differing from the two foregoing alkaloids in giving a yellow colour changing to red and then blue when mixed with malic acid and moistened with sulphuric acid. The lethal dose for dogs is 0·0005 grm. per kilogramme of body weight.

Staphisagroine, $C_{40}H_{46}O_7N_2$,[3] is an amorphous alkaloid, m.p. 275°–277°. It is insoluble in all ordinary solvents and remains as a yellow powder when the crude mixed alkaloids obtained as described above are dissolved in a little chloroform.

[1] *Chem. Cent.* 1890 [ii], 628. [2] *Arch. Pharm.* 1910, **248**, 648.
[3] Ahrens, *Berichte*, 1899, **32**, 1581, 1669.

ALKALOIDS OF *DELPHINIUM* SPP.

From *Delphinium bicolor*, *D. Menziesii*, *D. scopulorum*, and *D. Nelsonii* roots, Heyl isolated quantities varying from 0·27 to 1·30 per cent. of a mixture of alkaloids which he called "delphocurarine" since it exerted a strong curare-like action on peripheral nerve endings.[1]

The chief constituent is an alkaloid, $C_{23}H_{33}O_7N$, which crystallises in needles, m.p. 184°–185°, dissolves in alcohol or chloroform, but not in light petroleum, and yields methyl iodide corresponding to $O\dot{C}H_3$ = 18·03 per cent., when heated with hydriodic acid. The salts are amorphous and the alkaloid gives no colour reaction with sulphuric or nitric acid. According to Lohmann, delphocurarine can be employed in place of curarine in physiological investigations.[2]

ALKALOIDS OF *ECHINOPS* SPP.

Echinopsine, $C_{11}H_9ON$, is present in various species of the genus *Echinops*, but is best obtained from *Echinops Ritro* seeds by extracting these first with light petroleum to remove oil and then with alcohol containing acetic acid.[3] The alkaloid crystallises with $1H_2O$ in rhombs or, when anhydrous, in tufts of needles, m.p. 152°; it dissolves in 60 parts of water at 15°, or in 6 at 100°. The hydrochloride, $B.HCl.2H_2O$, large rhombic crystals, the sulphate, $B_2.H_2SO_4.2$ or $8H_2O$, long needles, and the picrate, m.p. 215°, have been prepared. Echinopsine is isomeric, but not identical with any known phenylpyridone; on reduction with zinc dust in a stream of hydrogen it yields a substance with an odour of pyridine. Pyridine and ammonia are formed on fusion with potash. It gives a blood-red coloration with ferric chloride.

Echinopsine is very bitter; its physiological action is similar to, but not identical with, that of a mixture of brucine and strychnine.

β-Echinopsine, m.p. 135°, and **echinopsëine** are also present in these plants.

[1] *Chem. Soc. Abstr.* 1903, **84** [i], 650. [2] *Pfluger's Arch.* 1902, **92**, 398.
[3] Greshoff, *Rec. Trav. Chim.* 1910, **19**, 360.

ALKALOID OF *ERYTHROPHLEUM GUINEENSE*

This tree yields the " sassy bark " used as an ordeal medicine and as an arrow poison in certain parts of West Africa.

Erythrophleine, $C_{28}H_{43}O_7N$, was isolated from this bark by Gallois and Hardy,[1] and was examined later by Harnack.[2] It is an amorphous yellow powder, soluble in ether or alcohol and insoluble in light petroleum ; heated with hydrochloric acid it is hydrolysed into methylamine and erythrophleic acid, $C_{27}H_{40}O_8$. It is a heart poison and resembles digitalin in its physiological action. It also possesses local anæsthetic properties, and the hydrochloride has been recommended for this purpose in dental surgery.

ALKALOIDS OF *ESCHSCHOLZIA CALIFORNICA*

From this plant Fischer [3] obtained protopine (p. 381), β- (or γ-) homochelidonine (p. 380), chelerythrine (p. 378), and sanguinarine (p. 381), the last two only in traces. The same author in conjunction with Tweeden [4] isolated two further alkaloids provisionally referred to as *a* and *b*. Alkaloid *a* is readily soluble in hot alcohol or chloroform, melts and decomposes at 242°–243°, and forms rosettes of thin prisms. Alkaloid *b* is granular, melts at 217°, and is sparingly soluble in alcohol, but readily in chloroform.

Quite recently Brindejonc [5] has stated that only one alkaloid, IONIDINE, $C_{19}H_{25}O_4N$, is present in the plant. This crystallises in flattened prisms, m.p. 154°–156°, is sparingly soluble in cold alcohol, and strongly basic ; the salts are gummy. It gives violet tints with Fröhde's reagent (sulphomolybdic acid) and with sulphuric acid containing nitric acid.

ALKALOID OF *FERREIREA SPECTABILIS*

Angeline, GEOFFROYINE (*Surnamine*), ANDIRINE, RHATANINE, $C_{10}H_{13}O_3N$, isolated by various workers from ***Ferreirea spectabilis,***

[1] *Bull. Soc. chim.* 1876 [ii], **26**, 39.
[2] *Arch. Pharm.* 1896, **234**, 561. *Cf.* Power and Salway, *Amer. Journ. Pharm.* August 1912.
[3] *Ibid.* 1901, **239**, 421.
[4] *Pharm. Arch.* 1902, **5**, 117.
[5] *Bull. Soc. chim.* 1911 [iv], **9**, 97.

Andira retusa (*Geoffræa surnamensis*), *Andira inermis*, and *Krameria triandra* respectively, has been shown to be identical with methyltyrosine, $C_9H_{10}(CH_3)O_3N$.[1] It forms colourless crystals, begins to melt at 233°, is completely melted at 240°, and with acids yields salts which are dissociated by water. The copper salt, $(C_{10}H_{12}O_3N)_2Cu$, forms microscopic violet needles. On fusion with potash *p*-hydroxybenzoic acid is formed. The alkaloid gives a deep red coloration with Millon's reagent, and a violet coloration with vanadium sulphate in acid solution.

The barks of *Andira inermis* and *A. retusa* were at one time used in European medicine as anthelmintics, and *A. inermis* bark is said to be still used in this way in the West Indies. The bark is stated to produce vomiting, fever, and delirium when taken in large doses.

ALKALOID OF *FRITILLARIA IMPERIALIS*

Imperialine, $C_{35}H_{60}O_4N$, was isolated by Fragner[2] from *Fritillaria Imperialis* by extracting the bulbs, previously mixed with lime, with chloroform. This liquid was then shaken out with tartaric acid solution, the alkaloidal tartrate decomposed by the addition of soda, and the precipitate crystallised from hot alcohol. It forms colourless needles, m.p. 254° (*decomp.*), $[\alpha]_D$ — 35·40° in chloroform. The hydrochloride, B.HCl, prepared by dissolving the base in alcoholic hydrochloric acid, forms large, colourless crystals; the platinichloride and aurichloride are amorphous. The alkaloid and its salts are intensely bitter and are heart poisons.

ALKALOIDS OF *GALIPEA CUSPARIA*

The bark of *Galipea Cusparia* (*Cusparia febrifuga*) has long been used as a febrifuge in the West Indies under the name angostura bark, and is still imported into Europe for use in medicine. The presence of an alkaloid in the bark was first noted by Oberlin and Schlagdenhauffen, and Körner and Böhringer isolated cusparine

[1] Hiller-Bombien, *Arch. Pharm.* 1892, **230**, 513; Blau, *Zeit. Physiol. Chem.* 1908, **58**, 153.

[2] *Berichte*, 1888, **21**, 3284.

and galipine from it in 1883.[1] Beckurts has also investigated this bark, and in addition to further characterising cusparine and galipine has obtained the new bases *galipidine*, *cusparidine*,[2] and *cuspareine*,[3] whilst Tröger and colleagues have extended our knowledge of most of the foregoing alkaloids and have added *galipoidine* to the list.[4] A method for the isolation and separation of the alkaloids is given by Tröger and Muller.[5] (*See also* Appendix, p. 450.)

Cusparine, $C_{20}H_{19}O_3N$, exists in two forms, needles, m.p. 90°–91°, and amber-tinted crystals, m.p. 110°–122°. It is readily soluble in alcohol or ether. The salts are colourless and sparingly soluble in water, and are thereby readily separated from the salts of the associated alkaloids; the hydrochloride, $B.HCl.3H_2O$, forms needles, the platinichloride, $B_2.H_2PtCl_6.3H_2O$, m.p. 210°, glancing yellow needles, and the aurichloride, $B.HCl.AuCl_3$, has m.p. 190°. Cusparine contains one methoxyl, but no hydroxyl group. It reacts with methyl iodide as a tertiary base, and the methiodide, yellow needles, m.p. 186°, gives methylcusparine, $C_{20}H_{18}O_3N.CH_3$, m.p. 190°, on treatment with silver oxide. With dilute nitric acid cusparine gives "nitrocusparine," $C_{17}H_{14}O_4N_2.H_2O$, m.p. 143°, which, like the parent base, contains one methoxyl group. With dilute nitric acid under pressure an oxidation product, $C_5H_5O_5N_3$, is formed. On fusion with potassium hydroxide, cusparine yields protocatechuic acid.

Cusparine gives a cherry-red coloration with sulphuric acid and a deep blue with Fröhde's reagent.

Cuspareine, $C_{18}H_{19}O_2N$, crystallises from light petroleum in long needles, m.p. 56°, b.p. 300° (*decomp.*), forms salts with difficulty, but yields a methiodide, $B.CH_3I.H_2O$, m.p. 156° (*decomp.*). Cuspareine contains two methoxyl groups, and on distillation with zinc dust yields quinoline.

Cusparidine, $C_{19}H_{17}O_3N$, crystallises from light petroleum in

[1] *Berichte*, 1883, **16**, 2305.
[2] *Arch. Pharm.* 1891, **229**, 591; 1895, **233**, 410; 1905, **243**, 470.
[3] *Apoth. Zeit.* 1903, **18**, 697.
[4] *Arch. Pharm.* 1910, **248**, 1 1911, **249**, 174. [5] *Ibid.* 1910, **248**, 1

microscopic needles, m.p. 79°, is soluble in ether, alcohol, or chloroform, and is the lower homologue of cusparine. The salts are crystalline; the aurichloride and platinichloride melt at 167° and 182° respectively; the methiodide, a yellow crystalline powder, melts at 149°. (*See also* Appendix, p. 450.)

Galipine, $C_{20}H_{21}O_3N$, crystallises from alcohol or ether in prisms, m.p. 115·5°, and yields yellow salts which are crystalline and more soluble than those of cusparine. The hydrochloride, $B.HCl.4H_2O$, forms leaflets; the aurichloride, $B.HAuCl_4$, and the platinichloride both melt at 174°–175°. The methiodide, $B.CH_3I$, forms yellow needles, m.p. 146°. Galipine contains three methoxyl groups. On oxidation with chromic acid it yields veratric, anisic, and cinchomeronic (?) acids. (*See also* Appendix, p. 450.)

Galipidine, $C_{19}H_{19}O_3N$, separates from light petroleum in colourless rhombic crystals, m.p. 111°, and is readily soluble in most organic solvents. The salts are pale yellow: the platinichloride, $B_2.H_2PtCl_6$, has m.p. 182°, and the aurichloride, $B.HAuCl_4$, m.p. 167°. The methiodide, $B.CH_3I$, is crystalline, has m.p. 142°, and with dilute aqueous potassium hydroxide yields methylgalipidine, needles, m.p. 166°. On fusion with potassium hydroxide, galipidine yields protocatechuic acid. On oxidation with chromic acid it yields two aromatic acids, of which one is probably veratric acid, formic acid and two basic products. (*See also* Appendix, p. 450.)

Galipoidine, $C_{19}H_{15}O_4N$, m.p. 233°, is sparingly soluble in most organic solvents; it forms a platinichloride, $B_2.H_2PtCl_6.2\frac{1}{2}H_2O$, crystallising in stout yellow prisms and decomposing at 158°, and an abnormal aurichloride, $(B.HCl)_2.AuCl_3.1\frac{1}{2}H_2O$, m.p. 170° (*decomp.*), crystallising in bright yellow needles.

Physiological Action

These alkaloids have not been investigated physiologically. Cusparia bark, as already indicated, is employed as a febrifuge and a bitter tonic.

ALKALOIDS OF *GEISSOSPERMUM VELLOSII*

The bark of this plant, known as "pereiro bark," is used in Brazil as a febrifuge. Hesse isolated from it the two alkaloids geissospermine and pereirine,[1] and a third, vellosine, was found by Freund and Favet.[2]

Geissospermine, $C_{19}H_{24}O_2N_2.H_2O$, crystallises from hot alcohol in small prisms, m.p. 160°, $[\alpha]_D$ — 93·37° in alcohol, becomes anhydrous at 100°, and is sparingly soluble in water, ether, or cold alcohol. The sulphate, $B_2.H_2SO_4$, is crystalline, and the platinichloride forms bright yellow needles. The alkaloid with sulphuric acid gives a colourless solution, which slowly turns blue on standing.

Pereirine, $C_{19}H_{24}ON_2$ (?), is amorphous; it gives a violet-red coloration with sulphuric acid.

Vellosine, $C_{23}H_{28}O_4N_2$, crystallises from hot alcohol in four-sided prisms, m.p. 189°, $[\alpha]_D$ + 22·8° in chloroform, is readily soluble in warm alcohol or benzene, or in cold chloroform or ether. It is a monoacidic base and yields crystalline salts; the hydrobromide, m.p. 194°–195°, and the hydriodide, m.p. 217°–218°, both crystallise with one molecule of water.

Vellosine contains two methoxyl groups and behaves as a tertiary base. On heating with mineral acids it loses water, forming *apo*vellosine, $C_{46}H_{54}O_7N_4$.

In physiological action it resembles brucine and is toxic to rabbits in doses of 0·075 grm. per kilogramme of body weight.[3]

ALKALOIDS OF *GELSEMIUM SEMPERVIRENS*

The rhizome and roots of this North American plant, known as "yellow jasmine" in the United States, have long been used in medicine and are still recognised in several pharmacopœias.

The existence of alkaloidal constituents in this drug was first demonstrated by Wormley;[4] some years later a crystalline alkaloid was isolated by Gerrard[5] and named gelsemine. The root was

[1] *Annalen*, 1880, **202**, 41. [2] *Ibid.* 1894, **282**, 247. *Cf.* Hesse, *ibid.* p. 266.
[3] *Loc. cit.* [4] *Amer. J. Pharm.* 1870, **42**, 1.
[5] *Pharm. Journ.* 1883 [iii], **13**, 641.

reinvestigated by Thompson [1] and shown to contain in addition to gelsemine an amorphous alkaloid, gelseminine. Gelsemine has been examined more recently by Spiegel [2] and by Göldner,[3] who agreed in assigning to it the formula $C_{22}H_{26}O_3N_2$. The drug has been re-nvestigated recently by Moore,[4] who obtained gelsemine in a pure state and assigned to it the new formula $C_{20}H_{22}O_2N_2$. According to Moore the drug also contains two other alkaloids, both amorphous, one of which corresponds to Thompson's "gelseminine."

Moore obtained gelsemine by percolating the ground drug with hot alcohol, concentrating the liquor to a thick extract, and treating this with water till nothing more dissolved. This aqueous liquid was shaken with chloroform, which removed scopoletin, and then with amyl alcohol, which extracted an amorphous non-basic product. The purified aqueous liquid was then made alkaline with sodium carbonate and extracted with ether, which removed gelsemine, and this was recrystallised from acetone.

Gelsemine, $C_{20}H_{22}O_2N_2$, crystallises from acetone with one molecule of the solvent in glistening prisms, m.p. 178°, which lose their acetone at 120°, has $[\alpha]_D + 15{\cdot}9°$ in chloroform, is readily soluble in alcohol, chloroform, or ether, and slightly so in water. The hydrochloride, B.HCl, crystallises from dilute alcohol or water in prisms, m.p. 300°, $[\alpha]_D + 2{\cdot}6°$ in water; the nitrate, $B.HNO_3$, crystallises from water in glistening prisms, m.p. above 280°.

Gelsemine contains one hydroxyl group, and with acetic anhydride yields acetylgelsemine, $C_{20}H_{21}ON_2.OAc$, which crystallises from methyl alcohol with one molecule of the solvent in colourless prisms, m.p. 60°–70° or 106°–108° (*dry*). Gelsemine methiodide, $B.CH_3I$, separates from alcohol in large prisms or from water in glancing leaflets containing $1H_2O$; when heated with potassium hydroxide solution it regenerates gelsemine. When boiled with hydrochloric acid, gelsemine takes up the elements of one molecule

[1] *Pharm. Journ.*. 1887 [iii], **17**, 803.
[2] *Berichte*, 1893, **26**, 1045. [3] *Ber. deut. pharm. Ges.* 1895, **5**, 330.
[4] *Trans. Chem. Soc.* 1910, **97**, 2223; 1911, **99**, 1231.

of water and forms *apo*gelsemine, $C_{20}H_{24}O_3N_2$, an amorphous base which yields crystalline salts, together with *isoapo*gelsemine and chloro*isoapo*gelsemine, $C_{20}H_{23}O_2N_2Cl$. The first two of these products both yield diacetyl derivatives.

Gelsemine dissolves in strong sulphuric acid, giving a colourless solution, which on the addition of a crystal of potassium dichromate becomes red, then violet, and finally green.

Amorphous Alkaloids. From the alkaline liquid from which gelsemine was extracted by ether, Moore [1] observed that amyl alcohol removed a small quantity of a basic product consisting of two amorphous alkaloids, of which the more basic probably corresponds with the substance named gelseminine by Thompson,[2] but no crystalline derivatives suitable for analysis could be obtained of either of these alkaloids.

Physiological Action

Cushny has shown [3] that gelsemine hydrochloride is inactive to mammals, but produces strychnine-like effects in frogs, and Dale, working with material prepared by Moore,[4] found that in doses of 0·1 grm. it produced no effect on rabbits. On the other hand, 0·001 grm. of the hydrochlorides of the mixed amorphous alkaloids injected into rabbits caused convulsions followed by death from respiratory failure. According to Cushny, the amorphous "gelseminine" resembles coniine in physiological action, but possesses a greater depressant action on the central nervous system and, unlike coniine, causes no rise in blood-pressure. It is also a powerful mydriatic when applied locally, but less so when taken internally.

ALKALOID OF *HYMENODICTYON EXCELSUM*

Hymenodictyonine (*Hymenodictine*), $C_{23}H_{40}N_2$, was isolated by Naylor [5] from the bark of this East Indian plant by extracting a mixture of the finely powdered bark and lime with chloroform. The alkaloid crystallises from ether in microscopic needles, m.p.

[1] *Loc. cit.* [2] *Loc. cit.* [3] *Berichte*, 1893, **26**, 1045.
[4] *Loc. cit.* [5] *Pharm. Journ.* 1882–83 [iii], **13**, 817; 1884–85 [iii], **15**. 195.

120°, and is soluble in water and organic solvents. The salts are all amorphous, but the diethiodide, $B.2C_2H_5I$, crystallises in rosettes.

The alkaloid dissolves in strong sulphuric acid, forming a yellow solution which changes to red and appears bronze-coloured by reflected light. The bark is used in India as an antipyretic.

ALKALOIDS OF *LAURELIA NOVÆ-ZELANDIÆ*

From the bark of this tree, which is known as the " Pukatea " in New Zealand, Aston [1] isolated the following three alkaloids :

Pukateine, $C_{17}H_{17}O_3N$, crystallises from alcohol, has m.p. 200°, $[\alpha]_D^{15} - 220°$ in alcohol, and is feebly basic, being extracted from acetic acid solution by chloroform. It is sparingly soluble in light petroleum, more soluble in chloroform or ether (0·62 in 100 at 17°), and very soluble in pyridine. It also dissolves in solutions of alkali hydroxides, forming metallic derivatives from which the alkaloid is regenerated by carbon dioxide. The hydrochloride, B.HCl, is crystalline. No methoxyl groups are present. Sulphuric acid gives a dull purple coloration with pukateine on warming. Nitric acid gives a dark red coloration. On exposing the alkaloid in sodium hydroxide solution to the air for a few hours it becomes green, and on acidifying with hydrochloric acid and shaking with ether the latter develops a purple tint.

According to Malcolm,[2] pukateine hydrochloride in doses of 0·25 grm. per kilogramme of body weight has a convulsant action on the nerve-cells of the spinal cord. In rabbits the convulsions resemble those induced by strychnine. On intravenous injection the blood-pressure falls slightly, the heart beats slowly, and death results from respiratory failure. Applied to the tongue, pukateine causes numbness. The alkaloid itself is inactive owing to its insolubility.

Laureline, $C_{19}H_{21}O_3N$, has been obtained only in the form of its salts. The sulphate, $B_2.H_2SO_4.7H_2O$, m.p. 105°, crystallises from dilute sulphuric acid ; the hydrochloride, B.HCl, is also crystalline.

[1] *Trans. Chem. Soc.* 1910, **97**, 1381. [2] Aston, *loc. cit.*

Laurepukine, $C_{16}H_{19}O_3N$, is yellowish white and amorphous.

ALKALOID OF *LOBELIA INFLATA*

Lobeline, $C_{18}H_{23}O_2N$, was first isolated from this North American plant by Procter,[1] and was obtained in a pure state by Lewis [2] as an oily viscous liquid having a strongly alkaline reaction and soluble in alcohol or ether, sparingly so in water. Several of the salts were analysed by Siebert,[3] who assigned to it the foregoing formula. The hydrochloride, $B.HCl.H_2O$, crystallises in needles, m.p. 129°; the platinichloride, $(B.HCl)_2.PtCl_4.3H_2O$, and the aurichloride are both crystalline.

According to Edmunds [4] lobeline causes first excitation, then depression of the central nervous system with loss of reflexes, and a curare-like action on the muscles. In cats and dogs it is a powerful emetic, and in large doses produces muscular twitchings, then convulsions, and finally death. In small doses it stimulates, and in large doses paralyses, the respiratory centre. On cold-blooded hearts it acts almost like nicotine, and also inhibits the action of muscarine. *Lobelia inflata* leaves were formerly used in medicine as an emetic, but at present they are only employed as a remedy for spasmodic asthma.

THE ALKALOIDS OF *LUPINUS* SPP.

The seeds of the various species of Lupinus have been the subject of several investigations, in the course of which four alkaloids have been isolated:[5] lupinine, $C_{10}H_{19}ON$, from *Lupinus luteus* and *L. niger*; sparteine (lupinidine), $C_8H_{15}N$, from *L. luteus* and *L. niger* (*see* p. 122); lupanine, $C_{15}H_{24}ON_2$, from *L. angustifolius*, *L. perennis*, and *L. albus*; and hydroxylupanine, $C_{15}H_{24}O_2N_2$, from *L. perennis*.

Lupinine, $C_{10}H_{19}ON$. The alkaloidal constituents of yellow

[1] *Amer. Journ. Pharm.* 1836, **9**, 98. *Cf.* Bastick, *Pharm. Journ.* 1850 [i], **10**, 270, 456. [2] *Pharm. Journ.* 1877–78 [iii], **8**, 56.

[3] *Inaug. Diss. Marburg*, 1891. [4] *Amer. Journ. Physiol.* 1904, **11**, 79.

[5] Schmidt and others, *Arch. Pharm.* 1897, **235**, 192, 199, 218, 229, 262, 342, 355; 1899, **237**, 566; Bergh, *ibid.* 1904, **242**, 416; Beckel, *ibid.* 1912, **250**, 691.

lupin seeds were first isolated by Cassola in 1835, but lupinine itself was first obtained pure by Baumert [1] and later by Schmidt and Berend.[2] The alkaloid is best prepared by percolating the ground seeds with alcohol containing 1 per cent. of hydrochloric acid. From this extract the solvent is distilled off, and the residue, after neutralisation with soda and extraction with ether to remove fat, treated with mercuric chloride to precipitate sparteine as the mercurichloride. The filtrate is then treated with hydrogen sulphide, made alkaline with soda, and the liberated lupinine extracted with ether. According to Willstätter and Fourneau, lupinine is readily extracted from a mixture of lupinine and sparteine by light petroleum.[3]

The alkaloid crystallises from light petroleum in rhombic crystals, m.p. 68·5°–69·2°, b.p. 255°–257°, in a current of hydrogen, $[\alpha]_D^{17} - 19°$; it is a strong base and liberates ammonia from its salts. The hydrochloride, B.HCl, forms rhombic prisms, m.p. 212°–213°, $[\alpha]_D$ — 14° in water, and the aurichloride, $B.HAuCl_4$, agglomerations of needles, m.p. 196°–197°.

Lupinine reacts with benzoic anhydride to form benzoyllupinine, minute needles, m.p. 49°–50°. When heated with phosphoric anhydride, lupinine loses one molecule of water, forming anhydrolupinine, $C_{10}H_{17}N$, a colourless oil, b.p. 216°–217°/726 mm.

When oxidised with chromic acid, lupinine forms lupininic acid, $C_9H_{16}N.CO_2H$, which crystallises in long needles, m.p. 255°. The nitrogen atom in lupinine has no methyl group attached to it, but it reacts as a tertiary nitrogen, giving a methiodide, from which methyllupinine can be prepared by the action of silver oxide. By repeating this process ("exhaustive methylation") lupininedimethylammonium hydroxide is obtained, and this when distilled breaks up into trimethylamine and an unsaturated alcohol, $C_{10}H_{15}OH$. These observations have led Willstätter and Fourneau [3] to suggest that lupinine contains a dicyclic nucleus with a nitrogen atom common to both rings similar to that existing in cinchonine (*see* p. 169).

[1] *Berichte*, 1881, **14**, 1150; 1882, **15**, 195. [2] *Arch. Pharm.* 1897, **235**, 263.
[3] *Berichte*, 1902, **35**, 1914.

Lupanine, $C_{15}H_{24}ON_2$.[1] This alkaloid occurs in the dextro- and inactive modifications in the white lupin, and in the dextro-form only, in the blue and perennial lupin. It is obtained by extracting the dried ground seeds with alcohol containing 1 per cent. of hydrochloric acid. The alcohol is distilled off and the residue heated with three times its volume of water. The liquid is filtered free from fat, neutralised with caustic soda, and evaporated to a small volume, then made alkaline and the liberated alkaloid extracted with chloroform. The residue left on distilling off the chloroform is made slightly acid with hydrochloric acid and evaporated to a thick syrup. This on standing deposits crystals of *d*-lupanine hydrochloride, and when this has all been deposited the mother liquors yield a supply of *i*-lupanine hydrochloride.

i-Lupanine crystallises from light petroleum in needles, m.p. 99°. It is strongly alkaline and dissolves in all ordinary solvents. The hydrochloride, $B.HCl.2H_2O$, has m.p. 127°–128° or 250°–252° (*dry*), $[\alpha]_D + 62°$, and the aurichloride, m.p. 177°–178° (*decomp.*), 200° (Beckel), is sparingly soluble in water.

d-Lupanine closely resembles the inactive alkaloid, but melts at 44°, and can be obtained from it by fractional crystallisation of the mixed thiocyanates formed from the racemic alkaloid. The hydrochloride, $B.HCl.2H_2O$, m.p. 127°, and the hydrobromide, m.p. 111°–112°, are both less soluble than the corresponding salts of the inactive base. With bromine *d*-lupanine furnishes a perbromide which on treatment with alcohol yields ethoxylupanine dihydrobromide, $C_{15}H_{23}ON_2.OC_2H_5.2HBr$.[2] Beckel [3] has compared the action of methyl iodide on *d*-lupanine and sparteine, and concludes that *d*-lupanine is not constituted similarly to sparteine.

l-*Lupanine* obtained as described above by fractional crystallisation of the thiocyanate of the inactive form, melts at 43°–44°. The aurichloride has m.p. 188°–189° (*decomp.*).

[1] Davis, *Apoth. Zeit.* 1896, **11**, 94.

[2] Beckel, *Arch. Pharm.* 1912, **250**, 709. *Cf.* Soldaini, *Chem. Centr.* 1902, i, 669; 1905, i, 826.

[3] *Arch. Pharm.* 1911, **249**, 329.

Hydroxylupanine, $C_{15}H_{21}O_2N_2.2H_2O$, crystallises in rhombic prisms, m.p. 76°–77° or 172°–174° (dry), $[\alpha]_D$ + 64·12°, is soluble in water or alcohol, and yields crystalline salts. The aurichloride $B.HAuCl_4$, m.p. 205°–206°, forms prisms from dry alcohol. On reduction with hydriodic acid the base yields *d*-lupanine.

In addition to these alkaloidal constituents, Schulze has shown that *Lupinus luteus* seedlings contain the following protein decomposition products :[1]

Aminovaleric acid.

Arginine (*see* p. 326).

Asparagine (aminosuccinamic acid).

Histidine (4- (or 5-) glyoxaline-α-aminopropionic acid).

Leucine (α-aminocaproic acid).

Lysine ($\alpha.\epsilon$-diaminocaproic acid).

Phenylalanine (phenyl-α-aminopropionic acid).

Tyrosine (hydroxyphenyl-α-aminopropionic acid).

The occurrence of histidine in these seeds is of some interest since it is a glyoxaline derivative (glyoxaline-4- (or 5-) α-aminopropionic acid) and therefore allied to pilocarpine (p. 304) and other natural alkaloids.

Physiological Action of Lupin Alkaloids. The physiological action of sparteine is discussed at p. 126. Lupinine is only slightly toxic. The *d*- and *i*- forms of lupanine are said to be equally active physiologically. They are bitter to the taste and poisonous.

ALKALOID OF *LYCOPODIUM COMPLANATUM*

Lycopodine, $C_{32}H_{52}O_3N_2$. This alkaloid was isolated by Bödeker by exhausting *Lycopodium complanatum* plants with boiling alcohol.[2] The residue obtained by distilling off the solvent was extracted with warm water, freed from colouring matter by addition of lead acetate, made alkaline with caustic soda, the liberated alkaloid extracted with ether and purified by conversion into the hydrochloride. Lycopodine crystallises in monoclinic prisms, m.p. 114°–115°, and dissolves readily in water, ether, alcohol, or chloro-

[1] *Zeit. physiol. Chem.* 1899, **28**, 465. [2] *Annalen*, 1881, **208**, 363.

form. The hydrochloride, $B.2HCl.H_2O$, and the aurichloride, $B.2HAuCl_4$, are both crystalline. The alkaloid and its salts have a bitter taste.

ALKALOID OF *LYCOPODIUM SAURURUS*

Pilijanine, $C_{15}H_{24}ON_2$, was isolated from the tropical plant *Lycopodium saururus* in 1886 by Adrian,[1] but was first prepared in a pure state by Arata and Canzoneri,[2] who obtained it by boiling a dried aqueous extract of the plant, previously mixed with lime, with alcohol. The residue obtained by distilling off the solvent was acidified with acetic acid, decolorised with lead acetate, evaporated to a small bulk, made alkaline with sodium carbonate solution, and extracted with chloroform. This was shaken out with dilute sulphuric acid and the free base obtained from the latter by addition of soda and extraction with light petroleum. This solution, as the solvent evaporated, deposited colourless needles of the alkaloid. It melts at 64°–65° and has a coniine-like odour. The sulphate, $B.H_2SO_4.2\frac{1}{2}H_2O$, forms rhombic prisms from hot alcohol, and the platinichloride, $(B.HCl)_2.PtCl_4$, yellow glistening plates, readily soluble in water. The free alkaloid, when distilled in a current of hydrogen, is converted into a base resembling nicotine.

It is a powerful poison; 0·1–0·2 grm. administered to a dog caused convulsions, vomiting, contraction of the pupil of the eye, and finally death.

ALKALOIDS OF *LYCORIS RADIATA*

Lycorine, $C_{32}H_{32}O_8N_2$, was obtained by Morishima [3] from the bulbs of the Japanese plant *Lycoris radiata*, together with a second alkaloid, sekisanine. Lycorine crystallises in polyhedra, melts at 250° (*decomp.*), and is sparingly soluble in water or organic solvents. The hydrochloride, $B.2HCl.2H_2O$, forms slender needles, m.p. 208°; the platinichloride, $B.H_2PtCl_6$, melts at 210°. The alkaloid is poisonous. In warm-blooded animals it acts as an

[1] *Compt. rend.* 1886, **102**, 1322.
[2] *Gazzetta*, 1892, **22**, i, 149.
[3] *Abstr. Chem. Soc.* 1899 [i], 92.

emetic, causing eventually collapse and death by paralysis of the central nervous system.

Sekisanine, $C_{34}H_{36}O_9N_2$,[1] occurs in the mother liquors from which lycorine has been obtained, and is extracted therefrom by ether. It crystallises in four-sided needles, m.p. 200°. It is moderately soluble in alcohol, but sparingly so in other solvents. The platinichloride melts at 194°.

ALKALOID OF *NARCISSUS PSEUDO-NARCISSUS*

An alkaloid was first isolated from the bulbs of this plant, the wild daffodil,[2] by Gerrard in 1878, and was obtained in a pure state and named narcissine by Ewins.[3] The resting bulbs contain about 0·2 and the flowering bulbs about 0·1 per cent. (*Cf.* p. 371.)

Narcissine, $C_{16}H_{17}O_4N$, crystallises from alcohol in colourless prisms, m.p. 266°–267°, $[\alpha]_D^{10}$ — 95·8° in dry alcohol, and is sparingly soluble in alcohol, more so in pyridine, but insoluble in ether or chloroform. The hydrochloride, B.HCl., forms long thin prisms, m.p. 198°–199°. Narcissine forms a deep red solution in sulphuric acid. It contains no methoxyl groups. The nitrogen atom appears to be tertiary. On fusion with potash a phenolic substance, giving a transient violet tint with ferric chloride, is produced.

With cats narcissine causes nausea and purgation.

N. princeps also contains a minute quantity of alkaloid.

ALKALOIDS OF *NECTANDRA RODIOEI*

Bebeerine, (*Bibirine, Pelosine*), $C_{18}H_{21}O_3N$. This alkaloid was first obtained by Maclagan and collaborators[4] from greenheart bark (*Nectandra Rodioei*) together with a second amorphous base, SEPEERINE (*flavobuxine, pellutēine*), $C_{18}H_{19}O_3N$. Subsequently Walz[5] asserted that bebeerine was identical with buxine prepared from the box plant, *Buxus sempervirens*, by Fauré.[6] Flückiger[7] to

[1] *Abstr. Chem. Soc.* 1899 [i], 92. [2] *Journ. Physiol.* 1878, **1**, 437.
[3] *Trans. Chem. Soc.* 1910, **97**, 2406.
[4] *Annalen*, 1843, **48**, 106; 1845, **55**, 105. [5] *Jahresberichte*, 1860, p. 548. *Jahresberichte Berz.* 1830 **11**, 245. [7] *Pharm. Journ.* 1869–70 [ii], **11**, 192.

some extent confirmed Walz' statement and in addition showed that bebeerine was identical with the PELOSINE obtained by Wiggers[1] from "Pareira brava" root (*Cissampelos Pareira*) and by himself from *Chondodendron tomentosum* root, true pareira brava (*see* p. 416). More recently Scholtz[2] has confirmed Flückiger's statement as regards the identity of pelosine with bebeerine, but states that buxine (p. 372) is distinct from bebeerine.

From greenheart wood Maclagan and Gamgee[3] subsequently obtained three other alkaloids, of which one, NECTANDRINE, $C_{20}H_{23}O_4N$, was analysed.

Bebeerine crystallises from methyl alcohol in small prisms, m.p. 214°. The solutions are optically active, $[\alpha]_D$ — 298°. The hydrochloride, B.HCl, forms small needles, m.p. 259°–260°; the platinichloride is amorphous; the methiodide, $B.CH_3I$, m.p. 268°–270°, and the monoacetyl and monobenzoyl derivatives, melting at 147°–148° and 139°–140° respectively, have been prepared and are crystalline.[4] Bebeerine contains one methoxyl group,[5] a phenolic hydroxyl group, and a $:NCH_3$ group.[4] Crystalline *l*-bebeerine readily passes into an amorphous modification when heated at 180°.

According to Scholtz[6] *l*-bebeerine of greenheart bark is not toxic when injected subcutaneously into rabbits, whereas the *d*- and *dl*- isomerides (*see* p. 416) are toxic; but Hildebrandt states that all the forms exercise a curare-like effect in frogs, that the *d*- form is much more toxic to cats than to dogs, and that the amorphous *l*- form is more toxic to dogs than the crystalline *l*-bebeerine.[7]

Greenheart bark is a tonic and febrifuge, and amorphous "bebeerine sulphate" was formerly used in medicine. (*See also* p. 452.)

[1] *Annalen*, 1840, **33**, 81.
[2] *Berichte*, 1896, **29**, 2054; *Arch. Pharm.* 1898, **236**, 530.
[3] *Pharm. Journ.* 1869–70 [ii], **11**, 19.
[4] Scholtz, *loc. cit.*
[5] Herzig and Meyer, *Monats.* 1897, **18**, 385.
[6] *Arch. Pharm.* 1906, **244**, 555.
[7] *Arch. exp. Path. Pharm.* 1907, **57**, 279.

ALKALOIDS OF "PAREIRA BRAVA" ROOT

Pareira brava root should consist of the roots of *Chondodendron tomentosum*, and this material is still official in the Pharmacopœia of the United States, whilst its substitute, *Cissampelos Pareira* root, is recognised in the Addendum to the British Pharmacopœia.

According to Flückiger,[1] both these products contain bebeerine (*see* p. 415) which is identical with the PELOSINE Wiggers isolated from pareira root.[2] Bödeker[3] has stated that *Cissampelos Pareira* root also contains sepeerine (*see* p. 414). Scholtz showed recently that true pareira root (*Chondodendron tomentosum*) contains *d*-, *l*-, and *dl*-bebeerine[4] (*cf.* p. 452), and Hildebrandt[5] examined the physiological action of these substances. The *d*- and *l*- forms have the characters and properties already given for *l*-bebeerine from greenheart bark (*see* p. 415), with the exception that the *d*- form is equally and oppositely active. The *dl*- form is amorphous and has m.p. 300°. The *d*- and *l*- forms yield amorphous modifications when heated. Hildebrandt[6] found that all the forms of the alkaloid exert a curare-like effect on frogs. In white mice the *d*- and *dl*- (amorphous) isomerides are more active than the *l*- form, and the amorphous *d*- and *l*- forms more active than the corresponding crystalline forms. In rabbits the amorphous *d*- form is the most active, 0·45 grm. of this being a fatal dose to a rabbit of 1·4 kg. weight, whilst the same dose of the crystalline *d*- form was inactive. In the case of the methiodide the physiological activity is much reduced. The alkaloid appears to be excreted in the urine as a glycuronate.

Chondrodine, $C_{18}H_{21}O_4N$. This alkaloid was subsequently obtained by Scholtz[7] from true pareira root. It is amorphous, m.p. 218°–220°, $[\alpha]_D$ — 75° in alcohol, but yields crystalline salts. The hydrochloride, B.HCl, forms yellow leaflets, m.p. 274°–275°, and the picrolonate greenish-yellow needles, m.p. 185°–186°. The

[1] *Pharm. Journ.* 1869–70 [ii], **11**, 192. [2] *Annalen*, 1840, **33**, 81.
[3] *Ibid.* 1849, **69**, 54.
[4] *Berichte*, 1896, **29**, 2054; *Arch. Pharm.* 1898, **236**, 530; 1899, **237**, 199; 1906, **244**, 555. [5] *Arch. exp. Path. Pharm.* 1907, **57**, 279.
[6] *Loc. cit.* [7] *Arch. Pharm.* 1911, **249**, 408.

methiodide, m.p. 273°, is crystalline. Chondrodine contains one $-CH_3O$ group, a CH_3N: group, and apparently two hydroxyl groups. With ethyl iodide it gives a diethyl ether, m.p. 205°–207°, which forms a hydrochloride, m.p. 258°. Chondrodine is provisionally regarded as hydroxybebeerine.

Pareira root was formerly used in medicine chiefly for the relief of chronic inflammation of the urinary passages. It is also said to possess tonic, aperient, and diuretic properties, but it is no longer used in medicine to any considerable extent.

ALKALOIDS OF *PEGANUM HARMALA*

The seeds of this plant were first examined by Goebel,[1] who isolated therefrom the alkaloid harmaline. They were examined some years later by Fritzsche,[2] who obtained a second alkaloid, harmine, which he regarded as dihydroharmaline. More recently these alkaloids have been examined by O. Fischer and collaborators,[3] who have also obtained from the seeds the phenolic base harmalol, which is also produced by the action of hydrochloric acid on harmaline.

The alkaloids are prepared by percolating the finely ground seeds with very dilute sulphuric acid and adding salt to the liquors, when the mixed alkaloidal hydrochlorides are precipitated and may be purified by washing with brine. The hydrochlorides are then dissolved in water, the solution decolorised with animal charcoal, warmed to 50°, and fractionally precipitated with ammonia, harmine coming out first and harmaline only in presence of a considerable excess of ammonia. Harmine is finally purified by crystallisation from methyl alcohol containing benzene, and harmaline by crystallisation from alcohol or benzene. If harmalol is to be isolated the original acid filtrate is concentrated, made alkaline with caustic soda, the precipitated harmine and harmaline collected, and separated as described above. The filtrate is made acid, then made

[1] *Annalen*, 1841, **38**, 363. [2] *Ibid.* 1847, **64**, 365.
[3] *Berichte*, 1885, **18**, 400; 1889, **22**, 637; 1897, **30**, 2481.

alkaline with sodium carbonate and the harmalol extracted with chloroform and finally recrystallised from water or alcohol. The seeds contain about 4 per cent. of alkaloids, of which about two-thirds is harmaline.

Harmaline, $C_{13}H_{14}ON_2$, crystallises from alcohol or benzene in large colourless crystals, m.p. 250° (*decomp.*), $[\alpha]_D$ 0°, is readily soluble in hot alcohol, but sparingly so in cold alcohol, ether, or water. The hydrochloride, $B.HCl.2H_2O$, forms slender yellow needles, sparingly soluble in brine or hydrochloric acid : the platinichloride is microcrystalline. Harmaline forms a characteristic crystalline double salt with mercuric chloride and a crystalline acid chromate, $B.H_2CrO_4$, which is insoluble in water. Solutions of salts of the alkaloid on addition of potassium cyanide give a precipitate of harmaline hydrocyanide, B.HCN, which behaves as a simple base and gives a crystalline hydrochloride, $C_{14}H_{15}ON_3.HCl$.

Harmaline gives a yellow, non-fluorescent solution with sulphuric acid, but alcoholic solutions of its salts fluoresce green.

Acetylharmaline, $B.C_2H_3O$, m.p. 204°–205°, forms colourless needles, and when boiled with hydrochloric acid furnishes a new strongly alkaline base, $C_{15}H_{18}O_3N_2$, which is reconverted into harmaline by the prolonged action of alcoholic potash.

Harmaline behaves as a secondary base, and with methyl iodide gives N-methylharmaline hydriodide from which the free base, needles, m.p. 162° (*decomp.*), is obtained by the action of baryta. This in turn yields a methiodide, m.p. 260°.

Alcoholic nitric acid in presence of sulphuric acid converts harmaline into nitroharmaline, $C_{13}H_{13}(NO_2)ON_2$, which crystallises in slender needles and when boiled with nitric acid yields nitroanisic acid, $C_6H_3[OMe : NO_2 : COOH = 1 : 2 : 4]$, and harminic acid, $C_8H_6(COOH)_2N_2$, which behaves as an orthodicarboxylic acid.[1]

Harmaline contains one methoxyl group, and when boiled with hydrochloric acid furnishes the phenolic base, HARMALOL, $C_{12}H_{12}ON_2.3H_2O$, which also occurs naturally in the seeds.[1] It

[1] O. Fischer, *Chem. Centr.* 1901 [i], 957.

crystallises from water in brown needles, m.p. 212° (*decomp.*), and is readily soluble in chloroform or acetone. (*See also* Appendix, p. 450.)

Harmine, $C_{13}H_{12}ON_2$, crystallises from methyl alcohol in colourless rhombic prisms, m.p. 257°–259°, and is sparingly soluble in water, alcohol, or ether. The hydrochloride forms colourless crystals, and the platinichloride, acid chromate and dioxalate are all crystalline. The salts show a blue fluorescence in alcoholic solution. The alkaloid forms characteristic double salts with potassium bromide, iodide, ferrocyanide, and ferricyanide.[1]

Harmine is formed by the gentle oxidation of harmaline, from which it differs only by two atoms of hydrogen. This and the fact that harmine yields with various reagents a series of derivatives completely analogous with those given by harmaline and differing only by two atoms of hydrogen, indicate that harmaline is a dihydroharmine.

On reduction with sodium in amyl alcohol, harmine gives tetrahydroharmine (dihydroharmaline), $C_{13}H_{16}ON_2$, m.p. 199°; this is a secondary base, giving acetyl, benzoyl, and nitroso derivatives. Harmine is a secondary amine and with methyl iodide gives N-methylharmine hydriodide, m.p. 298° (*decomp.*), from which the free base, m.p. 209°, is liberated by baryta;[2] it in turn gives a methiodide, which is stable towards alkalis.

When boiled with hydrochloric acid, harmine loses 1 mol. of methyl chloride and forms harmol, $C_{12}H_{10}ON_2$, m.p. 321°, which corresponds with the harmalol, $C_{12}H_{12}ON_2$, formed in like manner from harmaline.[3]

On oxidation with chromic acid both harmine and harmo furnish harminic acid, $C_8H_6(COOH)_2N_2$, which is also formed by the oxidation of harmaline (p. 418). When heated *in vacuo* at 250°–280° or with hydrochloric acid at 190°–200°, harminic acid loses 1 mol. of carbon dioxide and forms *apo*harminecarboxylic acid, whilst when heated alone at 330°, both carboxylic groups (probably in positions 2 and 3) are eliminated and *apo*harmine, $C_8H_8N_2$, is pro-

[1] Fritsche, *loc. cit.* [2] Fischer, *Berichte*, 1897, **30**, 2482.
[3] Fischer and Tauber, *ibid.* 1885, **18**, 402.

duced. This is crystalline, m.p. 183°, and yields crystalline salts: aurichloride, m.p. 240°, picrate, m.p. 247°.[1] (*See also* Appendix, p. 451.)

Physiological Action

Peganum Harmala seeds have been used as a remedy for tapeworms in man, and Flury, who has recently studied the pharmacology of the *Peganum Harmala* alkaloids,[2] states that harmaline has an anthelmintic action, probably by paralysing the musculature of the parasites. The same author states that harmine, harmaline, and tetrahydroharmine have a paralysing action on frogs, whilst *apo*harmine causes increased reflex irritability and tetanus. Harmine and harmaline paralyse the skeletal and cardiac muscles of the frog. In warm-blooded animals Flury states that harmine and harmaline cause convulsions, increase of saliva, interference with respiration, and depression of temperature.

According to Gunn [3] harmaline resembles quinine in being more toxic to mammals than to frogs, 0·1 grm. per kg. being a fatal dose for rabbits, guinea-pigs, and cats, whilst for frogs it was 0·25 grm. per kg. Death is due to paralysis of the respiratory centre. (*See also* Appendix, p. 452.)

ALKALOID OF *PENTACLETHRA MACROPHYLLA*

Paucine, $C_{27}H_{39}O_5N_5.6\frac{1}{2}H_2O$, was isolated by Merck [4] from the seeds of this West African tree. It crystallises from hot water in yellow leaflets, m.p. 126° (*decomp.*), and is insoluble in ether or chloroform. The hydrochloride, $B.2HCl.6H_2O$, forms colourless needles, m.p. 245°–247°, sparingly soluble in water; the picrate forms red prisms, m.p. 220° (*decomp.*), and the platinichloride, $B.H_2PtCl_6.6\frac{1}{2}H_2O$, melts at 185°. The base furnishes dimethylamine when heated with potassium hydroxide. Paucine is poisonous.

[1] Fischer and Buck, *Berichte*, 1905, **38**, 329. *Cf.* Hasenfratz, *Compt. rend.* 1912, **154**, 215, 704, 1520.
[2] *Arch. exp. Path. Pharm.* 1910, **64**, 105.
[3] *Trans. Roy. Soc. Edinb.* 1910, **47**, ii, 245.
[4] *Merck's Report*, 1894, p. 11.

ALKALOIDS OF *PHYSOSTIGMA VENENOSUM*

The seeds of this plant (Calabar beans) have long been employed in West Africa by natives as an ordeal bean. They were first examined by Jobst and Hesse,[1] who isolated the poisonous alkaloid, physostigmine, in an amorphous condition. Vee subsequently obtained this alkaloid in a crystalline state and named it eserine.[2] Since then Harnack and Witkowski announced a second alkaloid, CALABARINE,[3] antagonistic to physostigmine in physiological action, which later investigators have shown to be a mixture of decomposition products formed during the extraction of physostigmine. In 1888 Böhringer and Söhne [4] obtained the crystalline alkaloid eseridine, $C_{15}H_{23}O_3N_3$, and Ehrenberg in 1893 [5] isolated a third alkaloid, eseramine. The next addition to this list was *iso*physostigmine, obtained by Ogui.[6] The Calabar bean alkaloids have recently been re-examined by Salway,[7] who has also recorded the presence of a fifth alkaloid, physovenine.

Estimation. According to Salway [8] the process of estimation given in the United States Pharmacopœia for the ether-soluble alkaloids of Calabar beans only yields part of the alkaloids, and he suggests the following process in place of it : [9] Twenty grammes of Calabar beans in No. 60 powder are mixed with 200 c.c of ether and 10 c.c. of 10 per cent. sodium carbonate solution added, and the whole shaken occasionally during four hours. One hundred cubic centimetres of ether are withdrawn and $N/10$ sulphuric acid added in excess, and shaken. The acid is withdrawn and the treatment repeated twice, using each time 10 c.c. of $N/10$ acid. The combined acid liquids are made alkaline with 10 per cent. sodium carbonate solution and shaken with ether ten times, using 20 c.c. of ether each time. The combined ethereal extracts are shaken once with

[1] *Annalen*, 1864, **129**, 115 ; 1867, **141**, 913.
[2] *Jahresberichte*, 1865, p. 456. [3] *Arch. exp. Path. Pharm.* 1876, p. 401.
[4] *Pharm. Post*, 1888, **21**, 663.
[5] *Verh. Ges. Deut. Nat. Aertzte*, 1893, **11**, 102.
[6] *Apoth. Zeit.* 1904, **19**, 891. [7] *Trans. Chem. Soc.* 1911, **99**, 2148.
[8] *Loc. cit.* [9] *Amer. J. Pharm.* 1912, **84**, 49.

5 c.c. water, the ether solution separated and the solvent distilled off. The residue is dissolved in 5 c.c. *N*/10 acid and titrated with N/50 alkali, using iodeosin as indicator.

Physostigmine (*Eserine*), $C_{15}H_{21}O_2N_3$. It is best prepared by shaking with ether, in presence of excess of sodium carbonate, the water-soluble portion of an alcoholic extract of the beans. The ethereal extract is then shaken out with dilute sulphuric acid until the acid is neutralised by the alkaloid, and from this solution the physostigmine is precipitated as the salicylate, from which it may be regenerated by shaking with solution of sodium carbonate and extraction with ether.

Physostigmine crystallises in two forms, m.p. 86°–87° and m.p. 105°–106°, the latter being the more stable. It dissolves easily in alcohol, ether, or chloroform; the solutions are alkaline and lævorotatory, $[\alpha]_D$ — 75·8° in chloroform. The mercuric iodide derivative, $B.HI.HgI_2$, crystallises in small prisms, m.p. 170°, the benzoate forms prisms, m.p. 115°–116°, and the picrate crystallises from dilute alcohol in yellow feathery needles, m.p. 114°. The salicylate forms colourless acicular crystals, m.p. 178·9°. The sulphate, $B_2.H_2SO_4$, is a microcrystalline, deliquescent powder, m.p. 140°. The last two salts are used in medicine.

Physostigmine and its salts dissolve in nitric acid, forming a yellow solution, which on warming becomes red and on evaporation to dryness leaves a green residue. A neutral solution of the sulphate gives with excess of ammonia a white precipitate, which gradually becomes pink and dissolves in excess of the alkali, forming a reddish solution which eventually becomes yellowish green.

In presence of alkalis physostigmine is readily hydrolysed, forming methylamine, carbon dioxide, and eseroline, $C_{13}H_{18}ON_2$, a monoacidic, tertiary base (colourless prisms, m.p. 128°, $[\alpha]_D$ —107·2°), and this is oxidised by the air to rubreserine, $C_{13}H_{16}O_2N_2.H_2O$, crystallising from water in deep red needles, m.p. 152° (*dry*), and forming salts with acids and bases.[1]

[1] Salway, *loc. cit.* and *Trans. Chem. Soc.* **1912, 101, 978.**

Physostigmine reacts with acetic and benzoic anhydrides, and therefore contains either a hydroxyl or an imino group. The monomethiodide is a deliquescent, crystalline substance.[1] On distillation with zinc dust physostigmine gives ammonia and a mixture of 1- and 2-methylindoles.[2]

Eseramine, $C_{16}H_{25}O_3N_4$, was first obtained by Ehrenberg,[3] and its occurrence in Calabar beans has been confirmed by Salway.[4] It remains in the ethereal liquid after physostigmine has been extracted by dilute sulphuric acid (p. 422), and may be obtained by distilling off the solvent and treating the viscid residue with a small quantity of ether, when it remains as a granular powder, which on recrystal lisation from alcohol forms colourless needles, m.p. 245° (*decomp.*). It is sparingly soluble in ether, chloroform, or benzene, but readily in hot alcohol.

*iso***Physostigmine,** $C_{15}H_{21}O_2N_3$, obtained by Ogui,[5] is insoluble in ether and furnishes a crystalline sulphate, m.p. 200°–202°. Salway was unable to confirm its occurrence in Calabar beans.[6]

Eseridine, $C_{15}H_{23}O_3N_3$, was obtained by Böhringer and Söhne[7] and subsequently examined by Eber.[8] It is stated to melt at 132° and to be converted into physostigmine when heated with dilute mineral acids. Salway[9] was unable to obtain any evidence of the presence of eseridine in Calabar beans.

Physovenine, $C_{14}H_{18}O_3N_2$, was obtained by Salway[10] from the mother liquors left after the separation of eseramine (*see above*). It crystallises from a mixture of benzene and light petroleum in small colourless prisms, m.p. 123°, is very soluble in alcohol, benzene, or chloroform, less so in ether, but insoluble in water or light petroleum. Its salts are dissociated by water. With barium hydroxide, physovenine liberates carbon dioxide and assumes a deep red colour, and owing to the similarity of this behaviour with that of physostigmine, Salway suggests that physovenine may

[1] Petit and Polonowsky, *Bull. Soc. chim.* 1893 [iii], **9**, 1008.
[2] Salway, *loc. cit.* [3] *Loc. cit.* [4] *Loc. cit.*
[5] *Loc. cit.* [6] *Loc. cit.* [7] *Loc. cit.*
[8] *Pharm. Zeit.* 1892, **37**, 483. [9] *Loc. cit.* [10] *Loc. cit.*

be an intermediate product in the formation of eseroline from physostigmine, thus :

$$\underset{\textit{Physostigmine}}{C_{15}H_{21}O_2N_3} + H_2O = \underset{\textit{Physovenine}}{C_{14}H_{18}O_3N_2} + CH_3.NH_2$$

$$\underset{\textit{Physovenine}}{C_{14}H_{18}O_3N_2} = \underset{\textit{Eseroline}}{C_{13}H_{18}ON_2} + CO_2$$

Physiological Action

Physostigmine is intensely poisonous, causing depression of the central nervous system, with death from failure of respiration due to paralysis of the medullary centre. In many respects it resembles pilocarpine and muscarine in its physiological action, causing, for example, powerful contractions of the stomach and intestine, and increasing the activity of the secretory glands. Physostigmine is principally used in ophthalmic medicine on account of its property of contracting the pupil of the eye (myosis), either when applied locally or administered internally. Physostigmine is excreted in the urine mainly and appears in it a few minutes after injection.

Harnack's "calabarine," the existence of which has not been confirmed, was antagonistic to physostigmine, and resembled atropine in its general action.

Eseridine (*see* p. 423) is stated to exert the same kind of action as physostigmine, but to be much less poisonous. Eseramine and *iso*physostigmine have not been fully examined physiologically. Physovenine appears to be at least as poisonous as physostigmine. Rubreserine (p. 422) is inactive.[1]

ALKALOID OF *PSEUDOCINCHONA AFRICANA*

Corynanthine, $C_{12}H_{26}O_3N_2$. From the bark of this plant Fourneau obtained this alkaloid, which is isomeric with quebrachine (p. 370) and closely resembles yohimbine (p. 394). It crystallises from dry alcohol in hexagonal tablets or from dilute alcohol in spangles containing water of crystallisation, melts below 200° and remelts at 241°–242°, has $[\alpha]_D^{23}$ — 125° in alcohol, and yields

[1] Heubner, *Abstr. Chem. Soc.* 1905 [ii], 847.

crystalline salts. The hydrochloride forms hexagonal leaflets, m.p. 285°–290° from alcohol, or prismatic needles, $[\alpha]_D$ — 63°, with 2 to 3 H_2O from water. The normal sulphate forms hexagonal prisms and is very soluble in water. The methiodide occurs in prismatic needles, m.p. above 300°. Sodium ethoxide in alcohol converts the alkaloid into an acid, $C_{20}H_{24}O_3N_2$, which Fourneau and Fiore state is isomeric with the acid similarly obtained from yohimbine.[1]

ALKALOIDS OF *PSYCHOTRIA IPECACUANHA*

The roots of *Psychotria Ipecacuanha* constitute the ipecacuanha of commerce, which is obtained principally from Brazil, though small quantities are also procured from the native state of Johore in Malaya. A second commercial variety, probably derived from *Psychotria acuminata*, is obtained from Colombia and is known as Carthagena ipecacuanha. The British and German Pharmacopœias recognise the *P. Ipecacuanha* roots only, but the United States Pharmacopœia recognises both sorts.

The Brazilian roots contain up to 2·5 per cent. of total alkaloids in the ratio—emetine 72, cephaeline 26, and psychotrine 2; whilst the Carthagena roots contain up to 2·0 per cent. of alkaloids in the ratio—emetine 40, cephaeline 57, and psychotrine 3.[2] According to assays made in recent years by the United States Pharmacopœia process, the total alkaloids of commercial ipecacuanha vary from 1·62 to 2·38,[3] and 1·2 to 1·92.[4]

Estimation of Total Alkaloids. (1) *Root.* The United States Pharmacopœia (8th Rev.) gives the following method for the estimation of the total alkaloids in ipecacuanha root: Fifteen grammes of the root in No. 80 powder are shaken with 115 c.c. of ether and 35 c.c. of chloroform, and 3 c.c. of ammonia water (sp. gr. 0·958 at 25°) added, and the whole shaken at intervals during

[1] *Compt. rend.* 1909, **148**, 1770; 1910, **150**, 976; *Bull. Soc. Chim.* 1911 [iv], **9**, 1037.

[2] Paul and Cownley, *Pharm. Journ.* 1896 [iv], **2**, 321. *Cf.* Siedler, *Chem. Centr.* 1902, i, 823.

[3] Southall, *Lab. Report*, 1912.

[4] Evans, *Analytical Notes*, 1911.

thirty minutes. Ten cubic centimetres of distilled water are then added, the root gathered together in a mass by shaking, and 100 c.c. of the clear ether-chloroform solution decanted into a separator, where it is shaken with (*a*) 10 c.c. *N*-sulphuric acid and 10 c.c. water, (*b*) 3 c.c. *N*-sulphuric acid with 5 c.c. of water, (*c*) 10 c.c. of water, these acid liquids being run off in turn into a second separator, made alkaline with ammonia water, and the alkaloids re-extracted by shaking three times with ether, using 25, 20, and 10 c.c. in succession. The solvent is evaporated from the combined ethereal solutions, the residue dissolved in 12 c.c. *N*/10 sulphuric acid, five drops of cochineal solution added, and the excess of acid titrated with *N*/50 potassium hydroxide solution. The percentage of alkaloids in the root is given by the formula $(12 - n/5) \times 0{\cdot}238$, where n is the number of cubic centimetres of *N*/50 potassium hydroxide used. The United States Pharmacopœia requires that the root should contain at least 1·75 of alkaloids as determined by this method.

The German Pharmacopœia (5th edit.) prescribes a process similar in principle to the above, and requires that the root should contain 1·99 per cent. of alkaloids, calculated as emetine, *i.e.* 1 c.c. of *N*/10 hydrochloric acid = 0·2482 grm. of alkaloids.

(2) *Galenical Preparations.* The United States Pharmacopœia gives the following process for the fluid extract: Ten cubic centimetres of the liquid extract are evaporated at 100° until the alcohol has disappeared, and to the cold residue 5 c.c. of *N*-sulphuric acid and 20 c.c. of water are added, the whole thoroughly mixed, filtered into a separator, using 10 c.c. and 5 c.c. of water for washing, and after adding 20 c.c. of ether, made alkaline with ammonia water and shaken. The ether is then run into a beaker and the extraction repeated twice, using each time 10 c.c. of ether. The solvent is distilled from the combined ethereal liquids and the residue dissolved in 10 c.c. of *N*/10 sulphuric acid and titrated as described above, 10 being substituted for 12 in the formula. The Pharmacopœia requires the fluid extract to contain 1·5 per cent. of alkaloids (*i.e.* 1·5 grm. in 100 c.c.).

The British Pharmacopœia (1898) gives the following process for

the liquid extract: Twenty cubic centimetres of extract are diluted with 20 c.c. of water, the alcohol evaporated off on the water-bath, and the warm residue treated with excess of lead subacetate solution. The filtrate and washings are treated with dilute sulphuric acid to remove excess of lead, and the filtrate and washings from this are made alkaline with ammonia and shaken out three times, using 25 c.c. of chloroform each time, and the alkaloidal residue left on evaporating the chloroform dried below 80° and weighed. The liquid extract should contain 2·25 grm. of alkaloids as thus determined in 100 c.c. It should be noted that this process estimates the alkaloids soluble in chloroform, *i.e.* practically total alkaloids, whereas the United States and German Pharmacopœias estimate the ether-soluble alkaloids which are chiefly emetine and cephaeline

Emetine, $C_{30}H_{44}O_4N_2$, was first obtained by Pelletier[1] in 1816, and has been investigated by Glenard,[2] and more recently by Kunz-Krause,[3] who assigned to the alkaloid the formula $C_{30}H_{40}O_5N_2$, and by Paul and Cownley,[4] who have in addition isolated the crystalline alkaloids cephaeline and psychotrine.[5] The alkaloids are best obtained by extracting the finely powdered root with alcohol. The alcoholic extract is treated with lead subacetate solution, the filtrate freed from lead, and the solvent distilled off. The residue is dissolved in dilute acid, the solution made alkaline with caustic soda and extracted with ether, which removes emetine.

Emetine is a colourless amorphous powder, m.p. 68°; it dissolves readily in light petroleum, ether, or chloroform, but is scarcely soluble in water: the solutions are alkaline to litmus. The hydrochloride, $B.2HCl.3H_2O$, is crystalline and soluble in water; the hydrobromide, B.2HBr, forms feathery needles slightly soluble in water; the nitrate is crystalline and sparingly soluble in water. The haloid salts are precipitated from aqueous solution by addition of the respective acids. According to Keller the alkaloid contains

[1] *Ann. Chim. Phys.* 1817 [ii], **4**, 172; 1823 [ii], **24**, 180.
[2] *Ibid.* 1876 [v], **8**, 277.
[3] *Arch. Pharm.* 1887, **225**, 461; 1894, **232**, 466.
[4] *Pharm. Journ.* 1894–95 [iii], **25**, 111, 373, 641, 690; 1896 [iv], **2**, 321.
[5] *Cf.* Keller, *Arch. Pharm.* 1911, **249**, 512.

two methoxyl groups and a tertiary and a secondary nitrogen atom.

Cephaeline, $C_{28}H_{40}O_4N_2$, is obtained by acidifying the alkaline liquor from which emetine has been extracted, then making alkaline with ammonia or sodium carbonate and extracting with ether. It crystallises from ether in colourless needles, m.p. 93°–104°, darkens on exposure to light, dissolves readily in alcohol or chloroform, and is insoluble in water, but soluble in alkaline solutions ; the salts are amorphous.[1]

Psychotrine is isolated from the liquors from which emetine and cephaeline have been extracted, as described above, by extraction with chloroform. It crystallises in lemon-yellow transparent prisms, m.p. 140°. It occurs in the ordinary varieties of ipecacuanha root in small quantities and is not yet well characterised.[2]

The colour reactions of the ipecacuanha alkaloids are somewhat like those of morphine,[3] for which they have occasionally been mistaken ; the former may be distinguished (1) by solution in Fröhde's reagent, when a violet coloration is produced which on the addition of a drop of hydrochloric acid changes to a Prussian blue colour, and (2) by the formation of the characteristic crystals of psychotrine when a little of the alkaloidal residue is exposed on a glass slip to the action of ammonia vapour and then examined microscopically ; (3) the mixed ipecacuanha alkaloids also give with ferric chloride a blue colour changing to green.

Emetine has a bitter acrid taste, and when taken internally exercises a strong local irritant action, resulting in emesis. Injected hypodermically it induces nausea and vomiting, followed by collapse, and death from exhaustion. Cephaeline produces much the same effects as emetine, but is more powerful as an emetic and less valuable as an expectorant. Psychotrine is practically inactive.

Ipecacuanha is used in medicine as an emetic, and in small doses as an expectorant and as a diaphoretic. It is also used as a

[1] *Pharm. Journ.* 1894–95 [iii], **25,** 111, 373, 641, 690 ; 1896 [iv], **2,** 321.
[2] *Cf.* Paul and Cownley, *loc. cit.*
[3] Allen and Scott-Smith, *Analyst*, 1902, **27,** 350.

remedy for dysentery, but for this purpose the tannin present may be the chief active agent.

ALKALOID OF *QUEBRACHIA LORENTZII*

Loxopterygine, $C_{26}H_{34}O_2N_2(?)$, was obtained by Hesse [1] from the so-called " red quebracho bark " [2] derived from *Loxopterygium* (*Quebrachia*) *Lorentzii*, indigenous to South America. The alkaloid is amorphous, melts at 81°, is sparingly soluble in water, but dissolves in most other solvents, and is strongly alkaline. The salts are amorphous and have an intensely bitter taste. With nitric acid a blood-red colour is produced, whilst sulphomolybdic acid (Fröhde's reagent) is reduced, giving bluish-violet colours.

ALKALOID OF *RETAMA SPHÆROCARPA*

Retamine, $C_{15}H_{26}ON_2$, was obtained by Battandier and Malosse[3] from the bark and branches of *Retama* (*Genista*) *sphærocarpa*; it crystallises from light petroleum in colourless needles, m.p. 162°; $[\alpha]_D$ + 43·15° in alcohol; is strongly alkaline and soluble in water, alcohol, ether, or chloroform. The neutral salts, which are those of a diacidic base, are crystalline, and give the colour reactions of sparteine (p. 122), of which it may be a hydroxy derivative. The base is bitter, but physiologically inactive.

ALKALOID OF *RICINUS COMMUNIS*

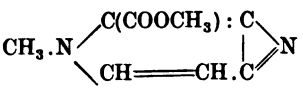
Ricinine, $C_8H_8O_2N_2$, was first isolated by Tuson [4] from the seeds of the castor-oil plant, *Ricinus communis*, and has since been examined by Soave,[5] Schulze,[6] who obtained it from castor seedlings, and by Evans.[7]

It is prepared by exhausting with alcohol an aqueous extract of

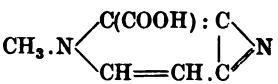
[1] *Annalen*, 1882, **211**, 274. [2] *Cf.* p. 370.
[3] *Compt. rend.* 1897, **125**, 360, 450.
[4] *Trans. Chem. Soc.* 1864, **17**, 195, 877.
[5] *Abstr. Chem. Soc.* 1896 [i], 386. [6] *Ibid.* 1898 [i], 42; 1905 [ii], 112.
[7] *Journ. Amer. Chem. Soc.* 1900, **22**, 39.

the oil-free seeds or by extracting the seedlings directly with alcohol. It crystallises in prisms, m.p. 201·5°, sublimes when gently heated, and dissolves readily in hot water or alcohol, less easily in ether or light petroleum. The solutions are neutral, and the alkaloid does not form salts, nor is it precipitated by the usual alkaloidal reagents with the exception of iodine or mercuric chloride.

Ricinine, evaporated with nitric acid, leaves a yellow residue which is turned purple by ammonia. When oxidised with permanganate, the dibasic ricininic acid, $C_7H_6O_2N_2$, is formed; the latter is also obtained together with methyl alcohol, when the alkaloid is hydrolysed with caustic soda. According to Maquenne and Philippe,[1] ricininic acid heated with hydrochloric acid at 150° yields carbon dioxide, ammonia, and hydroxymethylpyridone hydrochloride, and these authors have assigned the following formulæ to ricinine and ricininic acid:



Ricinine



Ricininic acid

ALKALOIDS OF *SENECIO* SPP.

A number of plants of this genus, to which the "common groundsel" (*Senecio vulgaris*) belongs, are known to be poisonous, and from three of them alkaloidal constituents have been isolated and examined, viz. *Senecio vulgaris*, *S. latifolius* DC., and *S. Jacobæa*. The two latter are the cause of a peculiar liver disease in cattle and horses in South Africa and elsewhere, and this has been traced to chronic poisoning by the alkaloids they contain.[2]

Senecio latifolius DC.

This plant was investigated by Watt [3] and shown to contain two poisonous alkaloids, which were named senecifoline and senecifolidine. In the plant before flowering the alkaloids amount to 1·20

[1] *Compt. rend.* 1904, **138**, 506; **139**, 840.
[2] *Bull. Imp. Inst.* 1911, **9**, 346. [3] *Trans. Chem. Soc.* 1909, **95**, 466.

per cent., but after flowering to only 0·49 per cent. They can be isolated by direct extraction with alcohol (p. 5). The crude alkaloidal residue is separated into its two components by neutralising with dilute nitric acid and evaporating *in vacuo*, when senecifoline nitrate crystallises out, leaving senecifolidine nitrate in solution. The latter can be obtained by evaporating to dryness *in vacuo* at atmospheric temperature and crystallising from dry alcohol by addition of ether.

Senecifoline, $C_{18}H_{27}O_8N$, crystallises from chloroform, on adding light petroleum, in colourless rhombic plates, m.p. 194°–195° (*decomp.*), $[\alpha]_D$ + 28° 8′ in alcohol, and is soluble in alcohol, ether, or chloroform, but insoluble in light petroleum or water. The nitrate forms rhombic prisms, m.p. 240° (*decomp.*), and, like all the salts, is lævorotatory, $[\alpha]_D$ — 15° 48′ in water; the hydrochloride forms slender needles, m.p. 260° (*decomp.*), $[\alpha]_D$ — 20°, and the aurichloride, $B.HAuCl_4.C_2H_5OH$, m.p. 220° (*dry*), crystallises from alcohol in golden-yellow, lath-shaped forms. On treatment with sodium hydroxide in alcohol, senecifoline is hydrolysed into senecifolic acid, $C_{10}H_{16}O_6$, and senecifolinine, $C_8H_{11}O_2N$. The former is probably a cyclic dihydroxydicarboxylic acid. Senecifolinine has only been obtained in the form of its salts; the hydrochloride separates from dry alcohol in rhombic prisms, m.p. 168°, $[\alpha]_D$ — 12° 36′, and the aurichloride forms rhombic prisms, m.p. 150°, from alcohol.

Senecifolidine, $C_{18}H_{25}O_7N$, crystallises from dry alcohol in colourless, rhombic plates, m.p. 212° (*decomp.*), $[\alpha]_D$ — 13° 56′ in alcohol, and is less soluble in chloroform, ether, or alcohol than senecifoline. The nitrate, $(B.HNO_3)_2.C_2H_5OH$, is readily soluble in water or dry alcohol and crystallises from the latter on addition of ether in acicular prisms, m.p. 145°, $[\alpha]_D$ — 24° 21′, containing alcohol: the aurichloride, $B.HAuCl_4$, separates from dry alcohol in golden-yellow, hair-like needles.

Both these alkaloids are bitter, and according to Cushny induce hepatic cirrhosis when administered to animals.

[1] *Proc. Roy. Soc.* 1911, B, **84**, 188.

Senecio Jacobæa

From this plant Watt has isolated a crystalline alkaloid, which has not yet been fully described.[1]

Senecio vulgaris

Senecionine, $C_{18}H_{25}O_6N$, was obtained from *Senecio vulgaris* by Grandval and Lajoux,[2] together with a second amorphous alkaloid, SENECINE, of unknown composition. Senecionine crystallises from dry alcohol in rhombic tablets, $[\alpha]_D$ — 80·49°, is soluble in chloroform and slightly so in ether. No crystalline salts have been obtained.

ALKALOID OF *SKIMMIA JAPONICA*

Skimmianine, $C_{32}H_{29}O_9N_3$, occurs in all parts of this plant, but most abundantly in the leaves. It separates from alcohol in yellow four-sided prisms, m.p. 175·5°, and is readily soluble in alcohol or chloroform, but sparingly in ether. The salts are crystalline, and intensely bitter. The alkaloid is poisonous to rabbits and frogs.[3]

ALKALOIDS OF *SOLANUM* SPP.

Among the Solanum species that have been chemically examined are *Solanum nigrum* (woody nightshade), *S. tuberosum* (potato), *S. lycopersicum*, Linn. (tomato), *S. Dulcamara* (bittersweet), *S. chenopodinum*, *S. verbascifolium*, and *S. sodomeum*. From all these an alkaloidal glucoside, which was first prepared by Desfosses,[4] has been obtained. This substance has been named solanine, but it is by no means certain that all these plants contain the same solanine, or that in most cases the solanine has been obtained in a pure state.

Firbas showed that probably at least two of these alkaloidal glucosides occur in this group of plants, viz. solanine, $C_{52}H_{93}O_{18}N.4\frac{1}{2}H_2O$, and solaneine, $C_{52}H_{83}O_{13}N.3\frac{3}{4}H_2O$, and that

[1] *Bull. Imp. Inst.* 1911, **9**, 347. [2] *Compt. rend.* 1895, **120**, 1120.
[3] Honda, *Arch. exp. Path. Pharm.* 1904, **52**, 83.
[4] *Jahresberichte*, 1820, **2**, 114.

these may be accompanied by the basic decomposition product of solanine, viz. solanidine, $C_{40}H_{61}O_2N$.[1] Firbas' formulæ for solanine and solanidine have been confirmed by Wittmann,[2] though Cazeneuve and Breteau [3] have suggested the simpler formula $C_{28}H_{47}O_{11}N.2H_2O$ for solanine, and others have been put forward by Davis [4] and by Colombano, viz. $C_{32}H_{51}O_{11}N$.[5]

Solanine, $C_{52}H_{93}O_{18}N.4\frac{1}{2}H_2O$ (Firbas), $C_{28}H_{47}O_{11}N.2H_2O$ (Cazeneuve and Breteau), $C_{42}H_{75}O_{12}N$ (Davis), $C_{32}H_{51}O_{11}N$ (Colombano), forms colourless, slender needles, m.p. 244° (Firbas), 250° (Cazeneuve and Breteau), 235° (Davis), almost insoluble in water, readily soluble in hot alcohol, but insoluble in ether or chloroform. The alkaloid has a bitter taste and is hardly alkaline to litmus. It dissolves in nitric acid with a yellow colour which slowly turns red, and gives a red colour with a mixture of sulphuric acid and sodium sulphate, and a green tint with sulphuric acid in alcohol. The salts are amorphous and gummy. Solanine is unaffected by alkalis, but when warmed with acids is hydrolysed into solanidine and a mixture of sugars including dextrose, rhamnose and galactose.[6] (For description of solanine from *S. sodomeum*, *see* p. 434.)

SOLANIDINE, $C_{40}H_{61}O_2N$ (Firbas), $C_{41}H_{71}O_2N$ (Davis), $C_{25}H_{39}ON$ (Colombano), forms needles, m.p. 191° (Firbas), 205° (Davis), 214° (Colombano), from ether, and is soluble in warm alcohol, less so in ether. The salts crystallise badly. Solanidine gives the same colour reactions as solanine. It yields a diacetyl derivative, m.p. 203°.

Solaneine, $C_{52}H_{83}O_{13}N.3\frac{1}{2}H_2O$ (Firbas), $C_{48}H_{78}O_{13}N$ (Davis), was obtained by Firbas from potato embryos and by Davis from *Solanum Dulcamara*. It forms a horn-like mass, m.p. 208°, and is rather more soluble in hot alcohol than solanine. Like the latter it is hydrolysed by acids into solanidine and a mixture of sugars.

[1] *Monats.* 1889, **10**, 541. [2] *Ibid.* 1905, **26**, 445.
[3] *Compt. rend.* 1899, **128**, 887. [4] *Pharm. Journ.* 1902 [iv], **15**, 160.
[5] *Gazzetta*, 1908, **38**, i, 19; 1912, **42**, ii, 101.
[6] Zwenger and Kind, *Annalen*, 1859, **109**, 244; Schulz, *Zeit. Zuck-ind. Böhm.* 1900, **25**, 89; Zeisel and Wittmann, *Berichte*, 1903, **36**, 3554; Votoček and Vondraček, *ibid.* p. 4372.

Solanine-S, $(C_{27}H_{46}O_9N)_2.H_2O$. This name has been applied by Oddo and collaborators to the solanine they have isolated from *Solanum sodomeum* by extracting the berries with 91 per cent. alcohol, filtering the liquors, acidifying with acetic acid, and then adding lime-water. The precipitate thus obtained on treatment with hot 80 per cent. alcohol gives a yield of solanine corresponding to 0·266 per cent. on the weight of berries used. This material is purified further by solution in dilute sulphuric acid, reprecipitating with alcoholic soda, and recrystallising repeatedly from 80 per cent. alcohol, from which it separates in aggregates of slender colourless needles, m.p. 245°–250° (*decomp.*), or from methyl alcohol in crystals, m.p. 275°–280°. The hydrochloride, B.HCl, forms microscopic scales, m.p. above 265°, and is insoluble in water. The aurichloride and platinichloride are microcrystalline. The colour reactions of solanine-S differ from those recorded by earlier workers for solanine from other sources. Solanine-S gives with sulphuric acid a yellow colour changing to deep red, violet, and brown. Alcoholic sulphuric acid gives a pale rose colour (not green, as stated by Cazeneuve and Breteau for other solanines, *see* p. 433). A solution of solanine-S when evaporated at 65°–70° with a few drops of platinic chloride solution gives a red colour changing to intense purple and violet if the heating is continued.[1] On hydrolysis by acids solanine-S gives solanidine-S, $C_{18}H_{31}ON$ (*see below*), along with galactose and probably dextrose and rhamnose. With acetic anhydride a deca-acetyl derivative is formed, and with nitrous acid non-nitrogenous products are obtained.

Solanidine-S, $(C_{18}H_{31}ON)_3.2H_2O$ or $C_{18}H_{31}ON$, purified through the hydrochloride forms nacreous, white scales, m.p. 197°–198°, from alcohol: it yields crystalline salts and an amorphous diacetyl derivative, $AcO.C_{18}H_{29}:NAc$.[2]

Physiological Action of Solanine. Solanine closely resembles certain of the non-alkaloidal glucosides, such as the saponins, in action, but it is much less poisonous. The most characteristic

[1] *Gazzetta*, 1905, **35**, i, 27; 1906, **36**, i, 310; 1911, **41**, i, 490.
[2] Oddo, *loc. cit.* 1911, **41**, i, 534.

property of these substances is their power of destroying red blood-corpuscles. Sprouting potatoes are stated to contain more solanine than ordinary potatoes, and the consumption of these has occasionally given rise to symptoms of poisoning such as headache, colic, vomiting, and diarrhœa, accompanied by general depression.[1] The toxicity is also shown by the hydrolytic product solanidine.

ALKALOID OF *SOPHORA ANGUSTIFOLIA*

Matrine, $C_{15}H_{24}ON_2$, was isolated by Nagai and later by Plugge[2] from the roots of *S. angustifolia* (*S. flavescens*). It melts at about 80°, is dextrorotatory in solution, and yields a platinichloride, aurichloride, and a crystalline ferrocyanide. The alkaloid is more toxic than cytisine, which appears to be the characteristic alkaloid of several species of *Sophora* (*see* p. 396).

ALKALOIDS OF *STYLOPHORUM DIPHYLLUM*

According to Schlotterbeck and Watkins[3] this plant contains chelidonine (p. 379), protopine (p. 381), sanguinarine (p. 381), and two new alkaloids, stylopine and diphylline.

Stylopine, $C_{19}H_{19}O_5N$, crystallises in colourless needles, m.p. 202°, is lævorotatory, behaves as a tertiary base, yields crystalline salts, and contains no methoxyl groups.

Diphylline is crystalline and melts at 216°.

ALKALOIDS OF *TABERNANTHE IBOGA*

Ibogaine, $C_{52}H_{66}O_2N_6$, obtained by Dybowsky and Landrin[4] from the African drug Iboga, prepared from the roots of the above plant, forms long amber-coloured prisms, m.p. 152°, $[\alpha]_D$ — 48·32° in alcohol, and is readily soluble in alcohol, ether, or chloroform. When exposed to air the base becomes yellowish brown and

[1] *Cf.* however, Wintgen, *Zeit. Nahr. Genussm.* 1906, **12**, 113.
[2] *Arch. Pharm.* 1895, **233**, 441. [3] *Pharm. Rev.* **1901**, **19**, 453.
[4] *Compt. rend.* 1901, **133**, 748.

amorphous. A crystalline hydrochloride was obtained. Ibogaine is said to resemble cocaine in taste and in small doses to stimulate the central nervous system. It possesses anæsthetic properties and in large doses may cause tetanus and convulsions.

Ibogine, $C_{26}H_{32}O_2N_2$, was obtained by Haller and Heckel [1] from Iboga obtained from the Congo and has characters similar to those given for ibogaine, with which it is probably identical. Lambert and Heckel [2] have shown that the subcutaneous injection of ibogine produces in frogs an abolition of voluntary and reflex movements without diminishing the excitability of the muscles and nerves. In animals convulsions, and eventually death from respiratory arrest, occur.

ALKALOID OF *TAXUS BACCATA*

Taxine, $C_{37}H_{52}O_{10}N$, is contained in the leaves, shoots, and fruits of the yew (*Taxus baccata*), from which it was first isolated by Lucas [3] in 1856. It was subsequently investigated by Marmé,[4] Hilger and Brande,[5] Amato and Capparelli, and recently by Thorpe and Stubbs.[6]

The alkaloid can be prepared by percolating powdered yew leaves with dilute sulphuric acid (1 per cent.), and exhausting this extract with ether after the addition of excess of dilute ammonia; from the solution in ether the base is obtained by agitation with dilute acid and subsequent precipitation from the acid solution with ammonia. The crude alkaloid so prepared may be purified by solution in ether, filtration, and evaporation of the filtrate at ordinary temperatures. According to Moss [7] a 1 per cent. solution of oxalic acid may be used for extraction in place of dilute sulphuric or hydrochloric acid.

Taxine, in the purest form in which it has yet been obtained, occurs in fine, glistening particles, m.p. 82° (60° Moss) (*decomp.*).

[1] *Compt. rend.* 1901, **133**, 850.
[2] *Ibid.* 1901, **133**, 1236.
[3] *Jahresberichte*, 1856, 550.
[4] *Bull. Soc. chim.* 1876 [ii], **26**, 417.
[5] *Berichte*, 1890, **23**, 464.
[6] *Trans. Chem. Soc.* 1902, **81**, 874.
[7] *Sci. Proc. Roy. Dubl. Soc.* 1909, **12**, 92.

It is soluble in ether, chloroform, or alcohol, but is insoluble in water or light petroleum. The salts are all amorphous, including the aurichloride, m.p. 132°–134°. Taxine methiodide is a yellow amorphous powder, m.p. 121°. The alkaloid possesses a bitter taste, acts as a cardiac depressant, and interferes with respiration so that death occurs from suffocation when it is administered to animals. It is said not to be poisonous to guinea-pigs.

ALKALOID OF *TETRANTHERA CITRATA*

Laurotetanine, $C_{19}H_{23}O_5N$, was obtained by Greshoff[1] from many East Indian species of Lauraceæ. It was investigated by Filippe,[2] who employed as a source the bark of *Tetranthera* (*Litsea*) *citrata*, which was extracted with alcohol containing acetic acid and the alkaloid isolated by concentrating the liquors, adding alkali and extracting with ether. It crystallises in rosettes of yellowish needles, m.p. 134°, dissolves readily in alcohol or chloroform, but less readily in water or ether. The hydrochloride, $B.HCl.6H_2C$, crystallises in prisms, m.p. 46°, and is dextrorotatory in aqueous solution.

With sulphuric acid the alkaloid gives a blue colour changing to violet. It reduces silver nitrate and alkaline copper solutions, and with ethyl iodide furnishes ethyllaurotetanine hydriodide, m.p. 127°–130°, and is therefore a secondary base; it contains three methoxyl groups and gives a dibenzoyl derivative, m.p. 194°. The formula may provisionally be written $C_{16}H_{12}O(OCH_3)_3(OH)(NH)$. With frogs the alkaloid acts as a tetanising poison, but is less active than strychnine.

ALKALOIDS OF VERATRUM SPECIES

This group of alkaloids is obtained from products derived from various plants, of which the rhizomes of *V. album* and *V. viride* and the seeds of *Schoenocaulon officinale* are the most important. The two former are commonly known as white and green "hellebores"

[1] *Berichte*, 1890, **23**, 3546. [2] *Arch. Pharm.* 1898, **236**, 601.

respectively, but are quite distinct from the true hellebores belonging to the natural order Ranunculaceæ. The alkaloids obtained from these sources are as follows :

1. Sabadilla seeds, *Schoenocaulon officinale*, A. Gray (*Asagraea officinalis*, Lindley), and perhaps also from *Veratrum Sabadilla*.	*Cevadine* (crystallised veratrine), $C_{32}H_{49}O_9N$. *Cevadilline* (Sabadilline), $C_{34}H_{53}O_8N$. *Sabadine*, $C_{29}H_{51}O_8N$. *Sabadinine*, $C_{27}H_{45}O_8N$ (?). *Veratridine* (amorphous veratrine), $C_{37}H_{53}O_{11}N$.
2. White hellebore, *Veratrum album* (*V. Lobelianum*).	*Jervine*, $C_{26}H_{37}O_3N$. *Pseudojervine*, $C_{29}H_{43}O_7N$. *Rubijervine*, $C_{26}H_{43}O_2N$. *Protoveratridine*, $C_{26}H_{45}O_8N$. *Protoveratrine*, $C_{32}H_{51}O_{11}N$. *Unnamed Base*, $C_{26}H_{40}O_{10}N$ (?).
3. Green hellebore, *Veratrum viride*[1]	*Cevadine*, $C_{32}H_{49}O_9N$. *Jervine*, $C_{26}H_{37}O_3N$. *Pseudojervine*, $C_{29}H_{43}O_7N$. *Veratridine*, $C_{37}H_{53}O_{11}N$.
4. *Veratrum nigrum*	*Jervine*, $C_{26}H_{37}O_3N$.

Sabadilla Seeds

Cevadine, $C_{32}H_{49}O_9N$ (crystallised veratrine), was first isolated from sabadilla seeds by G. Merck [2] in 1855, who assigned to it the name veratrine and the formula $C_{32}H_{52}O_8N$. The same alkaloid was subsequently obtained by Schmidt and Koppen [3] and by Wright and Luff,[4] who in order to distinguish it from the mixture of amorphous bases sold in commerce as "veratrine" introduced the name cevadine, which has been generally adopted in spite of the

[1] Wright and Luff, *Trans. Chem. Soc.* 1879, **35**, 421.
[2] *Annalen*, 1855, **95**, 200. [3] *Ibid.* 1877, **185**, 224.
[4] *Trans. Chem. Soc.* 1878, **33**, 338.

later suggestion of Ahrens[1] that it should be called "crystallised veratrine."

The alkaloid is prepared by percolating the finely powdered seeds with alcohol containing 1 per cent. of tartaric acid. The residue obtained by distilling off the solvent is poured into water to precipitate resin. The filtrate is made alkaline with sodium carbonate and shaken out with ether; from the ethereal solution the alkaloid is recovered by agitation with aqueous solution of tartaric acid. The purified solution thus obtained is again made alkaline and shaken out with ether, and from the latter the crystalline base may be obtained by addition of sufficient light petroleum to produce a slight cloudiness and setting aside the mixture until precipitation occurs, after which cevadine (containing veratridine and cevadilline) separates and may be recrystallised from warm alcohol by the addition of a little water.[2] The yield is about 0·1 per cent.

The alkaloid crystallises in rhombic prisms with two molecules of alcohol, which it loses at 130°–140°, m.p. 205° (anhydrous), dissolves readily in ether or hot alcohol, but is insoluble in water; it is optically inactive. The hydrochloride, B.HCl, crystallises in needles, and the aurichloride, $B.HAuCl_4$, from alcohol, in brilliant, yellow needles, m.p. 182° (*decomp.*). The platinichloride is amorphous and the nitrate crystalline. Cevadine gives a violet coloration with concentrated hyd ochloric acid, which becomes red on warming. With sulphuric acid it becomes yellow, then red. Mixed with sugar and then moistened with sulphuric acid, a deep green colour changing to blue is produced.

Cevadine contains one methoxyl group; it readily combines with four atoms of bromine, forming an amorphous tetrabromide. It yields a crystalline benzoyl derivative, m.p. 255°, and a methiodide, which decomposes at 210°–212°, and is converted by silver oxide into cevadinemethylhydroxide.[3] When warmed with alcoholic soda, cevadine undergoes hydrolysis into cevine and angelic and tiglic acids. When hydrogen chloride is passed into cevadine in

[1] *Berichte*, 1890, **23**, 2700. [2] Wright and Luff.
[3] Frankforter, *Amer. Chem. Journ.* 1898, **20**, 361.

alcohol, ethyl tiglate and cevine are formed, so that tiglic acid does not seem to be produced from angelic acid first formed in this reaction.[1]

CEVINE, $C_{27}H_{43}O_8N.3\frac{1}{2}H_2O$, was first prepared by Wright and Luff[2] in an amorphous form, but was subsequently obtained crystalline by Freund and Schwarz.[3] It forms triclinic prisms, sinters at 155°–160°, melts at 195°–200°, reduces Fehling's solution, and with alcoholic potash forms a characteristic crystalline potassium derivative. The hydrochloride, B.HCl, crystallises in needles, m.p. 240; the methiodide crystallises and melts at 240°–250°. Dibenzoylcevine, m.p. 195°–196°, crystallises in large tablets; diacetylcevine has m.p. 190°. On oxidation by hydrogen peroxide cevine forms cevine oxide. Cevine is a tertiary base and probably contains a double ring system.[4]

Cevadine is intensely poisonous. It stimulates the endings of the sensory nerves, giving rise to pricking sensations when applied to the skin and to violent sneezing if it comes into contact with the mucous membrane of the nose. It is owing to this action of this group of alkaloids that veratrum root is sometimes called sneeze-wort. This irritation is subsequently followed by a sensation of numbness and cold. Cevadine has a characteristic action on muscle, intensifying the contraction and prolonging it. It at first stimulates the central nervous system, but in large quantities causes paralysis, terminating in failure of the respiration. It resembles aconitine in its action on the circulation, but larger quantities are needed to produce the same effect. As in the case of aconitine and aconine, the removal of the acyl group from cevadine, with the production of cevine, results in a great fall in toxicity. Cevine is said, however, to produce local anæsthesia.

Veratridine (*amorphous veratrine*), $C_{37}H_{53}O_{11}N$. The name veratridine was first applied to this alkaloid by Bossetti.[5] The

[1] Horst, *Chem. Zeit.* 1902, **26**, 334.
[2] *Trans. Chem. Soc.* 1878, **33**, 338. *Cf.* Ahrens, *Berichte*, 1890, **23**, 2702.
[3] *Berichte*, 1899, **32**, 800.
[4] Freund and Speyer, *Berichte*, 1904, **37**, 1946.
[5] *Arch. Pharm.* 1883, **221**, 82.

alkaloid appears to be identical with Schmidt and Koppen's water-soluble amorphous veratrine [1] from sabadilla seeds, and with the amorphous veratrine obtained by Wright and Luff [2] and by Merck [3] from the same source. The synonym "amorphous veratrine" is liable to be misunderstood since commercial veratrine is amorphous and is the "total alkaloid" of sabadilla seeds and contains cevadine, veratridine, and cevadilline.

Veratridine is the chief constituent of the amorphous precipitate produced on the addition of light petroleum to the solution of the total alkaloids of sabadilla seeds in ether and is separated from the cevadilline also present by extraction with a small quantity of ether and is purified by conversion into the characteristic, insoluble nitrate.

The alkaloid is an amorphous varnish-like substance, m.p. 180°. The nitrate is almost insoluble in water; the sulphate, $B.H_2SO_4.xH_2O$, forms fine needles. Alcoholic soda hydrolyses the alkaloid into amorphous VERINE, $C_{28}H_{45}O_8N$, and veratric acid.[4] Veratridine is a sternutatory, and as "amorphous veratrine" is employed in medicine in neuralgic and similar complaints.

Cevadilline (*Sabadilline*), $C_{34}H_{53}O_8N$, is the amorphous residue, insoluble in ether, obtained in the purification of cevadine. Its salts are amorphous. When warmed with alcoholic soda, tiglic acid is formed.[5]

Sabadine, $C_{29}H_{51}O_8N$, was isolated by Merck [6] from sabadilla seeds. It crystallises from ether in needles, m.p. 238°–240° (*decomp.*), dissolves readily in alcohol or acetone, but is insoluble in light petroleum. The hydrochloride, $B.HCl.2H_2O$, forms needles, m.p. 282°–284° (*decomp.*), the nitrate, $B.HNO_3$, needles sparingly soluble in water, and the aurichloride, $B.HAuCl_4$, fine golden-yellow needles.

Sabadinine, $C_{27}H_{45}O_8N(?)$, was also obtained by Merck [6] from sabadilla seeds. It crystallises in hair-like needles from ether, dissolves readily in alcohol, but is sparingly soluble in light petroleum.

[1] *Berichte*, 1876, **9**, 1115.
[2] *Trans. Chem. Soc.* 1878, **33**, 341.
[3] *Annalen*, 1855, **95**, 200.
[4] Wright and Luff; Bossetti.
[5] Wright and Luff.
[6] *Merck's Report*, 1890.

White Hellebore

Jervine, $C_{26}H_{37}O_3N.2H_2O$, was first isolated from white hellebore in a pure state by Wright and Luff,[1] who assigned to it the foregoing formula. The alkaloid may be recovered from the crude phosphate obtained as described under protoveratrine, or better by mixing the dry ground rhizome with barium hydroxide and water and extracting the mixture with ether, which removes jervine, protoveratridine, and rubijervine. The syrup left on distilling off the ether slowly deposits crystals of crude jervine. On recrystallisation from dry alcohol protoveratridine separates first. The partially purified jervine obtained in the later fractions is digested with dilute sulphuric acid and so deposits the nearly insoluble jervine sulphate, whilst rubijervine sulphate remains in solution.[2] A method of estimation is given by Bredemann.[3]

Jervine crystallises from alcohol in stellate groups of long prisms, m.p. 238°–242° (241° Bredemann); dissolves readily in alcohol, chloroform, or acetone, but is less soluble in ether or light petroleum. The hydrochloride, $B.HCl.2H_2O$, crystallises in four-sided prisms; the nitrate, $B.HNO_3$, in hexagonal prisms, and the aurichloride, $B.HAuCl_4$, in golden-yellow prisms. Jervine dissolves in sulphuric acid, forming a yellow solution which becomes green on warming.

The alkaloid depresses the circulation and is less irritating and less poisonous than cevadine.

Pseudojervine, $C_{29}H_{43}O_7N$, was first obtained by Wright and Luff[4] and later by Salzberger as described under protoveratrine. It crystallises from alcohol in hexagonal tablets, m.p. 300°–307° (304° Bredemann), is slightly soluble in alcohol or benzene, but almost insoluble in light petroleum or ether. It dissolves with a green colour in sulphuric acid. The hydrochloride, $B.HCl.2H_2O$, and sulphate are crystalline, but the aurichloride is amorphous.

The alkaloid is not sternutatory and is stated to be physiologically inactive.

[1] *Trans. Chem. Soc.* 1879, **35**, 405.
[2] Salzberger, *Arch. Pharm.* 1890, **228**, 462.
[3] *Apoth. Zeit.* 1906, **21**, 41, 53.
[4] *Loc. cit.*

Rubijervine, $C_{26}H_{43}O_2N.H_2O$, also obtained by Wright and Luff and subsequently prepared by Salzberger as described under protoveratrine, crystallises in prisms, m.p. 240°–246° (234° Bredemann), somewhat resembling those of jervine.

The alkaloid dissolves in sulphuric acid with a yellow colour passing into orange-red. When warmed with hydrochloric acid it gives a reddish-violet coloration. It is readily distinguished from jervine by the solubility of its sulphate in water.

It is not sternutatory.

Protoveratrine, $C_{32}H_{51}O_{11}N$, was first isolated by Salzberger from the rhizome of *Veratrum album*, and is stated to be the substance to which the toxic properties of the rhizome are principally due. It is prepared by percolating the finely powdered drug first with light petroleum to remove fat, and then with 80 per cent. alcohol. The latter is distilled off under reduced pressure and the residual extract dissolved as far as possible in very dilute acetic acid, and to the decanted clear solution is added metaphosphoric acid so long as any precipitate (which contains insoluble phosphates of jervine and rubijervine) is formed. The filtrate is made alkaline with ammonia and extracted first with ether and then with chloroform. The ethereal extract on distillation leaves a crystalline residue of protoveratrine which may be purified by recrystallisation from absolute alcohol. The chloroform extract contains pseudojervine.

Protoveratrine crystallises in characteristic rectangular tablets m.p. 245°–250°, and is sparingly soluble in chloroform, dry alcohol, or boiling ether. The aurichloride, $B.HAuCl_4$, is an unstable crystalline precipitate.

The alkaloid dissolves in sulphuric acid, giving a green colour passing into blue and violet. Hydrochloric and phosphoric acids give a cherry-red solution which slowly develops an odour of *iso*-butyric acid.

Protoveratrine closely resembles cevadine in physiological action, but differs from it (1) in not prolonging muscular contraction, though it intensifies it; (2) in not ultimately paralysing the sensory

nerve terminations, though, like cevadine, it at first stimulates them. It is more poisonous than cevadine. The lethal dose for rabbits by subcutaneous injection is 0·5 mg. per kg. of body weight.

Protoveratridine, $C_{26}H_{45}O_8N$, according to Salzberger, probably does not occur in the rhizome, but is formed by the action of barium hydroxide on protoveratrine (*see* p. 442). It crystallises in rectangular tablets, m.p. 265°, and is intensely bitter, but not poisonous. It gives a violet colour changing to red with sulphuric acid, and a carmine-red coloration with hydrochloric acid.

Bredemann[1] has obtained a sixth alkaloid, m.p. 239°–241°, crystallising in spherical aggregates of needles, but the remaining alkaloids of white hellebore have not been completely characterised.

ALKALOID OF *WITHANIA SOMNIFERA*

This plant has been stated to possess sedative and hypnotic properties and to contain an alkaloid, "somniferine."[2] The whole plant has been examined by Power and Salway,[3] who obtained from the root a small quantity of an amorphous alkaloid yielding an amorphous aurichloride, m.p. 185°. The alkaloid on boiling with alcoholic potassium hydroxide gave a crystalline base, $C_{12}H_{16}N_2$, which crystallised from dilute alcohol in glistening leaflets, m.p. 116°, which can be sublimed. Both the alkaloid and alcoholic extracts of the plant were found to be physiologically inactive to dogs.

ALKALOID OF *WRIGHTIA ANTIDYSENTERICA*

Conessine (*Wrightine*), $C_{12}H_{20}N$, was isolated in 1858 by Haines,[4] and independently in 1864 by Stenhouse[5] from the bark and seed of the Indian plant *Wrightia antidysenterica* (*Holarrhena antidysenterica*). It has since been obtained by Polstorff and Schirmer from the bark of the African plant *Holarrhena africana*.

The alkaloid crystallises in silky needles, m.p. 122°, and is

[1] *Loc. cit.*
[2] *Amer. Journ. Pharm.* 1891, **63**, 77; Trebut, *Lancet*, 1886, **1**, 467.
[3] *Trans. Chem. Soc.* 1911, **99**, 490. [4] *Pharm. Journ.* 1865 [ii], **6**, 432.
[5] *Ibid.* 1864 [ii], **5**, 493.

soluble in organic solvents, but sparingly so in water. The hydrochloride, $B.HCl.H_2O$, crystallises in small needles; the platinichloride, $B_2.H_2PtCl_6.\frac{1}{2}H_2O$, in yellowish-red needles, and the aurichloride, $B.HAuCl_4.3\frac{1}{2}H_2O$, in golden-yellow needles. The methiodide, $B.CH_3I.1\frac{1}{2}H_2O$, crystallises from water in large tablets and on treatment with silver oxide yields methylconessine. On oxidation with potassium iodate in acid solution oxyconessine (oxywrightine), $C_{24}H_{42}O_2N_2$, is formed. When dissolved in strong sulphuric acid conessine gives a yellowish-green solution changing to bright purple.

Conessine is acrid to the taste and is poisonous. In physiological action it resembles morphine, producing narcosis and death from paralysis of the respiratory centre.

ALKALOIDS OF *ZANTHOXYLUM OCHROXYLUM*

According to Leprince[1] the bark of this South American plant contains two alkaloids, allied to berberine.

α-Xantherine, $C_{24}H_{36}O_6N$, crystallises from benzene in colourless needles, m.p. 186°–187°, and becomes yellow on exposure to air. The alkaloid paralyses the intracardial nervous system.

β-Xantherine differs from the α-isomeride mainly in the greater solubility of the hydrochloride in water.

ALKALOID OF *ZANTHOXYLUM SENEGALENSE*

Artarine, $C_{21}H_{23}O_4N$, was obtained by Giacosa and Soave[2] from the bark of *Zanthoxylum senegalense*. It is an amorphous, greyish-red powder, insoluble in water, but soluble in boiling alcohol; the hydrochloride, $B.HCl.4H_2O$, forms slender needles, m.p. 194°; the platinichloride, $[B.HCl]_2.PtCl_4$, bright yellow needles, m.p. above 290°, insoluble in water or alcohol.

The bark contains a small quantity of a second alkaloid of unknown composition.[3]

[1] *Bull. Sci. Pharm.* 1912, **18**, 337.
[2] *Gazz. Chim. Ital.* 1889, **19**, 303. [3] *Ibid.* 1887, **17**, 362.

MISCELLANEOUS ALKALOIDS

In the following table are given references to occurrences of alkaloids, not yet fully characterised :

Plant	Nature of Alkaloid	Reference
Agaricus phalloides	——	Kobert, *Abstr. Chem. Soc.* 1900, ii, 156
Anacyclus Pyrethrum	Resembles piperovatine, p. 38	Dunstan and Garnett, *Trans. Chem. Soc.* 1895, **67**, 100
Anchusa officinalis	Consolidine (paralyses central nervous system) Cynoglossine (B.HCl crystalline), paralyses peripheral nerves	Greimer, *Arch. Pharm.* 1900, **238**, 505
Anona muricata	Amorphous	Callan and Tutin, *Pharm. Journ.* 1911 [iv], **33**, 743
Bryonia dioica	Amorphous	Power and Moore, *Trans. Chem. Soc.* 1911, **99**, 937
Carum Petroselinum (Common parsley)	Pyrrole base, volatile	Pictet and Court, *Bull. Soc. chim.* 1907 [iv], **1**, 1001
Ceanothus americanus	Two crystalline alkaloids, m.p. 255° and m.p. 200°	Gordin, *Pharm. Rev.* 1900, **18**, 266
Cereus pecten aboriginum	Pectenine ; crystalline hydrochloride ; tetanising poison	Heyl, *Arch. Pharm.* 1901, **239**, 451
Cimicifuga racemosa	——	Finnemore, *Pharm. Jrn.* 1910 [iv], **31**, 142
Cynoglossum officinale *Echium vulgare*	Same constituents as *Anchusa officinalis*	*See above*
Erysimum aureum	Toxic (*cf.* p. 377)	Schlagdenhauffen and Reeb, *Compt. rend.* 1900, **131**, 753
Gastrolobium calycinum	Cygnine, $C_{12}H_{22}O_3N_2$; convulsant poison	Mann and Ince, *Proc. Roy. Soc.* 1907, **79**, B, 485
Larix decidua (*L. europœa*)	——	Tschirch and Weigel, *Arch. Pharm.* 1900, **238**, 387

Plant	Nature of Alkaloid	Reference
Lolium temulentum	Temuline, $C_7H_{12}ON_2$; liquid; toxic	Hofmeister, 1892
Lunaria biennis (*L. annua*)	Crystalline, m.p. 220°	Hairs, *Bull. Acad. roy. Belg.* 1909, p. 1042
Myrtus Jambos (*Eugenia Jambos*)	Jambosine; crystalline, m.p. 77°	Gerrard, *Chem. Soc. Abstr.* 1885, p. 396
Nandina domestica	Berberine (p. 285) and nandinine; amorphous, toxic	Eykman, *Chem. Soc. Abstr.* 1885, p. 565
Nymphæa lutea (*Nuphar luteum*)	Nupharine, $C_{18}H_{24}O_2N_2$; amorphous, physiologically inactive	Grüning, *Berichte*, 1883, **16**, 969. *Cf.* Goris and Crété, *Bull. Sci. Pharm.* 1910, Jan.
Oxylobium parviflorum	Lobine, $C_{23}H_{31}O_4N_3$; toxic	Mann and Ince, *Proc. Roy. Soc.* 1907, **79**, B, 485
Palicourea rigida	Crystalline, m.p. 235°, toxic	Santesson, *Arch. Pharm.* 1897, **235**, 143
Picea vulgaris (*P. excelsa*)	——	Tschirch and Brüning, *Arch. Pharm.* 1900, **238**, 616
Pilocereus sargentianus	Pilocereine, $C_{30}H_{44}O_4N_2$; amorphous; m.p. 82–86°; toxic	Heyl, *Arch. Pharm.* 1901, **239**, 451
Pinus pinaster	——	Tschirch and Brüning, *Arch. Pharm.* 1900, **238**, 630
Sarcocephalus Diderrichii (West African boxwood)	Cardiac poison	Gibson, *Bio-chem. Journ.* 1906, **1**, 39
Solanum grandiflorum, var. *pulverulente*	Grandiflorine; toxic	Freire, *Compt. rend.* 1887, **105**, 1074
Spigelia marilandica	Spigeline; liquid; toxic	Dudley, *Amer. Chem. Jrn.* 1881, **1**, 150
Valeriana officinalis	——	Chevalier, *Compt. rend.* 1907, **144**, 154
Zygadenus sp.	Toxic; m.p. 134°–135°	Heyl, *Südd. Apoth. Zeit.* 1903, **43**, Nos. 28–30. *Cf.* Mitchell and Smith, *Amer. J. Physiol.* 1911, **28**, 318

APPENDIX

THE following paragraphs give a summary of the more important papers on alkaloids which have appeared while this work was passing through the press :

***nor*Hyoscyamine** (*see* p. 80). This alkaloid is best separated from the hyoscyamine which accompanies it by crystallising the oxalates of the mixed alkaloids from water, that of *nor*hyoscyamine being the less soluble. The alkaloid crystallises from acetone in colourless prisms, m.p. 140·5°, $[\alpha]_D$ – 23·0° in alcohol, is readily soluble in alcohol or chloroform, less so in ether or acetone, sparingly in water (1 in 270 at 14°). It is a strongly alkaline base and may readily be titrated. The hydrochloride, B.HCl, forms rosettes of needles, m.p. 207°; the sulphate, $B_2.H_2SO_4.3H_2O$, silky needles, m.p. 249°, and the oxalate, $B_2.H_2C_2O_4$, long prisms, m.p. 245°–246°, soluble in water (1 in 20 at 15°). The aurichloride, $B.HAuCl_4$, separates from dilute alcohol in golden-yellow scales, m.p. 178°–179°, and the platinichloride, $B_2.H_2PtCl_6.3H_2O$, crystallises in handsome, reddish-yellow prisms of indefinite melting-point. The picrate forms needles, m.p. 220°. *nor*Hyoscyamine is approximately one-eighth as active as *l*-hyoscyamine in inducing mydriasis in the eye of a cat.[1]

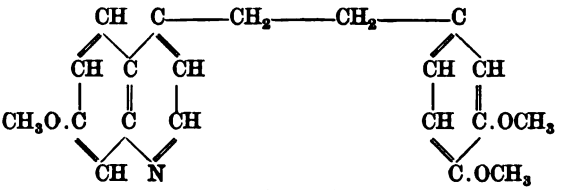
***nor*Atropine.** This alkaloid is produced by the racemisation of *nor*hyoscyamine (*see above*) by dilute alkalis. It crystallises from dry acetone or ether, melts at 113°–114° (*dry*), but also forms a monohydrate, m.p. 73°. The aurichloride, $B.HAuCl_4$, crystallises in dull, opaque yellow leaflets, m.p. 157°, from dilute alcohol: the picrate forms needles, m.p. 227°.[2]

Aconitine (*see* p. 341). Carr has shown[3] that aconitine on oxidation by acid permanganate yields acetaldehyde and oxonitine,

[1] Carr and Reynolds, *Trans. Chem. Soc.* 1912, **101**, 496. [2] *Ibid.*
[3] *Proc. Chem. Soc.* 1912, **28**, 253. *Cf.* Brady, *Proc. Chem. Soc.* 1912, **28**, 289.

$C_{10}H_9O_2NMe,(OBz)(OAc)(OMe)_3$, a neutral crystalline substance which is not acted on by acetic anhydride, methyl iodide or hydroxylamine.

Cusparia Alkaloids (*see* p. 402). Tröger and Kroseberg[1] find that angostura bark contains only three alkaloids, cusparine, galipine, and galipoidine: "galipidine" and "cusparidine" are probably mixtures of the first two. Galipine is colourless when pure and yields colourless salts. With nitric acid it gives nitrogalipine, $C_{20}H_{20}O_3N.NO_2$, m.p. 140°. On oxidation with alkaline permanganate the alkaloid yields veratric acid and 7(?)-methoxyquinolinecarboxylic acid. The following formula is provisionally assigned to the alkaloid; the position of the —OCH_3 group in the quinoline nucleus is uncertain:



Cusparine

Harmaline and Harmine (*see* p. 418). Fischer and Boesler have shown[2] that harmaline readily reacts with diazonium salts to form bisazo derivatives, and that it can be nitrated and sulphonated directly. Harmine does not react in these ways. Perkin and Robinson[3] find that harmaline condenses with benzaldehyde, giving a quantitative yield of benzylidenediharmaline [microcrystalline, m.p. 245° (*decomp.*)], whereas harmine reacts with benzaldehyde less readily, giving benzylideneharmine, which crystallises from alcohol in pale yellow prisms, m.p. 191°–192°, shows a violet-blue fluorescence in neutral solvents, and is oxidised by permanganate to *nor*harminecarboxylic acid, $C_{12}H_9ON_2.COOH$, which on heating in glycerol loses carbon dioxide and forms *nor*harmine, $C_{12}H_{10}ON_2$, crystallising from benzene in colourless

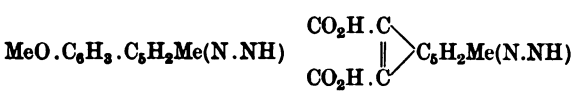
[1] *Arch. Pharm.* 1912, **250**, 494. [2] *Berichte*, 1912, **45**, 1930.
[3] *Trans. Chem. Soc.* 1912, **101**, 1775.

needles, m.p. 218°. Like harmine *nor*harmine gives the pyrrole reaction. This series of reactions indicates the presence of a methyl group in harmaline and harmine, and the property of condensing with aldehydes suggests that this methyl group is in the α-position to a cyclic nitrogen atom as in quinaldine.

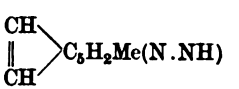
The chief facts established as regards the constitution of harmine are as follows :

(1) Formula, $C_{13}H_{12}ON_2$. (2) Secondary amine. (3) On treatment with hydrochloric acid gives methyl chloride and a phenol, harmol, $C_{12}H_{10}ON_2$, which on oxidation yields the *ortho*-dibasic harminic acid, $C_8H_6N_2(COOH)_2$, from which, on removal of the carboxyl groups, apoharmine, $C_8H_8N_2$, is formed. Harminic acid probably does not contain a carboxyl group in the α-position to a nitrogen atom, since it gives no coloration with ferrous sulphate. (4) Harmine, $C_{13}H_{12}ON_2$, results from the gentle oxidation of harmaline, $C_{13}H_{14}ON_2$, and the latter on treatment with nitric acid gives first nitroharmaline and eventually *m*-nitroanisic acid and harminic acid, $C_8H_6N_2(COOH)_2$ (*see above*).

These facts are explained by the following extended formulæ :



Harmine *Harminic acid*

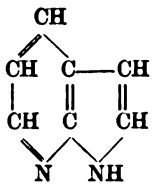


Apoharmine

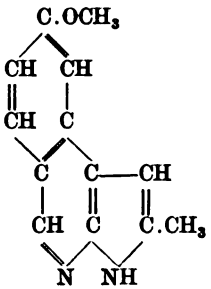
which make harmine the methylmethoxybenzo derivative of a base $C_7H_6N_2$, which Perkin and Robinson call apoharmyrine. The latter, as illustrated by the properties of apoharmine, which must be α-methylapoharmyrine, contains an : NH group and is very stable towards oxidising agents. These conditions, the same authors suggest,[1] are met by representing apoharmyrine as consisting of fused pyrrole and pyridine nuclei. Of the possible dicyclic

[1] *Loc. cit.* *Cf.* Hasenfratz, *Compt. rend.* 1912, **155**, 284.

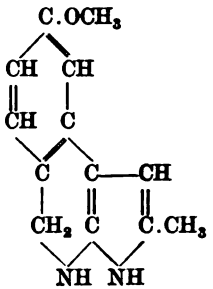
systems thus arrived at they regard I as the most probable, and from this formulæ II and III are advanced as representing harmine and harmaline respectively.



(I) *Apoharmyrine*



(II) *Harmine*



(III) *Harmaline*

The differences in reactivity of harmine and harmaline noted above are assumed to be due to the influence of the pyridine nucleus, which, when partially reduced as in harmaline, is supposed to exert less influence on the neighbouring benzene and pyrrole rings than when unreduced as in harmine. Consequently in harmaline the benzene ring can be nitrated and sulphonated, and the pyrrole ring behaves in the normal way with diazonium salts.

Physiological Action. Gunn finds that in mammals harmine produces a fall in blood-pressure due to weakening of heart contractions, and cardiac failure is the chief cause of death. It stimulates respiration in small doses, but in large doses paralyses it. The minimal toxic dose for rabbits is 0·23 grm. per kilogramme of body weight.[1]

Pareira Root Alkaloids (*see* p. 416). Faltis [2] has stated that commercial "bebeerine sulphate" contains three isomeric alkaloids of the formula $C_{21}H_{23}O_4N$, viz. β-bebeerine, *iso*-bebeerine, and bebeerine-B.

[1] *Trans. Roy. Soc. Edinb.*, 1912, **48**, i, 83.

[2] *Monats.* 1912, **33**, 873. *Cf.* Scholtz, *Arch. Pharm.* 1912, **250**, 684.

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