THE INDOLE ALKALOIDS EXCLUDING HARMINE AND STRYCHNINE

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Alkaloids containing the indole ring system occur widely in Nature, and have so far been isolated from upwards of twenty genera of plants and trees. They include many important and widely used alkaloids, such as the ergot bases, valuable as oxytocic drugs in childbirth, strychnine, valuable as a general tonic and also employed as a vermin killer, yohimbine, used in veterinary medicine as an aphrodisiac, and the extracts of *Rauwolfia serpentina* Benth., used in India for several purposes, chiefly as a sedative. In addition, extracts of *Alstonia* barks have been used in the Far East in the treatment of malaria, but pharmacological experiments have shown that this reputation is undeserved.

The pharmacological properties of all these plant extracts have stimulated chemical investigation into the structures of the alkaloidal constituents, and so far the structures of approximately fifty alkaloids have been completely elucidated.

The object of the present Review is to summarise the present knowledge of these indole alkaloids. No attempt will be made to cover the field exhaustively, particularly for those groups where work has almost ceased owing to the elucidation of the structures of the alkaloids and their confirmation by synthesis. The alkaloids of *Peganum harmala*, and those of the *Strychnos* species which will be reviewed elsewhere, have been omitted entirely from the discussion; so have the alkaloids of the *Amaryllidaceæ* (*e.g.*, lycorine), *Erythrina* (*e.g.*, β-erythroidine), and *Cryptocarya bowiei* (*e.g.*, cryptowoline iodide), which, although they may be regarded as containing a hydroindole structure, are not related biogenetically to the remaining indole alkaloids, since they are probably formed in the plant from dihydroxyphenylalanine and not from tryptophan.

Activity in certain fields, for example, the *Yohimbe* and *Rauwolfia* groups, has been intense during the last five years, and substantial contributions have been made to our knowledge of the alkaloids occurring in the plants of the species, and their structures. Hence, emphasis will be given here to the recent developments in these series. Papers available up to July 1st, 1955, have been covered.

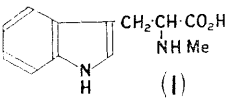
A brief and authoritative account of the structural relations and probable course of the biosynthesis of these alkaloids has been given by Sir Robert Robinson in the recently published Weizmann lectures.[1] For a comprehen-

[1] Robinson, "The Structural Relations of Natural Products", Oxford Univ. Press, 1955.

sive account of the earlier work on the indole alkaloids the reader is referred to Volume II of " The Alkaloids ".[2]

Simple Indole Derivatives.—Indole itself occurs in certain plants, and has been obtained from the distilled oil of jasmine flowers and from the decaying wood of *Celtis reticulosa*. However, it is not a true alkaloid, and probably arises by degradation of more complex indole derivatives, *e.g.*, tryptophan.

Four comparatively simple, monosubstituted indole bases have been isolated from natural sources. They are abrine (I) [3] from the seeds of *Abrus precatorius* L., hypaphorine (II) [4] from the seeds of various *Erythrina* species, gramine (III) [5] from barley leaves and *Arundo donax*, and donaxarine, $C_{13}H_{16}O_2N_2$,[6] also from the leaves of *A. donax*.



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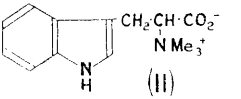

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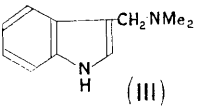

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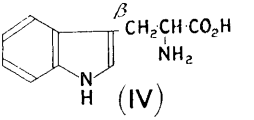


(IV)

The relation of abrine and hypaphorine to tryptophan is evident. Gramine, on the other hand, was formerly regarded as arising by condensation of indole with equivalents of dimethylamine and formaldehyde, a reaction analogous to the usual laboratory preparation. Leete and Marion [7] have shown, however, that, in common with the other indole alkaloids, gramine is produced from tryptophan. In their experiments, tryptophan (IV) containing ^{14}C in the 2- and the β-position was fed to sprouting barley. The gramine isolated after eleven days was shown to possess activity in both labelled positions in the same ratio as in the original tryptophan. Thus it would seem that the β-carbon bond in indole is not ruptured during the transformation.

The structure of donaxarine has not yet been elucidated, and little is known about it beyond its formula.

The Ergot Alkaloids.—The evidence leading to the structures of the ergot alkaloids, and the attempts to synthesise them, have been reviewed [8] by

[2] " The Alkaloids ", Vol. 2, eds. Manske and Holmes, Academic Press, New York, 1952.

[3] Ghatak and Kaul, *J. Indian Chem. Soc.*, 1932, **9**, 383 ; Hoshino, *Annalen*, 1935, **520**, 31 ; Gordon and Jackson, *J. Biol. Chem.*, 1935, **110**, 151 ; Miller and Robson, *J.*, 1938, 1910.

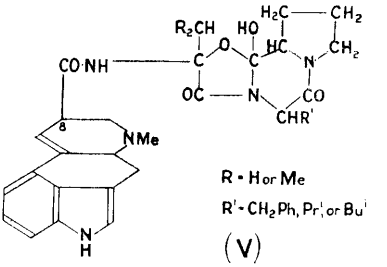
[4] References 11–21 in " The Alkaloids ", Vol. 2 (see ref. 2), p. 481.

[5] Euler and Hellström, *Z. physiol. Chem.*, 1932, **208**, 43 ; Orekhov, Norkina, and Maximova, *Ber.*, 1935, **68**, 436 ; Wieland and Hsing, *Annalen*, 1936, **526**, 188 ; Kuhn and Stein, *Ber.*, 1937, **70**, 567.

[6] Madinaveitia, *J.*, 1937, 1927.

[7] Leete and Marion, *Canad. J. Chem.*, 1953, **31**, 1195.

[8] Stoll, " Progress in the Chemistry of Natural Products ", Vol. IX, Springer Verlag, Vienna, 1952, p. 114 ; Glenn, *Quart. Rev.*, 1954, **8**, 192.



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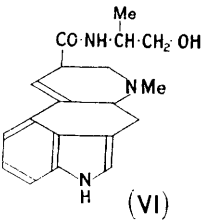

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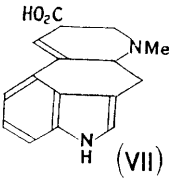

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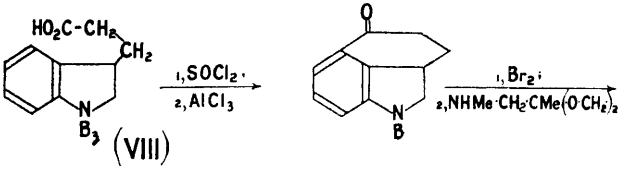

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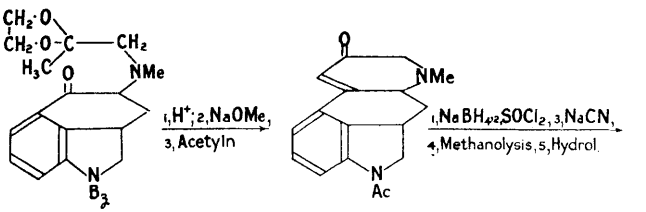
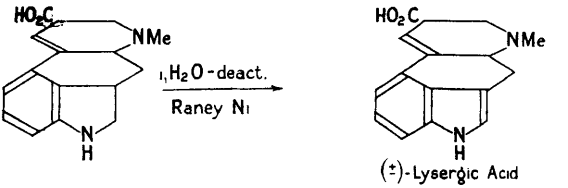
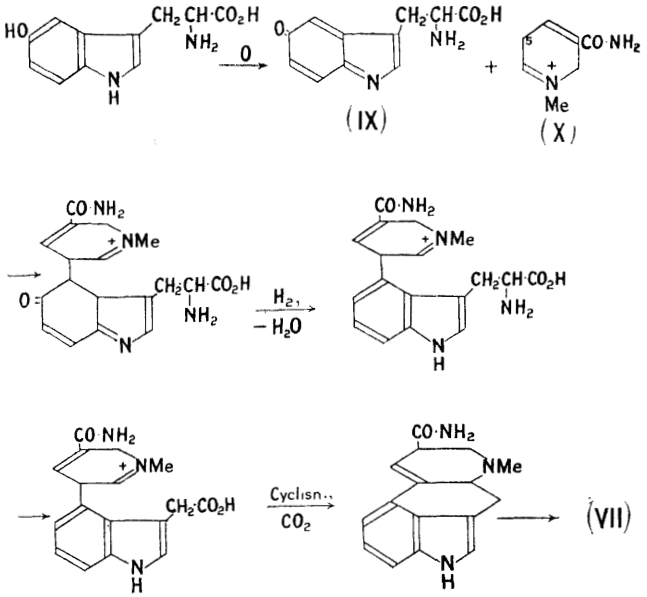




(±)-Lysergic Acid

Stoll and by Glenn, who summarise the evidence available up to the end of 1953, by which time the general formulæ for the alkaloids were firmly established as (V). Ergometrine, the simplest alkaloid of the series, has structure (VI).

Recent work in this field has been concentrated on lysergic acid (VII), the common structural unit of the alkaloids, and has culminated in the elegant synthesis by Woodward and his collaborators of (±)-lysergic acid, by the route shown below, starting from *N*-benzoyl-3-2′-carboxyethyl-2 : 3-dihydroindole (VIII).[9] In order to direct ring closure on to the 4-position of the indole nucleus, a dihydroindole derivative was employed as starting material. The lysergic acid ring system was then synthesised by standard methods, and the indole double bond introduced in the final stage by a catalytic dehydrogenation in neutral aqueous solution at a deactivated Raney nickel catalyst. Both the acid and the hydrazide were completely identified by comparison with naturally occurring samples. Since the hydrazide had already been resolved and converted into ergometrine,[10] this constitutes the first total synthesis of an ergot alkaloid.



Four schemes for the biosynthesis of lysergic acid have been proposed recently. The first, proposed by van Tamelen,[11] involves condensation of dihydronicotinic acid, or its equivalent [*e.g.*, dihydrotrigonelline, or (X)] with a didehydro-5-hydroxytryptophan (IX), the doubly activated 5-position

[9] Kornfeld, Fornefeld, Kline, Mann, Jones, and Woodward, *J. Amer. Chem. Soc.*, 1954, **76**, 5256.

[10] Stoll and Hofmann, *Helv. Chim. Acta*, 1943, **26**, 922, 944.

[11] Van Tamelen, *Experientia*, 1953, **9**, 457.

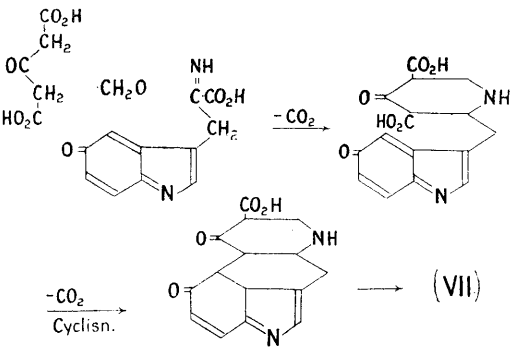
of the former coupling with the 4-position of the latter. Subsequent stages include the removal of the oxygen from the indole ring, transamination, oxidation of the product to an indolylacetic acid derivative, cyclisation, and isomerisation to lysergic acid (see previous page).

This scheme is evidently not rigid, and many variants can be envisaged, for example, the use of 5-hydroxy-3-indolylacetic acid as starting material. Since trigonelline and nicotinic acid [and so presumably dihydrotrigonelline and (X)] can arise in biological systems from tryptophan, and since both tryptophan and 5-hydroxytryptophan are possibly formed from tyrosine, the whole biosynthesis can be achieved by starting from tyrosine ; so it is noteworthy that tyrosine has been found to be associated with the ergot alkaloids.[12]

Sir Robert Robinson,[12] commenting on this biosynthesis, pointed out that although all the stages are feasible, no 5-hydroxy-indole analogues of lysergic acid have been found in Nature, as would be expected if this scheme were correct. In addition, quinones of type (IX) are not known, although this does not mean that they cannot be formed transiently *in vivo*. Harley-Mason's suggestion [13] suffers from these same disadvantages.

Since lysergic acid contains a tryptamine residue, it is reasonable to assume that the two nitrogen atoms of the tryptophan precursor are retained, and are the two nitrogen atoms of lysergic acid. This is the fundamental postulate of the other proposed biosyntheses.

Harley-Mason's scheme consists of condensation of tetradehydro-5-hydroxytryptophan with acetonedicarboxylic acid and formaldehyde by the standard Mannich reaction : [13]



The starting material could, presumably, also be didehydro-5-hydroxytryptophan (IX).

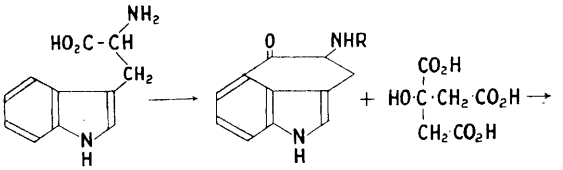
The third mechanism, proposed by Wendler,[14] starts from tryptophan itself, which is presumed to undergo ring closure to a tricyclic amino-ketone. Addition of citric acid, dehydration, and further ring closure then give

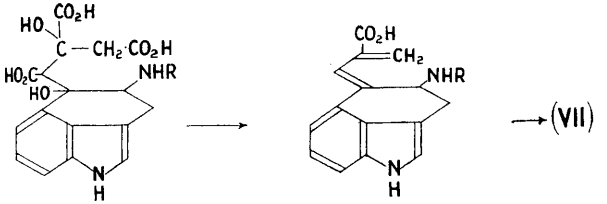
[12] Beadle, Mitchell, and Nye, *Proc. Nat. Acad. Sci. U.S.A.*, 1947, **33**, 155 ; Mitchell and Nye, *ibid.*, 1948, **34**, 1 ; Dalgliesh, *Quart. Rev.*, 1951, **5**, 227 ; Robinson, *Chem. and Ind.*, 1952, 358 ; Fränkel and Rainer, *Biochem. Z.*, 1916, **74**, 167.

[13] Harley-Mason, *Chem. and Ind.*, 1954, 251.

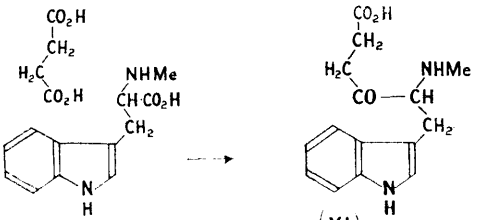
[14] Wendler, *Experientia*, 1954, **10**, 338.

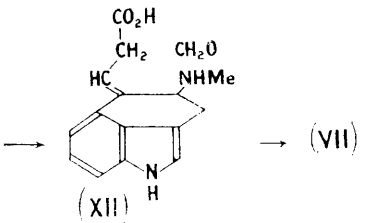
lysergic acid. The first stage, which assumes anionoid reactivity of the 4-position of the indole nucleus, is supported by the results of nitration of 2-methylindole and dihydropentindole, which are nitrated in the 4-position,[15]





and is also a feature of the most recent and most elegant scheme, proposed by Robinson.[1] The initial stage in this biosynthesis involves condensation of tryptophan and succinic acid to give the keto-acid intermediate (XI), which then gives the tricyclic intermediate (XII) by ring closure and dehydration.





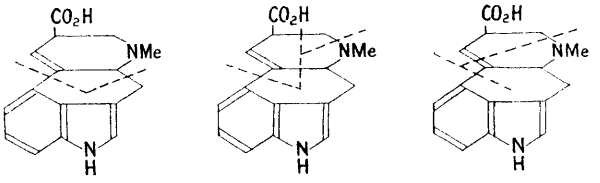
Condensation with formaldehyde (or its equivalent) completes the synthesis. This ketonisation to give the hypothetical intermediate (XII) is analogous to the proved formation of aminolævulic acid from glycine and succinic acid:[16]

$$NH_2{\cdot}CH_2{\cdot}CO_2H + HO_2C{\cdot}CH_2{\cdot}CH_2{\cdot}CO_2H \longrightarrow NH_2{\cdot}CH_2{\cdot}CO{\cdot}CH_2{\cdot}CH_2{\cdot}CO_2H$$

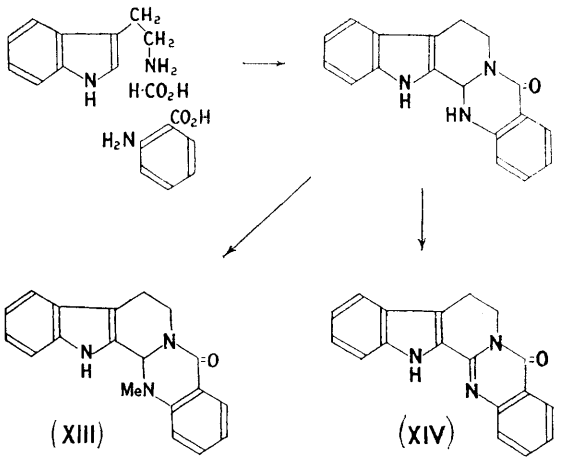
[15] Plant, *J.*, 1929, 2493; Mathur and Robinson, *J.*, 1934, 1415.

[16] Shemin and Russell, *J. Amer. Chem. Soc.*, 1953, **75**, 4873.

These four biosyntheses postulate dissection of the lysergic acid molecule according to the various modes annexed. While it is not possible at present to appraise the relative merits of these theories, they should stimulate investigations involving the application of tracer-element techniques.



Alkaloids of *Evodia rutæcarpa* and *Cryptolepis* spp.—Condensation of tryptamine with its biological degradation product, anthranilic acid, and formaldehyde or formic acid, leads to the alkaloids evodiamine (XIII) and rutæcarpine (XIV), which occur in the Chinese drug, wü chü yü, the dried fruit of *Evodia rutæcarpa*. These formulæ were proposed by Asahina, and have been amply confirmed by synthesis.[17]

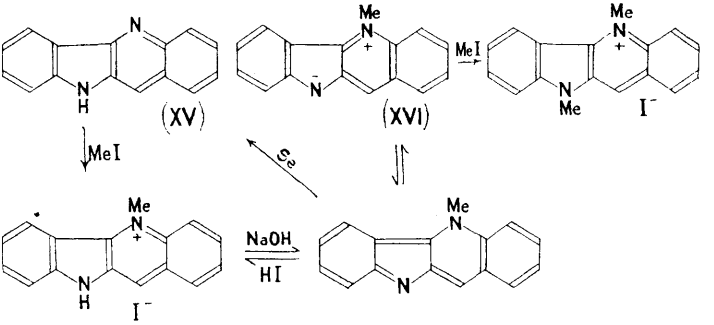


Cryptolepine, $C_{16}H_{12}N_2$, was originally isolated by Clinquart [18a] from *Cryptolepis triangularis* N. E. Br., and differs from all known alkaloids in that it is dark violet, giving rise to yellow salts. The constitution was elucidated by Gellert, Raymond-Hamet, and Schlittler,[18b] who obtained it from *C. sanguinolenta*. Dehydrogenation by selenium gave a colourless

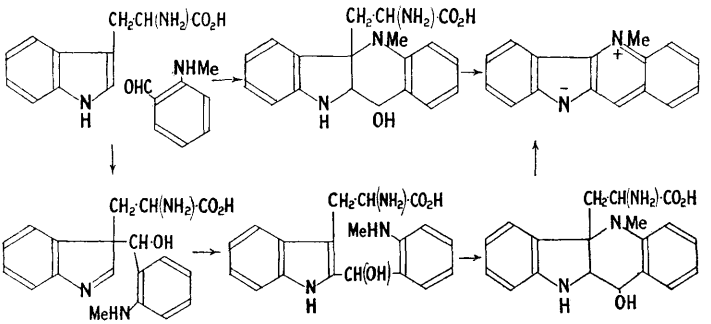
[17] Asahina and Kashiwaki, *J. Pharm. Soc. Japan*, 1915, **405**, 1293 ; Asahina, *ibid.*, 1924, **503**, 1 ; Asahina, Irie, and Ohta, *ibid.*, 1927, **543**, 51 ; Asahina, Manske, and Robinson, *J.*, 1927, 1708 ; Asahina and Ohta, *J. Pharm. Soc. Japan*, 1928, **48**, 313 ; *Ber.*, 1928, **61**, 319 ; Ohta, *J. Pharm. Soc. Formosa*, 1938, **51**, 2 ; *J. Pharm. Soc. Japan*, 1940, **60**, 311 ; Schöpf and Steuer, *Annalen*, 1947, **558**, 124.

[18] (*a*) Clinquart, *Bull. Acad. med. belges*, 1929, **9**, 627 ; (*b*) Gellert, Raymond-Hamet, and Schlittler, *Helv. Chim. Acta*, 1951, **34**, 642.

base, $C_{15}H_{10}N_2$, which was converted into cryptolepine hydriodide by reaction with methyl iodide, showing that the degradation simply involved removal of a methyl group from a nitrogen atom. The parent ring system was identified as quindoline (XV), which was already known. Hence cryptolepine hydriodide is quindoline methiodide, and cryptolepine is (XVI).



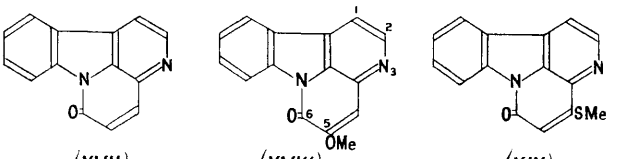
It is tempting to explain the origin of this alkaloid in the plant by condensation of tryptophan with anthranilic acid or *o*-aminobenzaldehyde, followed by loss of the ethanamine side chain, but there is little or no evidence at present to indicate that such a course of reaction is possible. There is no doubt that the mechanism of formation is much more complex, and it may involve preliminary condensation of the aldehyde at the 3-position of the indole nucleus, followed by rearrangement and cyclisation, with elimination of the ethanamine side chain :



Alkaloids of Australian *Rutaceæ*.—The Australian rain-forest tree, *Pentaceras australis* Hook, has yielded three alkaloids, containing a ring system not hitherto found in Nature.[19] The alkaloids have been shown by Price and his co-workers to be 6-oxocanthine (XVII) and its 5-methoxy- (XVIII) and 4-methylthio-derivative (XIX). The first two alkaloids occur in the leaves of the plant, whereas the first and the last are present in the wood.

[19] Haynes, Nelson, and Price, *Australian J. Sci. Res.*, 1952, **5**, *A*, 387 ; Nelson and Price, *ibid.*, pp. 563, 768.

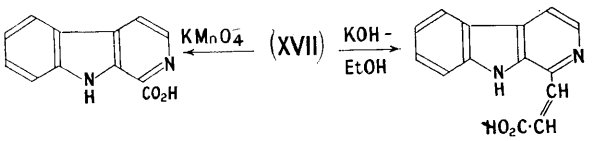
Oxidation of 6-oxocanthine gave β-carboline-1-carboxylic acid (XX), which was readily identified, and hydrolysis gave the acrylic acid derivative



(XVII) (XVIII) (XIX)

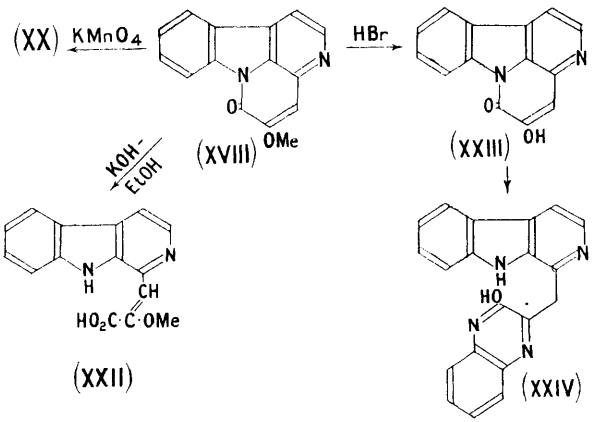
(XXI), which was obtained in both *cis*- and *trans*-forms. As expected, only the former of these was reconvertible into the alkaloid.

The second alkaloid, 5-methoxy-6-oxocanthine also gave β-carboline-1-carboxylic acid on oxidation, and a β-carbolinylacrylic acid derivative



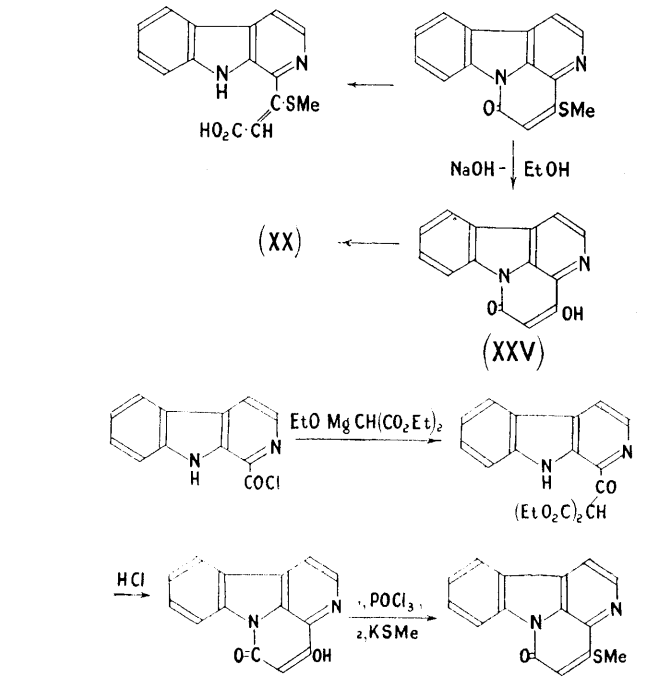
(XX) (XXI)

(XXII) on hydrolysis, which was easily reconverted into the alkaloid. Hence the methoxyl group must be at position 4 or 5. Hydrogen bromide demethylated the alkaloid to anenol (XXIII), which readily condensed with *o*-phenylenediamine to give the quinoxaline (XXIV), showing that the methoxyl group is at position 5.



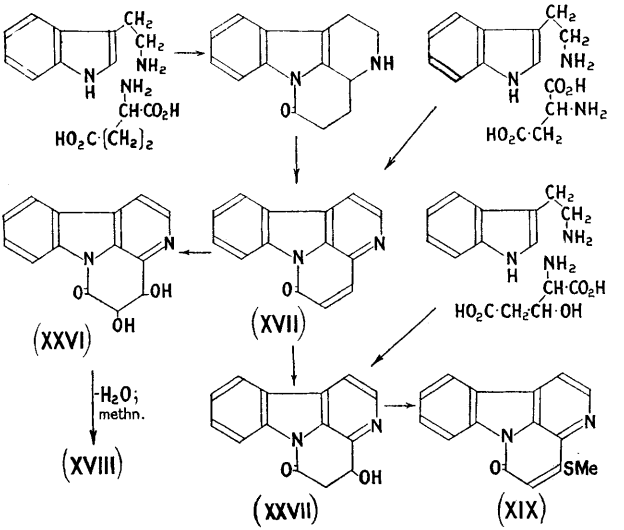
(XXII) (XXIV)

The third alkaloid isolated from this plant is unique in that it contains sulphur. It is slowly attacked by alcoholic alkali to give an acidic substance (XXV) and methanethiol. The acidic substance, which gave β-carboline-1-carboxylic acid on oxidation, did not condense with *o*-phenylenediamine, and hence the second oxygen atom and the methylthio-group in the alkaloid must be at position 4. This was proved by synthesis of the derivative



(XXV), and the alkaloid itself, from β-carboline-1-carboxylic acid, by the annexed reactions.

Biogenetically these alkaloids could arise by condensation of tryptamine with glutamic or hydroxyglutamic acid. The former condensation leads to

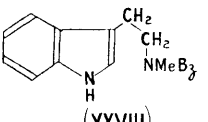


hexahydro-6-oxocanthine, which is then oxidised to 6-oxocanthine, or to 5-methoxy-6-oxocanthine (*via* XXVI) which on methylation gives the alkaloid, 5-methoxy-6-oxocanthine. The second condensation leads directly to 4-hydroxy-6-oxocanthine (XXVII), which can be converted by oxidation and substitution of a methylthio-group for a hydroxyl group into the third alkaloid, 4-methylthio-6-oxocanthine. Alternatively, a thio-analogue of hydroxyglutamic acid may be used as starting material.

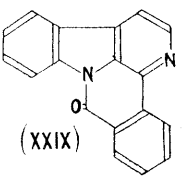
Sir Robert Robinson[1] prefers condensation of tryptamine or tryptophan and aspartic acid to give 6-oxocanthine directly. 5-Hydroxy-6-oxocanthine is then derived as above, and the third alkaloid *via* the hydroxy-ketone (XXVII), the product of hydration of 6-oxocanthine.

Alkaloids of *Calycanthaceæ*.—The alkaloid calycanthine has been isolated from various species of *Calycanthaceæ*, *e.g.*, *C. glaucus* Willd., *C. floridus* L., *C. occidentalis* Hook and Arn., and *Meratia præcox* Rehder and Wilson.[20] A second alkaloid, calycanthidine, has been isolated from *C. glaucus* Willd. Recently, a third alkaloid, folicanthine, has been isolated by Eiter and Svierak from *C. floridus*.[20]

Calycanthine and calycanthidine. Calycanthine, $C_{22}H_{26}N_4$, is a diacidic base, which contains two methylimino-groups. Its ultraviolet spectrum shows that it is a true dihydroindole, and the infrared spectrum shows the presence of an NH group. Quantitative coupling indicates that the molecule contains two reactive *para*-positions, and oxidation with potassium nitrosodisulphonate shows that there are two NH groups attached to benzene rings.[21] Benzoylation and oxidation of calycanthine afford *N*-benzoyl-*N*-methyltryptamine (XXVIII), which was identified by synthesis.[22] When heated with phthalic anhydride, calycanthine yields a substance identical



(XXVIII)



(XXIX)

with that obtained from tryptamine and phthalic anhydride, which has been formulated as (XXIX).[23] Benzoylcalycanthine, when treated with soda lime, affords 2-phenylindole and quinoline but, on the other hand, calycanthine itself gives *N*-methyltryptamine and a base, which is probably a methyl-β-carboline.[24] Degradation with lead, copper oxide, sulphur, or selenium produces calycanine, $C_{16}H_{10}N_2$. Selenium also produces β-carbo-

[20] Eccles, *Proc. Amer. Pharm. Assoc.*, 1888, **84,** 382 ; Manske, *J. Amer. Chem. Soc.*, 1929, **51,** 1836 ; Manske and Marion, *Canad. J. Res.*, 1939, **17,** *B*, 293 ; Barger, Jacobs, and Madinaveitia, *Rec. Trav. chim.*, 1938, **57,** 548 ; Eiter and Svierak, *Monatsh.*, 1951, **82,** 186 ; 1952, **83,** 1453.

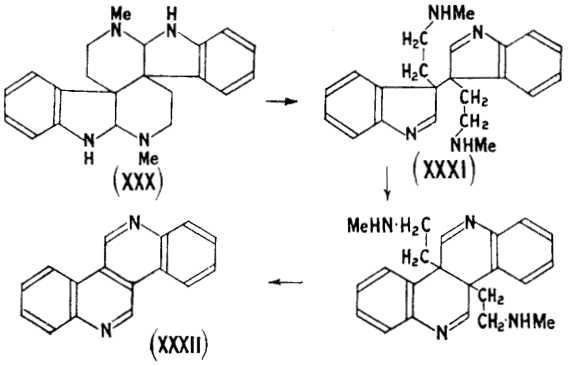
[21] Robinson and Teuber, *Chem. and Ind.*, 1954, 783.

[22] Manske, *Canad. J. Res.*, 1931, **4,** 275.

[23] Marion and Manske, *ibid.*, 1938, **16,** *B*, 432.

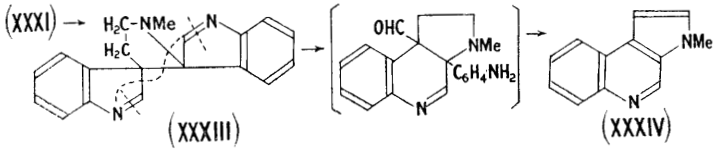
[24] Barger, Madinaveitia, and Streuli, *J.*, 1939, 510.

line, skatole, 3-ethylindole, and lepidine. These confusing results were explained in various ways by different investigators, but none of the earlier formulæ was completely satisfactory. Robinson has proposed a symmetrical oxidatively coupled *N*-methyltryptamine dimer structure (XXX) for calycanthine.[21] There are other possible formulæ involving αα- or ββ-coupling of the two indole nuclei, but this one is preferred. The degrada-



tion product, calycanine, can be explained as arising from fission of the MeN–C–N system, followed by rearrangement of the bisindolenine intermediate (XXXI), loss of the two ethanamine chains, and aromatisation. Calycanine (XXXII) is thus formulated as quinolino(4′ : 3′-3 : 4)quinoline ; this has now been confirmed by synthesis.[24a]

Oxidation of calycanthine with silver acetate produces a pyrroloquinoline, identified by synthesis as 1′-methylpyrrolo(2′ : 3′-3 : 4)quinoline (XXXIV).[25] This could arise from a hexahydro-β-carboline by oxidation and ring closure, a reaction reminiscent of Witkop and Goodwin's ozonolysis experiments in the yohimbine series,[26] but its formation can also be explained on the basis of formula (XXX) for calycanthine. Loss of an ethanamine chain from the intermediate (XXXI), followed by oxidative coupling of the other ethanamine chain to the β-position of the indole nucleus, would give the hypothetical intermediate (XXXIII). Rearrangement to give a quinoline



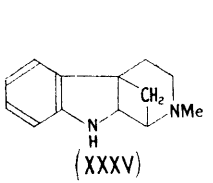
ring system analogous to the above rearrangement of (XXXI), followed by loss of aniline and aromatisation, would give the required pyrroloquinoline. Hence the formation of the substance (XXXIV) does not necessarily imply the presence of a β-carboline or pyrroloquinoline ring system in calycanthine.

[24a] Clark and Woodward, personal communication.

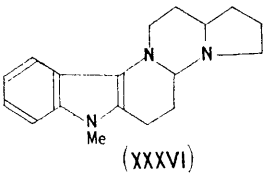
[25] Späth, Stroh, Lederer, and Eiter, *Monatsh.*, 1948, **79**, 11, 17 ; Eiter and Nagy, *ibid.*, 1949, **80**, 607.

[26] Witkop and Goodwin, *J. Amer. Chem. Soc.*, 1953, **75**, 3371.

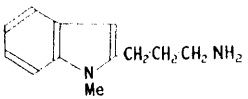
Calycanthidine, $C_{13}H_{16}N_2$, the second alkaloid obtained from *C. glaucus* Willd., is a dihydroindole, containing a NH group linked directly to a benzene ring. It affords a quinone on oxidation, and couples with diazonium salts.[21] Zinc dust distillation gave norharman, and since the alkaloid contains no *C*-methyl group and no double bond, it must be represented by a bridged-ring formula, *e.g.*, (XXXV). The position of the bridge and the indole structure require confirmation.



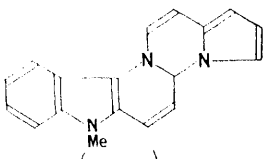
(XXXV)



(XXXVI)



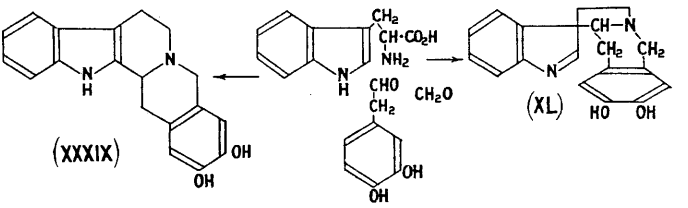
(XXXVII)

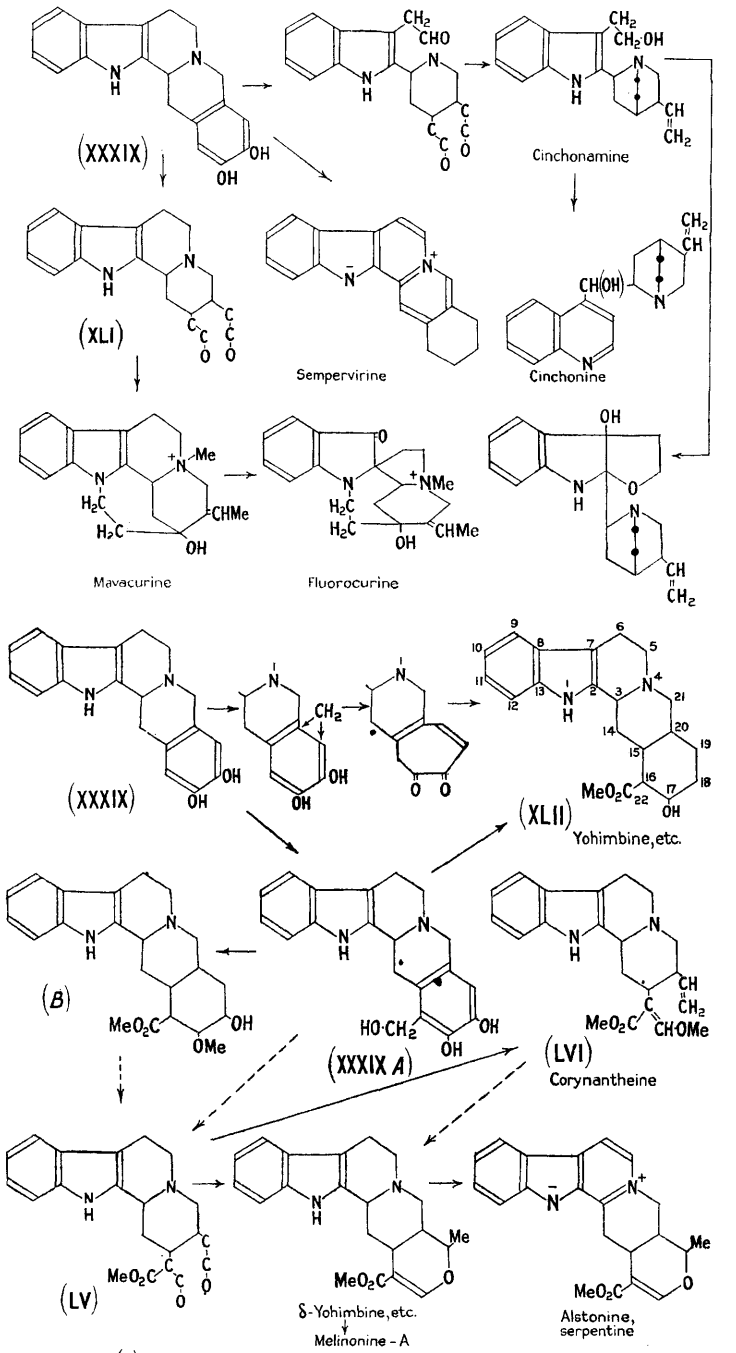


(XXXVIII)

Folicanthine. The constitution (XXXVI) has been suggested for folicanthine, $C_{18}H_{23}N_3$, by Eiter and Svierak, from the following evidence.[20] It was degraded by hydrogen chloride to a base, $C_{12}H_{16}N_2$, which was formulated as 2-3′-aminopropyl-1-methylindole (XXXVII) although it was not unequivocally identified. This indole base was also obtained by acetylation of the alkaloid followed by hydrolysis. In contrast to this, folicanthine itself was unaffected by alkalis. Hofmann degradation of folicanthine methiodide gave a base, $C_{13}H_{18}N_2$, identical with that obtained by methylation of the base (XXXVII), and oxidation of the alkaloid by silver acetate gave dehydrofolicanthine, formulated as (XXXVIII). Eiter and Svierak's formula requires this alkaloid to be an indole derivative containing one *N*-methyl group, but the evidence recorded by these authors would seem to indicate a dihydroindole structure (ultraviolet spectrum) containing two *N*-methyl groups.

The Yohimbine Group of Alkaloids.—By far the majority of the indole alkaloids can be regarded as originating in the plant from tryptophan, dihydroxyphenylalanine, and formaldehyde or their biochemical equivalents.

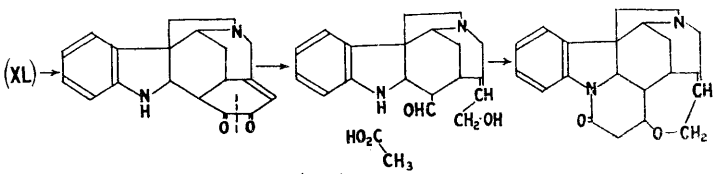



(XXXIX)
Cinchonamine
(XLI)
Sempervirine
Cinchonine
Mavacurine
Fluorocurine
(XXXIX)
(XLII)
Yohimbine, etc.
(B)
(XXXIX A)
(LVI)
Corynantheine
(LV)
δ-Yohimbine, etc.
Melinonine - A
Alstonine, serpentine
(B) → Deserpidine (reserpine and rescinnamine in methoxylated series)

The primary product of this condensation could be either of the dihydric phenols (XXXIX) or (XL), depending on whether reaction occurs at the 2- or the 3-position of the indole nucleus. The former possibility leads to the yohimbine series of alkaloids (called by Robinson the α-series), and may even lead to such apparently unrelated alkaloids as cinchonine, in which the indole moiety has been converted into a quinoline derivative. The principal transformations of the primary condensation product (XXXIX) are given in the accompanying scheme. Occasionally mono- or di-methoxylated derivatives occur in Nature alongside the unsubstituted alkaloids, but their biogenesis offers no difficulty, since we can equally well start with a mono- or a di-methoxytryptamine. It is frequently possible to explain the formation of an alkaloid by alternative routes, and these have in some cases been indicated. One point of unusual interest is the origin of the methoxycarbonyl group in yohimbine and its congeners. It could arise by simple condensation of the intermediate (XXXIX) with formaldehyde, followed by oxidation and methylation. An alternative suggestion, by Robinson, postulates conversion of the intermediate (XXXIX) into a tropolone by introduction of a single carbon atom. Reduction and a benzilic acid type of rearrangement then lead to yohimbine.

It should be noted that, in contrast to many natural processes, this series of transformations appears not to be stereospecific. Thus, for example, nine stereoisomers of yohimbine are known, and these differ, not simply in the orientation of ring substituents, but also in the stereochemistry of the C–D and D–E ring junctions.

The formation of structure (XL) by the alternative condensation of dihydroxyphenylalanine with tryptophan and formaldehyde was postulated by Woodward to account for the biogenesis of the *Strychnos* alkaloids.[27]



(XLA)

Fission of the aromatic ring between the hydroxyl groups gives an intermediate which, on condensation with an acetic acid equivalent, leads to strychnine directly. The probability that this convincing and revolutionary theory was essentially correct was increased when it was applied by Robinson, with marked success, to derive the structure of emetine.[27] It was still further increased when laboratory analogies for the formation of the compound (XL) were realised.[28]

These two reactions, namely, the β-condensation and the fission of the aromatic ring, are probably the key stages in the formation of the other

[27] Woodward, *Nature*, 1948, **162**, 155; Robinson, *ibid.*, p. 524.

[28] Robinson and Saxton, *J.*, 1953, 2596; Woodward, Cava, Ollis, Hunger, Daeniker, and Schenker, *J. Amer. Chem. Soc.*, 1954, **76**, 4749.

dihydroindole alkaloids. Unfortunately, the structures of many of them, *e.g.*, gelsemine, akuammine, and aspidospermine, are still unknown. In these examples, Woodward's theory is used as an invaluable aid in deriving the structures of the alkaloids, to act as a basis for discussion and investigation until further evidence becomes available.

The features of both types of alkaloids may be combined in ajmaline (see below), which results from an internal β-condensation in an intermediate (XLI) of the α-series.

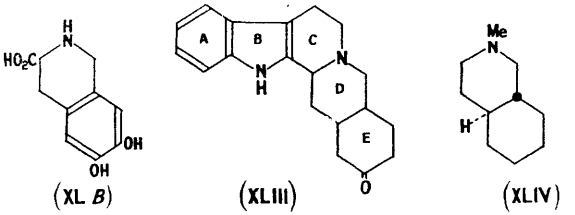
It is necessary to emphasise here that although biogenetic schemes are frequently written with definite chemical substances as intermediates, it is not intended to convey the impression that these specific entities are involved to the exclusion of all others. For example, the use of dihydroxyphenylalanine in the early stages implies the participation of this or of any biochemical equivalent, *e.g.*, dihydroxyphenylacetaldehyde. Similarly, the use of formaldehyde implies the intervention of formaldehyde or any possible equivalent or progenitor, *e.g.*, glycine. The theories are justified by the structural relations observed between the alkaloids, and by the (at present) limited evidence from experiments *in vivo* (*e.g.*, the conversion of tryptophan into gramine in barley). The results of laboratory analogies in this respect (*e.g.*, Robinson's synthesis of tropinone [28a]) are frequently encouraging, although the greatest caution must be exercised in their interpretation and application to reactions *in vivo*. Further, these speculations do not even presume an exact order in which the various stages occur, particularly the simpler ones of methylation or acetylation, which can be expected to proceed at any convenient stage in the biosynthesis. Thus, as Robinson points out,[28b] all the alkaloids in this series contain the " berberine bridge " carbon atom, provided by the formaldehyde equivalent. This may mean the initial condensation of dihydroxyphenylalanine with formaldehyde to give an intermediate of type (XL*B*), which subsequently condenses with tryptophan to yield (XXXIX).

The Alkaloids of Yohimbehe Bark.—Yohimbehe bark is the main source of yohimbine and its congeners, and is obtained from a tree (*Pausinystalia yohimba* Pierre ; syn. *Corynanthe yohimbe* K. Schum.) found in the Cameroons and the French Congo. Included among the yohimbehe alkaloids are those obtained from *Pseudocinchona africana* A. Chev. Of the thirteen alkaloids isolated from these sources, nine are stereoisomers of yohimbine, and by 1950 their structure was firmly established as (XLII). The final link in the chain of evidence leading to this structure, namely, the proof of the position of the hydroxyl group, was provided by Swan, who achieved the total synthesis of yohimbone (XLIII).[29]

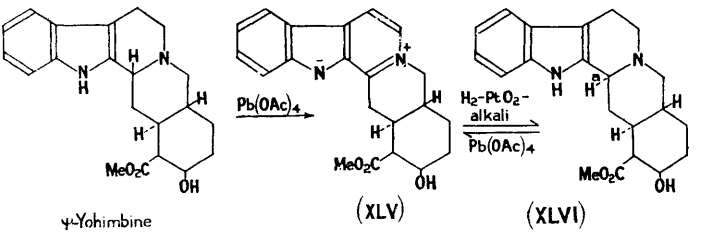
The nuclear structures of the alkaloids having been established, attention was directed towards the configurations of the asymmetric centres. Witkop was the first to adopt this approach, and obtained evidence relating to the stereochemistry of the D–E ring junction by degrading yohimbic acid to an optically active *trans*-decahydro-*N*-methyl*iso*quinoline (XLIV) and 3-vinyl-

[28a] Ref. 1, p. 63. [28b] Ref. 1, p. 124. [29] Swan, *J.*, 1950, 1534.

indole (not isolated). Hence, in yohimbine the rings D and E must be *trans*-fused, provided that no change in stereochemistry has occurred during the degradation.[30]



Utilising this result, and the methods of conformational analysis, Janot and Goutarel and their co-workers have derived the stereochemistry of yohimbine and several of its isomers.[31] Thus, since yohimbine and ψ-yohimbine give the same tetradehydroyohimbine (XLV) with lead tetra-acetate, these two bases differ only in the configuration at position 3. Catalytic reduction of this tetradehydroyohimbine regenerated yohimbine, which is presumably the more stable isomer, and therefore contains the greater number of equatorial carbon–carbon bonds, as shown in (XLVI).



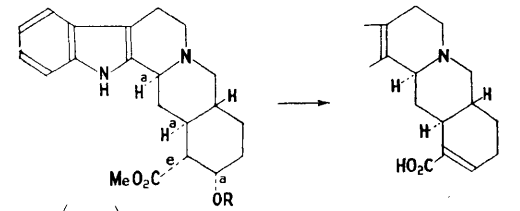
The configurations of the hydroxyl and methoxycarbonyl groups remain to be determined. Since corynanthine can be converted into yohimbine by alkaline hydrolysis and re-esterification, these two substances are identical with the exception of the configuration at position 16. The hydroxyl and the methoxycarbonyl group are therefore *cis* in one isomer and *trans* in the other. The different behaviour of the hydrogen sulphates of yohimbine and corynanthine towards dilute alkali allows the conformations to be determined: yohimbine hydrogen sulphate (XLVII; R = SO_3H) gives an unsaturated acid, whereas corynanthine hydrogen sulphate (XLVIII; R = SO_3H) gives an unsaturated hydrocarbon by simultaneous decarboxylation. Since this reaction proceeds by elimination of axial groups, it may be deduced that the hydroxyl group and the 16-hydrogen atom are in the axial positions in yohimbine, and that the hydroxyl and the methoxycarbonyl group are in the axial positions in corynanthine. This conclusion is confirmed by the readier hydrolysis of the equatorial ester group, *i.e.*, yohimbine

[30] Witkop, *J. Amer. Chem. Soc.*, 1949, **71**, 2559.

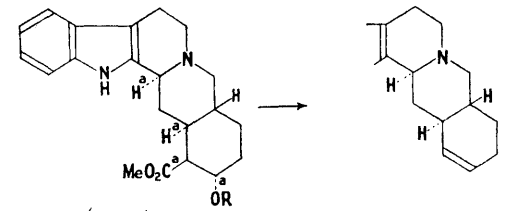
[31] Janot, Goutarel, Le Hir, Amin, and Prelog, *Bull. Soc. chim. France*, 1952, 1085; Le Hir, Janot, and Goutarel, *ibid.*, 1953, 1027; Le Hir and Goutarel, *ibid.*, p. 1023; Bader, Dickel, Huebner, Lucas, and Schlittler, *J. Amer. Chem. Soc.*, 1955, **77**, 3547.

should be more easily hydrolysed than corynanthine, as found by experiment. Hence, yohimbine is (XLVII ; R = H) and corynanthine is (XLVIII ; R = H). Cookson and Klyne have arrived at the same relative configurations, and the latter has also presented evidence that (XLVII) represents the absolute configuration of yohimbine.[32]

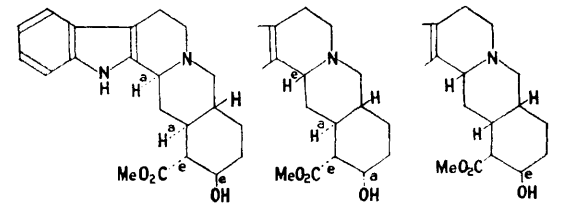
Similar reasoning allows the conformations of β-yohimbine (XLIX), ψ-yohimbine (L), *allo*yohimbine (LI), α-yohimbine (corynanthidine) (LI), and 3-*epi*-α-yohimbine [$C_{(3)}$ epimer of (LI)] to be established, with the exception of the methoxycarbonyl group in the three last-named alkaloids.[31] Thus, derivatives of all four possible yohimbanes have been found in Nature.



(XLVII)



(XLVIII)



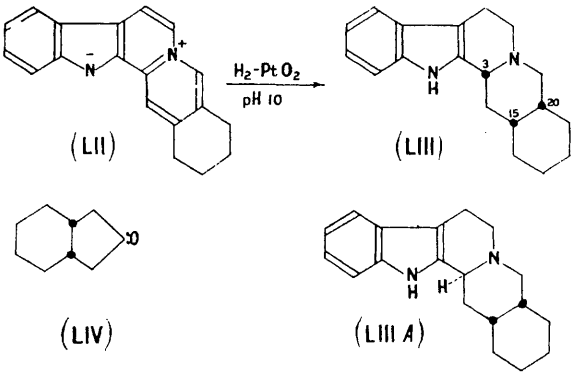
(XLIX) (L) (LI)

Two alkaloids of *Rauwolfia serpentina* Benth.—*iso*rauhimbine [33] and serpine [34]—have also been formulated as stereoisomers of yohimbine. It has been suggested that the latter differs from ψ-yohimbine only in the configuration of the methoxycarbonyl group.

The elucidation of the stereochemistry of these alkaloids stimulated attempts at stereospecific syntheses, and a certain amount of success has

[32] Cookson, *Chem. and Ind.*, 1953, 337 ; Klyne, *ibid.*, p. 1032.
[33] Hofmann, *Helv. Chim. Acta*, 1954, **37**, 314.
[34] Chatterjee and Bose, *Experientia*, 1954, **10**, 246.

already been achieved. Attention was naturally paid initially to the synthesis of the four yohimbanes. *allo*Yohimbane (LIII), the first isomer to be synthesised, had already been obtained by direct hydrogenation of sempervirine (LII),[35] and it was prepared later, together with its stereoisomer, 3-*epiallo*yohimbane (LIII*A*), by synthesis from *cis*-perhydroindan-2-one (LIV).[36] An analogous synthesis starting from *trans*-perhydroindan-2-one, led to (±)-yohimbane [epimeric with (LIII) at $C_{(20)}$].[36] Comparison of synthetic *allo*yohimbane and yohimbane with material obtained from the related alkaloids, demonstrated that the derived stereochemistry of the C–D and D–E ring junctions in these alkaloids was correct.*



Corynantheine, δ-yohimbine, and their derivatives. Introduction of a carbon atom into the aromatic ring E of the intermediate (XXXIX) followed by conversion into an ester and Woodward-type fission between the hydroxyl groups, leads to a hypothetical intermediate, written formally as (LV), which may be the precursor of corynantheine (LVI) and many alkaloids in which ring E is heterocyclic. Corynantheine, the only tetracyclic alkaloid of this series, may thus be regarded as the biogenetic link between the yohimbine isomers on the one hand, and the δ-yohimbine type, with a heterocyclic ring E, and the cinchonine type, in which further complex transformations have occurred, on the other.

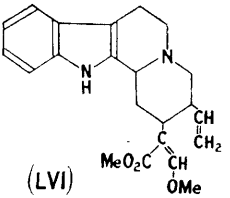
Corynantheine, $C_{22}H_{26}O_3N_2$, obtained from *Pseudocinchona africana*, is a tertiary indole base, which gives alstyrine (LVII) on dehydrogenation by selenium. A whole series of transformations proved conclusively the

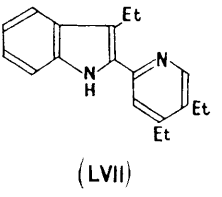
[35] Le Hir, Janot, and Goutarel, *Bull. Soc. chim.* (*France*), 1952, 1091.

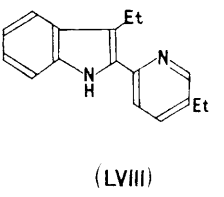
[36] Stork and Hill, *J. Amer. Chem. Soc.*, 1954, **76**, 949; van Tamelen, and Shamma, *ibid.*, p. 950; Janot, Goutarel, Le Hir, Tsatsas, and Prelog, *Helv. Chim. Acta*, 1955, **38**, 1073.

* The assumption that hydrogenation of sempervirine gives a *syn-cis*-product, and hence the accepted stereochemistry at $C_{(3)}$ in *allo*yohimbine, α-yohimbine, 3-*epi*-α-yohimbine, reserpine, deserpidine, and rescinnamine, have been challenged by Janot, Goutarel, Le Hir, Tsatsas, and Prelog, who deduced from a study of the molecular rotation changes observed during dehydrogenation of yohimbane and *allo*yohimbane that these two substances possess the same configuration at $C_{(3)}$.[36] Hence, these authors believe that all the above-mentioned alkaloids are epimers at $C_{(3)}$ of the generally accepted formulations. In the absence of further evidence the earlier structures are used here.

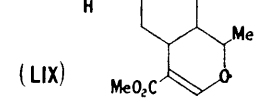
presence of the grouping $MeO_2C{\cdot}C : CH{\cdot}OMe$, and when the base was finally obtained analytically pure, the presence of a vinyl group was also demonstrated. Many early specimens of the alkaloid were contaminated with dihydrocorynantheine, which accompanies it in the plant. The mixture therefore yielded formaldehyde on ozonolysis and acetic acid in the Kuhn–Roth determination. The constitution (LVI) for corynantheine, based on these results by Janot, Goutarel, and Prelog,[37] was confirmed by degradation of the alkaloid to 3-ethyl-4-*iso*propylpyridine and de-ethylalstyrine (LVIII), which were identified by synthesis.[37]

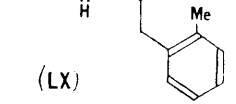

(LVI)

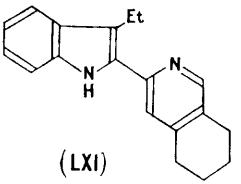

(LVII)

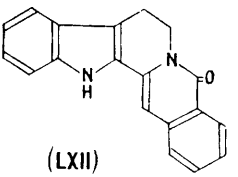

(LVIII)

δ-Yohimbine, $C_{21}H_{24}O_3N_2$, was first isolated from the mother-liquors of yohimbine preparations, and has more recently been obtained from *Rauwolfia serpentina* and named ajmalicine and raubasine.[38] Its ultraviolet spectrum is typical of an indole containing the system $MeO_2C{\cdot}C : C{\cdot}OR$, with maxima at 230 and 290 mμ, and an inflexion near 250 mμ. The infrared spectrum


(LIX)


(LX)


(LXI)


(LXII)

[37] Prelog, Karrer and Enslin, *Helv. Chim. Acta*, 1949, **32**, 1390 ; Chatterjee and Karrer, *ibid.*, 1950, **33**, 802 ; Janot and Goutarel, *Bull. Soc. chim.* (*France*), 1951, 588 ; Janot, Goutarel, and Prelog, *Helv. Chim. Acta*, 1951, **34**, 1207 ; Karrer and St. Mainoni, *ibid.*, 1953, **36**, 127 ; Prelog, Janot, Goutarel, and Mirza, *ibid.*, p. 337 ; Karrer, Schwyzer, and Flam, *ibid.*, 1952, **35**, 851 ; Janot and Goutarel, *Compt. rend.*, 1944, **218**, 852 ; Karrer, Blumenthal, and Eugster, *Helv. Chim. Acta*, 1954, **37**, 787 ; Janot, Goutarel, and Chabasse-Massonneau, *Bull. Soc. chim* (*France*), 1953, 1033 ; Anderson, Clemo, and Swan, *J.*, 1954, 2962.

[38] Siddiqui and Siddiqui, *J. Indian Chem. Soc.*, 1931, **8**, 667 ; Heinemann, *Ber.*, 1934, **67**, 15 ; Raymond-Hamet and Goutarel, *Compt. rend.*, 1951, **233**, 431 ; Goutarel and Le Hir, *Bull. Soc. chim.* (*France*), 1951, 909 ; Klohs, Draper, Keller, Malesh, and Petracek, *J. Amer. Chem. Soc.*, 1954, **76**, 1332 ; Popelak, Spingler, and Kaiser, *Naturwiss.*, 1953, **40**, 625.

confirms the presence of this grouping, with characteristic twin peaks at 5·89 and 6·21 μ. Selenium dehydrogenation gave alstyrine (LVII). Since the alkaloid contains *C*-Me but no isolated double bonds, it must be pentacyclic, and was formulated by Goutarel and Le Hir as (LIX).[38] The production of alstyrine on degradation is characteristic of all the alkaloids in this series in which ring E is opened or heterocyclic, and is in striking contrast to the behaviour of yohimbine and its isomers, which on similar treatment yield a mixture of yobyrine (LX), tetrahydroyobyrine (LXI), and ketoyobyrine (LXII).

The alkaloids mayumbine, from *Pseudocinchona mayumbensis*, and akuammigine, from *Picralima nitida*, are formulated as stereoisomers of δ-yohimbine.[39]

Alkaloids of *Rauwolfia* Species.—These alkaloids are obtained from the various species of *Rauwolfia* and in particular from *R. serpentina* Benth., indigenous to the Dehra Dun valley or the Bihar district of India, and from *R. canascens* Linn. Extracts of *R. serpentina* have been used medicinally for centuries in India. The drug has been prescribed for various disorders, *e.g.*, as a febrifuge, as a cure for dysentery, and as a hypnotic and sedative. It is also recommended for insomnia, hypochondria, and some forms of insanity, but its most important action consists in its ability to reduce the blood pressure. The plant extracts vary somewhat in pharmacological activity depending on their origin, those collected from the Dehra Dun valley being more active as a sedative and less active in the treatment of insanity than those obtained from the state of Bihar. This indicated the presence of several active principles in varying proportions in the different specimens, and stimulated the chemical and pharmacological investigations, which have been intense during the last few years. No less than 24 alkaloids have been isolated from this species alone, although as yet some of them are not well known or characterised. The Table opposite gives a list of alkaloids isolated from *Rauwolfia* species, complete up to October 1st, 1955. This group of alkaloids has recently been reviewed by Schlittler, Schneider, and Plummer, and by Chatterjee.[40]

The versatility of the *Rauwolfia* species in respect of their pharmacological properties is paralleled by their ability as biosynthetical agents. In contrast to yohimbehe bark, which contains only alkaloids of the α-series, extracts of *Rauwolfia* yield alkaloids of both the α- and the β-series, together with mono- and di-methoxylated derivatives of the parent alkaloids. The presence of the unrelated alkaloids, thebaine and papaverine, has even been reported, but this may prove to be due to contamination of the samples by opium: Hofmann, and Chatterjee and Talapatra, report that these two alkaloids were not present in their plant extracts.[41]

[39] Raymond-Hamet, *Compt. rend.*, 1951, **232**, 2354; Janot, Goutarel, and Massonneau, *ibid.*, 1952, **234**, 850; Robinson and Thomas, *J.*, 1954, 3479.

[40] Schlittler, Schneider, and Plummer, *Angew. Chem.*, 1954, **66**, 386; Chatterjee, "Progress in the Chemistry of Natural Products", Vol. X, Springer Verlag, Vienna, 1953, p. 390.

[41] Hofmann, *Helv. Chim. Acta*, 1954, **37**, 849; Chatterjee and Talapatra, *Naturwiss.*, 1955, **42**, 182.

Alkaloids of Rauwolfia *species*

	Formula	M.p.	Rotation †	Source ‡
Ajmalicine (δ-yohimbine, raubasine)	$C_{21}H_{24}O_3N_2$	250—252° *	− 58·1° (C)	*s, c, h*
Ajmaline	$C_{20}H_{26}O_2N_2$	158—160	+ 128 (C)	*s, c, h, d, cf*
*iso*Ajmaline	$C_{20}H_{26}O_2N_2$	264—266 *	+ 72·8 (E)	*s*
*neo*Ajmaline	$C_{20}H_{26}O_2N_2$	205—207		*s*
Ajmalinine	$C_{20}H_{26}O_3N_2$	180—181	− 97 (C)	*s*
Alstonine	$C_{21}H_{20}O_3N_2$	254 *		*o, v, ht*
Aricine	$C_{22}H_{26}O_4N_2$	188 *	− 58·3 (E)	*c, h*
Corynanthine (rauhimbine)	$C_{21}H_{26}O_3N_2$	218—225	− 82 (P)	*s*
Deserpidine (canescine)	$C_{32}H_{38}O_8N_2$	228—232 *	− 137 (C)	*c*
Methyl reserpate	$C_{23}H_{30}O_5N_2$	244—245	− 106 (P)	*s*
Papaverine	$C_{20}H_{21}O_4N$	147	0	*s*
Perakenine		236 *		*p*
*iso*Rauhimbine	$C_{21}H_{26}O_3N_2$	225—228	− 104 (P)	*s*
Raumitorine	$C_{22}H_{26}O_4N_2$	138	+ 60 (C)	*v*
Rauwolfinine	$C_{19}H_{26}O_2N_2$	235—236 *	− 34·7 (E)	*s*
Rauwolscine (α-yohimbine)	$C_{21}H_{26}O_3N_2$	231—232 *	− 40 (E)	*c, h, ht*
Rescinnamine	$C_{35}H_{42}O_9N_2$	224—226	− 98 (C)	*s, v*
Reserpiline	$C_{23}H_{28}O_5N_2$	Amorphous	− 38 (E)	*s, c*
*iso*Reserpiline	$C_{23}H_{28}O_5N_2$	211—212 *	− 82 (P)	*c*
Reserpine	$C_{33}H_{40}O_9N_2$	263	− 117 (C)	*s, c, h, v, ht, t, d, p, m*
Reserpinine (raubasinine)	$C_{22}H_{26}O_4N_2$	238—239	− 117 (C)	*s, c*
*iso*Reserpinine	$C_{22}H_{26}O_4N_2$	225—226 *	− 5 (P)	*c*
Sarpagine (raupine)	$C_{19}H_{22}O_2N_2$	325 *	+ 63 (A)	*s, c, ht*
Semperflorine	$C_{21}H_{26}ON_2$	295 *		*se*
Seredine	$C_{23}H_{30}O_5N_2$	291	− 1 ± 1 (C)	*v*
Serpentine	$C_{21}H_{20}O_3N_2$	158	+ 292 (M)	*s, c, h*
Serpentinine	$C_{21}H_{22}O_3N_2$	263—265	+ 52 (M)	*s, t*
Serpine	$C_{21}H_{26}O_3N_2$	213	+ 70·1 (P)	*s*
Serpinine	$C_{20}H_{24}ON_2$ or $C_{21}H_{26}ON_2$	315 *		*s*
Tetraphyllicine **	$C_{20}H_{24}ON_2$	320—322	+ 21 (P)	*t*
Tetraphylline	$C_{22}H_{26}O_4N_2$	220—223 *	− 73 (C)	*t*
Thebaine	$C_{19}H_{21}O_3N$	195	− 279 (P)	*s*
Yohimbine	$C_{21}H_{26}O_3N_2$	235—237	+ 105 (P)	*s, c, h*
*allo*Yohimbine	$C_{21}H_{26}O_3N_2$	135—136	− 72·7 (P)	*s*
3-*epi*-α-Yohimbine	$C_{21}H_{26}O_3N_2$	181—183	− 90 (P)	*s*
β-Yohimbine	$C_{21}H_{26}O_3N_2$	246—249	− 48 (P)	*c*
γ-Yohimbine	$C_{21}H_{26}O_3N_2$	258—259	− 28·3 (P)	*s*
ψ-Yohimbine	$C_{21}H_{26}O_3N_2$	265—278	+ 27 (P)	*c*
Unnamed		323		*se*

* With decomp.

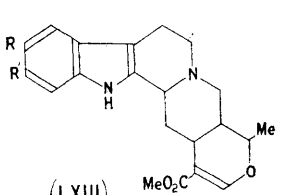
† Solvents : A, aqueous acetic acid ; C = chloroform ; E = ethanol ; M = methanol ; P = pyridine

‡ *c* = *R. canescens.* *ht* = *R. hirsuta.* *s* = *R. serpentina.*
cf = *R. caffra.* *m* = *R. micrantha.* *se* = *R. semperflorens.*
d = *R. densiflora.* *o* = *R. obscura.* *t* = *R. tetraphylla.*
h = *R. heterophylla.* *p* = *R. perakensis.* *v* = *R. vomitoria.*

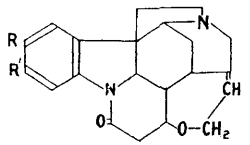
** This is now known to be didehydrodeoxyajmaline ; rauvomitine, a recently isolated alkaloid, is probably its tri-*O*-methylgalloyl derivative (Djerassi, Gorman, Pakrashi, and Woodward, personal communication).

Several of these alkaloids, *e.g.*, yohimbine, *allo*yohimbine, and δ-yohimbine, have already been discussed, and hence need no further comment. The monomethoxy-derivatives of δ-yohimbine are represented by reserpinine

(from *R. serpentina*) and *iso*reserpinine (from *R. canascens*), which are formulated as stereoisomers of 11-methoxy-δ-yohimbine (LXIII; R = H, R′ = OMe).[38, 41, 42] It is noteworthy that reserpinine has also been



(LXIII)



(LXIV): R = R′ = H (LXIVB): R′ = H, R = OMe
(LXIVA): R = H, R′ = OMe (LXIVC): R = R′ = OMe

obtained from *Vinca major* L., collected in Normandy by Janot and Le Men [43]; this is the first reported occurrence of an alkaloid of the yohimbine series in a plant indigenous to Europe. Aricine (10-methoxy-δ-yohimbine) (LXIII, R = OMe, R′ = H) occurs in *R. canascens* and *Cinchona pelletierana* Wedd.,[42, 44] and its stereoisomer raumitorine in *R. vomitoria*.[45] The series is completed by the extraction of reserpiline (from *R. serpentina*) and *iso*reserpiline (from *R. canascens*), which are stereoisomers of 10 : 11-dimethoxy-δ-yohimbine (LXIII, R = R′ = OMe).[42, 46] Thus, we find a quartet of alkaloids in the *Rauwolfia* species completely analogous to the *Strychnos* alkaloids, strychnine (LXIV), α- and β-colubrine (LXIV*A* and *B* respectively), and brucine (LXIV*C*). As with the yohimbines, the stereoisomerism within the series illustrates the fact that the biogenetic pathway is not stereospecific. The *Strychnos* alkaloids, on the other hand, in common with most alkaloids of the β-series, must be produced by a much more selective mechanism, since such stereoisomerism is not encountered.

Taking cognisance of the fact that dehydrogenation reactions frequently participate in natural processes (cf. the biosynthesis of nicotine and papaverine), it would be surprising if none of the alkaloids of this group existed in a more highly oxidised state than that represented by yohimbine or δ-yohimbine. Several such alkaloids are known, which are coloured, and belong to the class of anhydronium bases. Their true constitution is intermediate between the zwitterion structure and the alternative quinonoid form.

Sempervirine (LII) is the simplest of these alkaloids, and occurs in *Gelsemium sempervirens* and *Mostuea buchholzii*.[47] In view of the compre-

[42] Weisenborn, Moore, and Diassi, *Chem. and Ind.*, 1954, 375; Schlittler, Saner, and Müller, *Experientia*, 1954, **10**, 133; Stoll, Hofmann, and Brunner, *Helv. Chim. Acta*, 1955, **38**, 270.

[43] Janot and Le Men, *Compt. rend.*, 1954, **238**, 2550; 1955, **240**, 909.

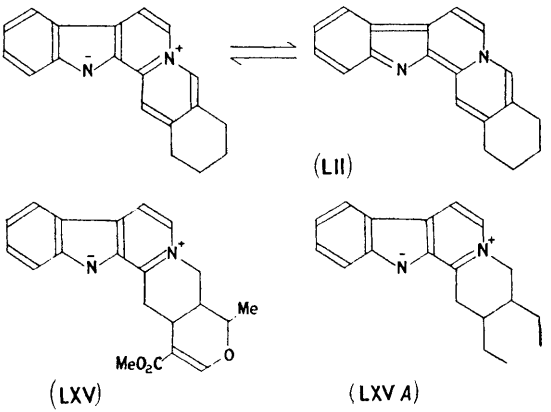
[44] Pelletier and Corriol, *J. Pharm.*, 1829, **15**, 565; Goutarel, Janot, Le Hir, Corrodi, and Prelog, *Helv. Chim. Acta*, 1954, **37**, 1805; Raymond-Hamet, *Compt. rend.*, 1945, **221**, 307.

[45] Goutarel, Le Hir, Poisson, and Janot, *Bull. Soc. chim.* (*France*), 1954, 1481.

[46] Klohs, Draper, Keller, and Malesh, *Chem. and Ind.*, 1954, 1264.

[47] Forsyth, Marrian, and Stevens, *J.*, 1945, 579; Goutarel, Janot, and Prelog, *Experientia*, 1948, **4**, 24; Prelog, *Helv. Chim. Acta*, 1948, **31**, 588; Bentley and Stevens, *Nature*, 1949, **164**, 141; Woodward and Witkop, *J. Amer. Chem. Soc.*, 1949, **71**, 379; Woodward and MacLamore, *ibid.*, p. 379; Gellért and Schwarz, *Helv. Chim. Acta*, 1951, **34**, 779.

hensive range of alkaloids isolated from *Rauwolfia* species, it is perhaps surprising that this comparatively simple one does not occur there. Its structure was derived from a study of its dehydrogenation products (LX—LXII), which are typical of the pentacyclic yohimbane system, and its spectra, and was confirmed by Woodward's synthesis of sempervirine methochloride and sempervirine itself.



Serpentine, serpentinine, and alstonine. The coloured anhydronium base alkaloids are represented in the *Rauwolfia* series by serpentine, serpentinine, and alstonine. The last-named was originally found in *Alstonia constricta* F. Muell., in which it is the principal alkaloid. It is of interest that alstonine has not been found in any of the remaining ten *Alstonia* species which have been investigated.

The structure of serpentinine is at present obscure, although it is evidently closely related to serpentine and alstonine (LXV), which are stereoisomers.[38, 48] The constitutions of these two alkaloids were derived independently, and indeed it was only very recently realised that they are isomeric, since serpentine was initially believed to contain two hydrogen atoms more than alstonine.

The isolation of alstyrine (LVII) on dehydrogenation of serpentine by selenium, and the close similarity of the spectra of the alkaloid and tetradehydroyohimbine (XLV), indicated the presence of the partial structure (LXV*A*). Proof of the presence of an ester group, an ether link, *C*-Me, and finally, a double bond, indicated the formula (LXV), which was proved by identification of *py*-tetrahydroserpentine with δ-yohimbine.[38, 49]

The reputation of *Alstonia* barks in the Far East as an antimalarial and febrifuge stimulated investigation of the alkaloidal constituents in the search for possible quinine substitutes. However, reliable pharmacological experiments have failed to substantiate this claim, and *Alstonia* extracts are no

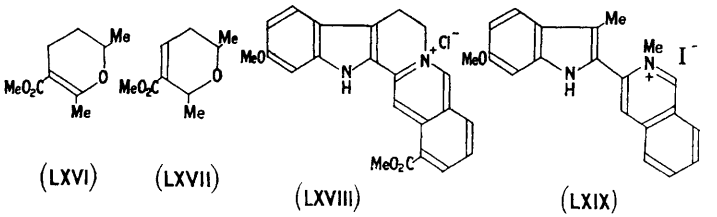
[48] Schlittler, Huber, Bader, and Zahnd, *Helv. Chim. Acta*, 1954, **37**, 1912.

[49] Schlittler and Schwarz, *ibid.*, 1950, **33**, 1463; Bader and Schwarz, *ibid.*, 1952, **35**, 1594.

longer included in the official British Pharmacopœia. These investigations resulted in the isolation of several minor alkaloids, but of these only alstoniline has been studied in any detail.

The presence of the partial structure (LXV*A*) in alstonine was readily proved, but the constitution of ring E presented more difficulty, until it was realised that the anomalous behaviour of tetrahydroalstonol (obtained by reduction to a tetrahydrocarboline and the change ($CO_2Me \longrightarrow CH_2{\cdot}OH$) was due to the presence of the grouping $\cdot O{\cdot}C : C{\cdot}CO_2Me$, which on reduction gave a labile allyl alcohol derivative, which rearranged in acid solution, and yielded ethers with comparative ease.

Comparison of the spectra and reactions of tetrahydroalstonine with those of the model compounds (LXVI) and (LXVII) by Bader proved conclusively the position of the double bond, and the structure of alstonine was firmly established as (LXV).[50]



Reaction of tetrahydroalstonine with methyl chloride yields the quaternary salt, melinonine-A, which occurs in the bark of South American *Strychnos melinoniana* Baillon.[51]

The alkaloid alstoniline, $C_{22}H_{19}O_3N_2{\cdot}OH$, is characterised by the brilliant red colour of its salts, the hydrochloride being obtained directly from the bark, without previous addition of acid. It thus appears that alstoniline exists in Nature as the chloride, a very rare occurrence in the alkaloid series. In spite of the fact that in alstoniline chloride the ring system is in a very highly dehydrogenated state, this compound does not contain the chromophore of alstonine, since the spectra of the two alkaloids are quite different. On the other hand, the spectra of alstoniline and tetrahydroalstoniline resemble those of ketoyobyrine (LXII) and 6-methoxyindole, respectively. Surprisingly, dehydrogenation by selenium gave no identifiable products, but potash fusion gave 2-methyl*iso*phthalic acid. Elderfield and Wythe's tentative formula (LXVIII) for alstoniline chloride is supported by comparison of its spectrum with that of 3-(6-methoxy-3-methyl-2-indolyl)-2-methyl-*iso*quinolinium iodide (LXIX).[52] Hence, in the formation of alstoniline chloride from an intermediate of type (XXXIX), ring C has remained hydroaromatic and ring E aromatic (although this may involve reduction and

[50] Sharp, *J.*, 1934, 287; Sharp, *J.*, 1938, 1353; Leonard and Elderfield, *J. Org. Chem.*, 1942, **7**, 556; Elderfield and Gray, *ibid.*, 1951, **16**, 506; Bader, *Helv. Chim. Acta*, 1953, **36**, 215.

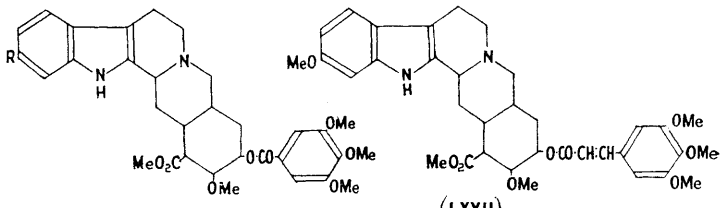
[51] Schlittler and Hohl, *Helv. Chim. Acta*, 1952, **35**, 29.

[52] Hawkins and Elderfield, *J. Org. Chem.*, 1942, **7**, 573; Elderfield and Wythe, *ibid.*, 1954, **19**, 683, 693.

re-aromatisation stages), while ring D has suffered dehydrogenation. The fully aromatic system, in which ring C is also aromatic, has not so far been found in Nature.

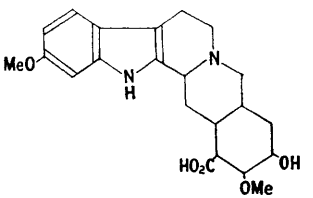
Reserpine, rescinnamine, and deserpidine. Retention of all three substituents in ring E of (XXXIX*A*), followed by further obvious transformations, leads to the important drug, deserpidine (canescine) (LXX), found in *Rauwolfia canascens*. The methoxylated derivative reserpine (LXXI) occurs in *R. serpentina* and several other *Rauwolfia* species, while an analogous derivative of trimethoxycinnamic acid, rescinnamine (LXXII), is also present in *R. serpentina* and *R. vomitoria*.[53] All three alkaloids are extremely valuable hypotensive and sedative agents, and the limited amounts available have led to the prohibition of their export from the Indian sub-continent. In this connection, the isolation of reserpine from Australian *Alstonia constricta* is important, since it may provide an alternative source of this alkaloid for medical use.[54]

Reserpine, $C_{33}H_{40}O_9N_2$, the first of these three alkaloids to be isolated, was easily shown to be an ester alkaloid by hydrolysis to reserpic acid (LXXIII) and trimethoxybenzoic acid. Rescinnamine similarly gave reserpic acid and trimethoxycinnamic acid. Reserpic acid was shown



(LXX) R = H
(LXXI) R = OMe

(LXXII)



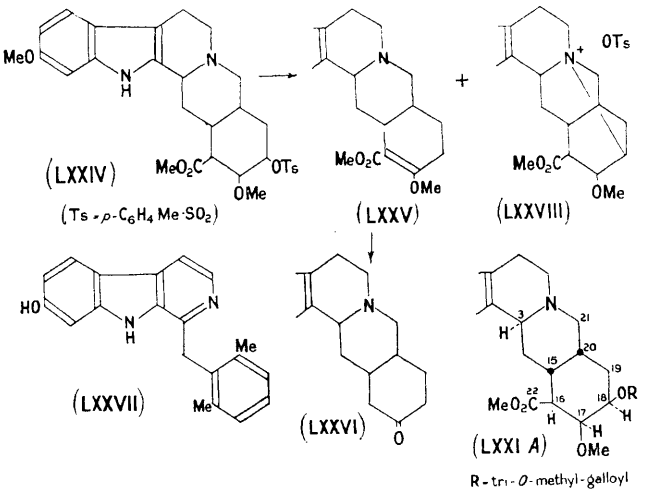
(LXXIII)

to be a derivative of yohimbane by degradation to 4-methoxy-*N*-oxalylanthranilic acid, 5-hydroxy*iso*phthalic acid, and yobyrine (LX), and by its colour reactions, which were characteristic of a tetrahydro-β-carboline. The relative positions of the hydroxyl and the carbonyl group were indicated by formation of a γ-lactone and by isolation of 5-hydroxy*iso*phthalic acid.

[53] Müller, Schlittler, and Bein, *Experientia*, 1952, **8**, 338 ; Haack, Popelak, Spingler, and Kaiser, *Naturwiss.*, 1954, **41**, 214 ; Klohs, Draper, and Keller, *J. Amer. Chem. Soc.*, 1954, **76**, 2843 ; Schlittler, Ulshafer, Pandow, Hunt, and Dorfman, *Experientia*, 1955, **11**, 64 ; Stoll and Hofmann, *J. Amer. Chem. Soc.*, 1955, **77**, 820.

[54] Report from C.S.I.R.O., Melbourne, quoted in the London *Times*, May 26th, 1955.

These results enabled Schlittler and his co-workers and Neuss, Boaz, and Forbes to propose formula (LXXI) for reserpine.[55] The methoxyl group was placed at position 17 for purely biogenetic reasons, but was supported by conversion of methyl *O*-toluene-*p*-sulphonylreserpate (LXXIV) into a derivative (LXXV) containing the chromophore $MeO_2C{\cdot}C : C{\cdot}OMe$, which by acid hydrolysis and decarboxylation yielded reserpone (LXXVI). The position of the carboxyl group, and hence the positions of the other substituents, was proved by degradation of reserpinol (LXXIII ; $CH_2{\cdot}OH$ in place of CO_2H) to 7-hydroxymethylyobyrine (LXXVII), which was identified by synthesis of its methyl ether.[56]

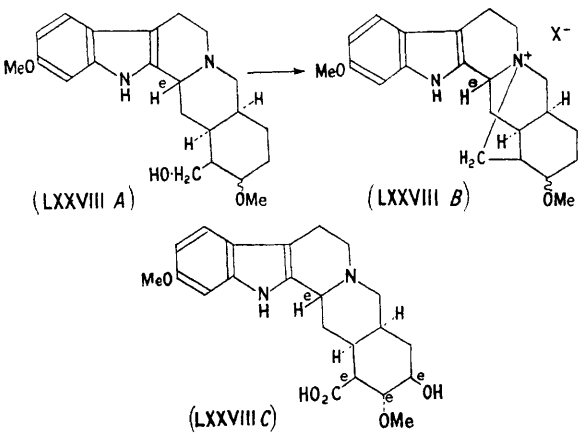


By analogy with this, deserpidine, which exhibits very similar pharmacological properties to reserpine, was formulated as (LXX).[55] The stereochemistry of the ring system was elucidated by conversion of deserpidine into α-yohimbine, a derivative of *allo*yohimbane (LIII). Since the alkaloid is known to have the less stable configuration at position 3, and since one of the stages in this series of transformations involves epimerisation at this centre, deserpidine, and hence reserpine, can be formulated as derivatives of 3-*epialloy*ohimbane. The configurations of the substituents in ring E remain to be determined. Since reserpic acid readily gives a lactone, it can be assumed that the carboxyl and the hydroxyl group are in the *cis*-position relative to one another. These conclusions were supported by Diassi,

[55] Furlenmeier, Lucas, MacPhillamy, Müller, and Schlittler, *Experientia*, 1953, **9**, 331 ; Dorfman, Huebner, MacPhillamy, Schlittler, and St. André, *ibid.*, p. 368 ; Dorfman, Furlenmeier, Huebner, Lucas, MacPhillamy, Müller, Schlittler, Schwyzer, and St. André, *Helv. Chim. Acta*, 1954, **37**, 59 ; Neuss, Boaz, and Forbes, *J. Amer. Chem. Soc.*, 1954, **76**, 2463 ; Schlittler, MacPhillamy, Dorfman, Huebner, and St. André, *ibid.*, 1955, **77**, 1071.

[56] Huebner, MacPhillamy, St. André, and Schlittler, *J. Amer. Chem. Soc.*, 1955, **77**, 472 ; Schlittler, MacPhillamy, Dorfman, Huebner, and St. André, *ibid.*, p. 1071 ; Diassi, Weisenborn, Dylion, and Wintersteiner, *ibid.*, p. 2028.

Weisenborn, Dylion, and Wintersteiner, who obtained the quaternary salt (LXXVIII) in addition to the unsaturated ester by removal of the toluene-*p*-sulphonyl group from methyl *O*-toluene-*p*-sulphonylreserpate. Since quaternary salt formation was assumed to involve inversion at $C_{(18)}$, the 18-oxygen bond must be *cis* with respect to the 15- and 20-hydrogen atoms. Finally, if *trans*-elimination occurs in formation of the unsaturated ester (LXXV), then the 17-methoxyl group must also be *cis* with respect to the hydroxyl and the carboxyl group. Reserpine was therefore completely represented by formula (LXXI*A*).[56] More recent studies, however, have shown that these deductions were not entirely correct. The stereochemistry of the D–E ring junction has been confirmed by Huebner's synthesis of (±)-reserpane [11-methoxy-3-*epialloyo*himbane (LXXVI), with $CO \rightarrow CH_2$],[56a] but the spontaneous quaternisation which occurred on treatment of reserpinol (LXXVIII*A*) or 3-*iso*reserpinol with toluene-*p*-sulphonyl chloride to give the mixed salt (LXXVIII*B*; $X^- = Cl^-$ or OTs^-) indicated that the $C_{(16)}$–$C_{(22)}$ bond must be *trans* with respect to the 15- and 20-hydrogen atoms instead of *cis* as at first assumed.[56b] Since reserpine can be hydrolysed, and methyl reserpate can be treated with sodium methoxide in boiling methanol, without inversion, the methoxycarbonyl group must be equatorial. Application of Hudson's lactone rule to reserpic lactone indicates that the 18-hydroxyl group has the β-configuration, and therefore reserpic acid is correctly represented by (LXXVIII*C*) with reservations with regard to the configuration of the methoxyl group. According to van Tamelen and



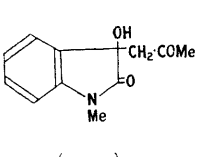
Hance, this methoxyl group is probably *trans* with respect to the 16- and 18-substituents, and the formation of (LXXV) and (LXXVIII) from (LXXIV) probably occurs by neighbouring-group participation. Quaternisation therefore proceeds with double inversion and retention of

[56a] Huebner, *Chem. and Ind.*, 1955, 1186.

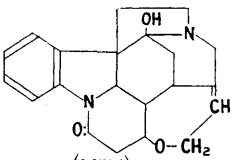
[56b] Huebner and Wenkert, *J. Amer. Chem. Soc.*, 1955, **77**, 4180; Diassi, Weisenborn, Dylion, and Wintersteiner, *ibid.*, p. 4687; van Tamelen and Hance, *ibid.*, p. 4692.

configuration at $C_{(18)}$. The all-*trans*-arrangement also explains the ready isomerisation of reserpine and its analogues to *allo*yohimbane derivatives.[56c]

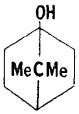
Dihydroindole Alkaloids of the *Rauwolfia* Species.—*Ajmaline.* The principal alkaloid [38] of *Rauwolfia serpentina*, and one of the first to be isolated, is ajmaline, $C_{20}H_{26}O_2N_2$. Its ultraviolet spectrum and colour reactions, the production of *ind*-*N*-methylharman on distillation with zinc dust, and the oxidation of ajmaline with potassium permanganate in acetone to 3-acetonyl-2 : 3-dihydro-3-hydroxy-1-methyl-2-oxoindole (LXXIX) indicate clearly that the alkaloid is a derivative of 2 : 3-dihydro-1-methylindole.[57] Robinson and his co-workers have provided abundant evidence that the second nitrogen atom of ajmaline is contained in a carbinolamine grouping. However, it does not behave as a normal carbinolamine, *e.g.*, ψ-strychnine (LXXX). Thus, the alkaloid shows reducing properties, and



(LXXIX)



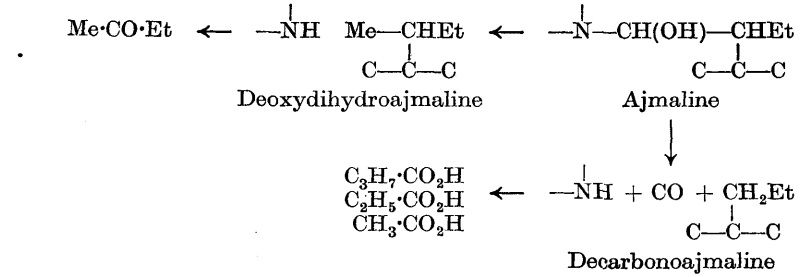
(LXXX)



(LXXXI)

gives an oxime, which, on dehydration and reduction of the nitrile with lithium aluminium hydride, regenerates ajmaline. It can also be reduced by the Huang-Minlon procedure, and on treatment with Raney nickel at 130° loses carbon monoxide [$N{\cdot}CH(OH{\cdot}\dot{C}{\cdot} \longrightarrow {\cdot}NH{\cdot}\ H\dot{C}{\cdot} + CO$], the products from both reactions being secondary bases. On the other hand, the basic strength of ajmaline (pK_a 8·15) is much higher than expected (cf. ψ-strychnine, pK_a 5·60), and it gives *O*-acetyl derivatives without fission of the C–N bond and is not reduced by zinc and acid. These results are interpreted by assuming that in ajmaline the carbinolamine grouping is so situated in a bridged-ring system that participation of the ammonium form (—$^+$NH:CH—) is impossible.[57]

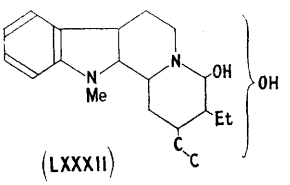
Deoxydihydroajmaline gives ethyl methyl ketone on oxidation, while similar treatment of decarbonoajmaline gives butyric acid (and traces of the lower homologues). These results can be accommodated in the following partial formulæ :



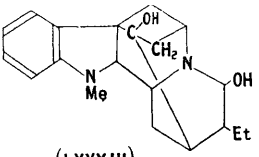
[56c] Wenkert and Liu, *Experientia*, 1955, **11**, 302 ; Huebner, MacPhillamy, Schlittler, and St. André, *ibid.*, p. 303.

The second hydroxyl group in ajmaline was assumed to be tertiary, since, although it can be acetylated, it is comparatively inert towards oxidation. The failure of dehydration and replacement reactions indicates that the hydroxyl group may be situated at the apex of a bridged-ring system, as it is in *apo*camphan-l-ol (LXXXI), which behaves similarly. Dehydrogenation of deoxydihydroajmaline and deoxyajmaline with palladised charcoal at 325° yields bases of the alstyrine type, but their structures have not yet been completely elucidated.

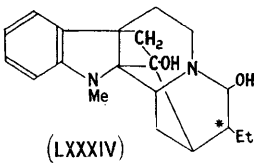
The structure of ajmaline poses a fascinating problem. So far it is the only dihydroindole alkaloid known which gives alstyrine-like degradation products. The above results require that this alkaloid possess the partial formula (LXXXII). By postulating an internal condensation at position 3 of the indole nucleus with one of the fragments of the ruptured benzene ring, Robinson has expanded this to the alternatives (LXXXIII) and (LXXXIV).[57]



(LXXXII)



(LXXXIII)



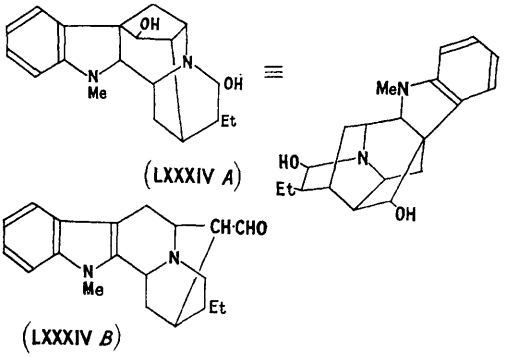
(LXXXIV)

The constitution of ajmaline was finally established in an elegant series of degradations by Schenker and Woodward, who conclusively proved that it possesses the structure (LXXXIV*A*).[58] Oxidation of deoxyajmaline with lead tetra-acetate led to the rapid formation of an indole-aldehyde (LXXXIV*B*), which suggested that one of the carbon atoms attached to position 2 or 3 of the dihydroindole moiety contains the inert hydroxyl group, which must, moreover, be secondary, since the product is an aldehyde and not a ketone. This was confirmed by isolation of a dihydroindole-ketone by the prolonged oxidation of deoxyajmaline with benzophenone and potassium *tert.*-butoxide. Reduction of this ketone by sodium borohydride gave *epi*deoxyajmaline, which gave the same aldehyde (LXXXIV*B*) as deoxyajmaline with lead tetra-acetate. The infrared absorption of the dihydroindole-ketone (carbonyl band at 5·74μ) suggested that the carbonyl group was present in a five-membered ring. These facts, together with biogenetic considerations, led to the formula (LXXXIV*A*) for ajmaline,

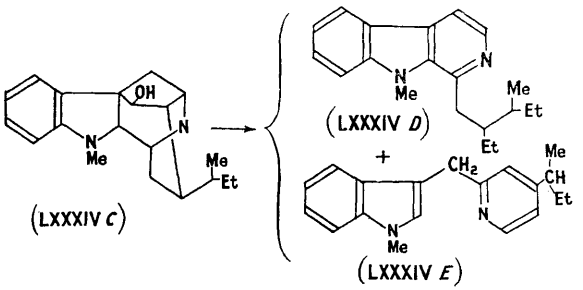
[57] Mukherji, Robinson, and Schlittler, *Experientia*, 1949, **5**, 215 ; Raymond-Hamet, *Compt. rend.*, 1949, **229**, 1165 ; Anet, Robinson, Chakravarti, and Schlittler, *J.*, 1954, 1242 ; Robinson (with Anet, Finch, and Hobson), *Chem. and Ind.*, 1955, 285 ; Finch, Hobson, Robinson, and Schlittler, *ibid.*, p. 653.

[58] Schenker and Woodward, personal communication.

which was soon confirmed by a study of the dehydrogenation of deoxydihydroajmaline (LXXXIV*C*) by palladised charcoal at 250°. The four products isolated included $N_{(a)}$-methylharman, ajarmine (LXXXIV*D*; as racemate), ajmyrine (LXXXIV*E*), and a base, $C_{20}H_{24}N_2$, probably identical



with one of Robinson's dehydrogenation products, which had a spectrum almost superimposable on that of $N_{(a)}$-methylalstyrine. Final confirmation of this structure was obtained by synthesis of ajarmine (LXXXIV*D*) from $N_{(a)}$-methylharman. The isolation of ajarmine and ajmyrine, whose structure (LXXXIV*E*) has now been confirmed by synthesis,[58a] demonstrates conclusively that $N_{(b)}$ in deoxydihydroajmaline is common to two six-membered rings, and that in ajmaline it must be common to three such rings. The formulation of this alkaloid as a product of both α- and β-type biogenetic condensations is thus confirmed.



R. serpentina also contains *iso*ajmaline, and a consideration of the chemical properties, which are identical with those of ajmaline, shows that this compound is simply a stereoisomer of the latter.[57, 59] In accordance with this conception *iso*ajmaline can be produced from ajmaline by the action of heat or alkali, and, since the two alkaloids give the same decarbonoajmaline, they differ only in the configuration of the carbon atom adjacent to the carbinolamine grouping (denoted by an asterisk in LXXXIV).

[58] Woodward and Yang, personal communication.
[59] Siddiqui and Siddiqui, *J. Indian Chem. Soc.*, 1935, **12**, 37.

The existence of *neo*ajmaline, reported by Siddiqui, is now regarded as doubtful. An examination of Siddiqui's specimen by the Oxford workers suggests that it is very probably ajmaline.[60]

Little is known about the remaining dihydroindole alkaloids which have been isolated from *R. serpentina*. Both rauwolfinine, $C_{19}H_{26}O_2N_2$, and serpinine, $C_{20}H_{24}ON_2$ or $C_{21}H_{26}ON_2$, show weak reducing properties, which may indicate the presence of a potential aldehyde group. Rauwolfinine shows certain other superficial resemblances to ajmaline, hence it may possess a similar constitution, and it is significant that in some specimens of *R. serpentina* ajmaline is replaced by rauwolfinine, and the latter is the major alkaloid of the plant growing in North-Western India. It is therefore surprising that it was not isolated earlier.[61]

The Quebracho Alkaloids.—The quebracho alkaloids are obtained from various species of *Aspidosperma* and *Vallesia*, which are hard-wood trees found in South America. Several alkaloids have been isolated from these sources, the four principal ones being aspidospermine, vallesine, quebrachine (yohimbine), and quebrachamine.[62] The remaining alkaloids are aspidosamine, haslerine and quirandine, which were extracted from *Aspidosperma quirandy* Hassler by Floriani,[63] and aspidospermicine, aspidospermatine, and hypoquebrachine, obtained from *Aspidosperma quebrachoblanco* Schlecht.[62] Very little is known about these alkaloids, and indeed the status of two of them as true alkaloids is open to question. Ewins has suggested that aspidosamine and hypoquebrachine are simply decomposition products of aspidospermine.[63]

Aspidospermine, $C_{22}H_{30}O_2N_2$, is the principal alkaloid of the group, and occurs along with quebrachine in *A. quebrachoblanco*, with vallesine in *Vallesia glabra*, and in several related species. It is a monoacidic base, containing methoxyl, methylimino-, and *N*-acetyl groups. Hydriodic acid removes the *N*-acetyl group and ruptures the ether link to give aspidosine, $C_{19}H_{26}ON_2$, which behaves in all respects as an aminophenol. The position of the phenolic hydroxyl is shown by a study of the ultraviolet and infrared spectra of the demethylated alkaloid, which show a marked resemblance to those of vomicine (LXXXV). In particular, there is no hydroxyl band in the infrared spectrum, owing to hydrogen bonding with the acetyl group. The presence of a dihydroindole group is proved by isolation of a mixture of indoles on dehydrogenation with zinc dust or palladium. The first formula (LXXXVI) proposed for aspidospermine explained readily all these experimental results, and was easy to justify biogenetically, but could not account for the occurrence of 3 : 5-diethylpyridine among the products of zinc dust distillation, or for the result of Kuhn–Roth determination, which

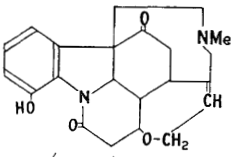
[60] Siddiqui, *J. Indian Chem. Soc.*, 1939, **16**, 421.

[61] Bose, *ibid.*, 1954, **31**, 47, 691 ; *Naturwiss.*, 1955, **42**, 71.

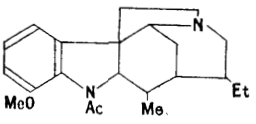
[62] Fraude, *Ber.*, 1878, **11**, 2189 ; 1879, **12**, 1560 ; Schlittler and Rottenberg, *Helv. Chim. Acta*, 1948, **31**, 446 ; Hesse, *Annalen*, 1882, **211**, 249 ; Fourneau and Page, *Bull. Sci. pharm.*, 1914, **21**, 7.

[63] Floriani, *Rev. centro Estud. farm. bioquim.*, 1935, **25**, 373, 423 (*Chem. Abs.*, 1936, **30**, 1415) ; Ewins, *J.*, 1914, **105**, 2738.

indicates only one *C*-Me for deacetylaspidospermine. Indeed, the isolation of 3 : 5-diethylpyridine is unexpected, since all the alkaloids discussed above, whether they belong to the α- or the β-series, are 3 : 4-disubstituted pyridine

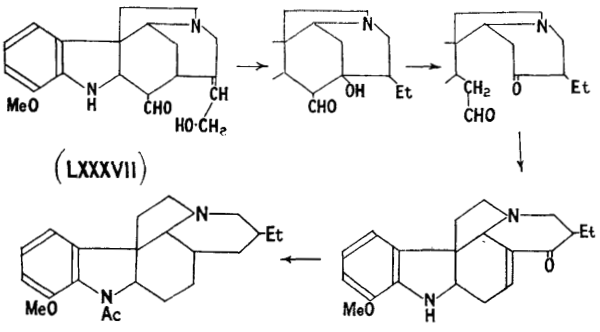


(LXXXV)



(LXXXVI)

derivatives. Witkop's alternative formula (LXXXVII) for aspidospermine explains readily its known behaviour, but its possible biogenesis is not so apparent. Openshaw's ingenious suggestion is that it is formed from a methoxy-aldehyde (LXXXVII) analogous to the Wieland–Gumlich aldehyde (XL*A*), which represents an intermediate stage in Woodward's biogenesis of strychnine. Reduction of the aldehyde, followed by oxidation in the β-position to the carbonyl group (*i.e.*, position 1 of the dihydroxyphenylalanine precursor) yields an aldol, which, on fission, recyclisation, reduction, and acetylation gives aspidospermine (LXXXVIII).[64]



(LXXXVII)

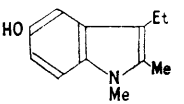
(LXXXVIII)

Vallesine, the second alkaloid isolated from these sources, is probably deacetyl-*N*-formylaspidospermine. Schlittler and Rottenberg [62] have shown that deformylvallesine and deacetylaspidospermine are identical in chemical and physical properties, but in spite of this, and the identity of Röntgen powder diagrams and infrared spectra, these authors formulate deacetylaspidospermine as a homologue of deformylvallesine, for reasons which are not clear. Witkop states that the last-named substances are identical.[64]

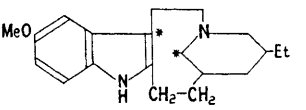
Alkaloids of Tabernanthe iboga. The only other alkaloid known which gives a 3 : 5-disubstituted pyridine on degradation is ibogaine, $C_{20}H_{26}ON_2$, obtained from *Tabernanthe iboga* Baillon. Extracts of the root bark of the

[64] Raymond-Hamet, *Compt. rend.*, 1948, **226**, 2154 ; Witkop, *J. Amer. Chem. Soc.*, 1948, **70**, 3712 ; Witkop and Patrick, *ibid.*, 1954, **76**, 5604 ; Openshaw, Smith, and Chalmers, 13th Internat. Congr. Pure Appl. Chem. 1953, Abs., p. 223.

shrub are used by West African natives to increase resistance to fatigue, and so this species has attracted wide attention from pharmacologists. Its chemical study, however, is in a much more elementary stage, and although four alkaloids have been isolated and characterised none of their structures is known.[65] Ibogaine is a monoacid base containing methoxyl, *C*-methyl, and imino-groups. Its ultraviolet spectrum and colour reactions disclose the presence of an indole nucleus, and this is confirmed by the production of 5-methoxy-*N*-oxalylanthranilic acid on oxidation. Alkali fusion gives 3-ethyl-5-hydroxy-1 : 2-dimethylindole (LXXXIX), which was identified by synthesis, and 3-ethyl-5-methylpyridine.[66] Assuming from the isolation of the latter a relation to aspidospermine, Robinson derives the constitution (XC) for a dihydroibogaine by fission of the bond between the carbon atoms marked with an asterisk. Ibogaine must then contain another ring, since there is no evidence for the presence of a double bond.



(LXXXIX)



(XC)

Alkaloids of *Picralima nitida*.—The dihydroindole alkaloids discussed above show few structural analogies with those of the α-series, with the possible exception of ajmaline. Aspidospermine is presumed to be formed by fission of the aromatic ring of the dihydroxyphenylalanine precursor, followed by various reactions involving rupture and formation of further rings. The comparatively simple recombination of the aromatic ring fragments to give a six-membered ring similar to ring E of δ-yohimbine might also be expected, and this has been postulated by Robinson to account for the behaviour of two alkaloids, akuammine and ψ-akuammigine, isolated from *Picralima nitida* Stapf., extracts of which are used by West African natives in the treatment of malaria and as an antipyretic. This reputation led Henry and Sharp to investigate the alkaloidal constituents, but the investigations were not pursued when it was shown that the extracts are inactive in avian malaria. More recently, however, Raymond-Hamet has demonstrated that the principal alkaloid, akuammine, has a local anæsthetic action almost equal to that of cocaine, and the investigations have been resumed by Robinson and his co-workers.[67] Of the eight alkaloids so far isolated, only akuammigine has been studied in addition to akuammine

[65] Dybowski and Landrin, *Compt. rend.*, 1901, **133**, 748 ; Haller and Heckel, *ibid.*, p. 850 ; Delourme-Houdé, *Ann. pharm. franç.*, 1946, **4**, 30 ; Burckhardt, Goutarel, Janot, and Schlittler, *Helv. Chim. Acta*, 1952, **35**, 642 ; Goutarel and Janot, *Ann. pharm. franç.*, 1953, **11**, 272.

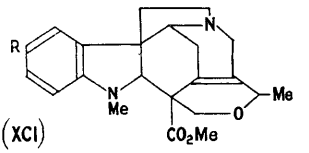
[66] Janot, Goutarel, and Sneeden, *Helv. Chim. Acta*, 1951, **34**, 1205 ; Raymond-Hamet, *Compt. rend.*, 1949, **229**, 1359 ; Goutarel, Janot, Mathys, and Prelog, *ibid.*, 1953, **237**, 1718 ; Schlittler, Burckhardt, and Gellért, *Helv. Chim. Acta*, 1953, **36**, 1337.

[67] Henry and Sharp, *J.*, 1927, 1950 ; Goodson, Henry, and MacFie, *Biochem. J.*, 1930, **24**, 874 ; Raymond-Hamet, *Arch. exp. Pathol. Pharmakol.*, 1942, **199**, 399 ; Janot, Le Men, Aghoramurthy, and Robinson, *Experientia*, 1955, **11**, 343.

and ψ-akuammigine. Its constitution as a stereoisomeride of δ-yohimbine has already been mentioned.

Akuammine,* $C_{22}H_{26}O_4N_2$, is a ditertiary dihydroindole base containing hydroxyl, *C*-methyl, *N*-methyl, and methoxyl groups, which dissolves readily in methanolic alkali, giving a solution from which it can be regenerated. Its colour reactions are strongly reminiscent of those of *p*-methylaminophenol, and the presence of a similar grouping (based on 2 : 3-dihydro-5-hydroxy-1-methylindole) also explains the relative instability of the alkaloid, which has been known to decompose during attempted recrystallisation. Zinc dust distillation of the product gave 3-ethylpyridine, and, probably, skatole. Hydrogenation was inconclusive and requires further study, but presence of a double bond is considered probable by Robinson and Thomas, who have combined these results in the provisional formula (XCI ; R = OH) for akuammine.[68]

The second alkaloid, ψ-akuammigine, is believed to be deoxyakuammine (XCI ; R = H). It contains similar functional groups (with the exception of the phenolic hydroxyl group), but its basic strength and colour reactions are anomalous. Thus its basic strength is closer to that of strychnine than



(XCI)

to that of strychnidine. Further, ferric chloride gives a colour only on warming, and diazo-coupling occurs reluctantly and only in buffered acetic acid. However, nitration and nitrosation proceed normally. On the other hand, the lithium aluminium hydride reduction product, ψ-akuammigol, behaves like strychnidine in all respects. These peculiar properties are interpreted in formula (XCI ; R = H) by assuming that the proximity of the dihydroindole nitrogen atom and the ester group results in deactivation of the potentially basic group across space by the carbonyl group. This proximity, apparent from a study of molecular models, and the tertiary nature of the ester group, also explain the difficulty of hydrolysis of ψ-akuammigine, which was unaffected by vigorous treatment with alcoholic alkali.[68]

Alkaloids of *Gelsemium* Species.—The North American plant *Gelsemium sempervirens* has been known since 1870 to contain alkaloids ; Wormley [69a] isolated an amorphous base, later obtained crystalline by Gerrard,[69b] and named gelsemine. Although a number of bases has been isolated in addition to gelsemine, only four of these, namely, sempervirine, gelsemicine, gelsedine,

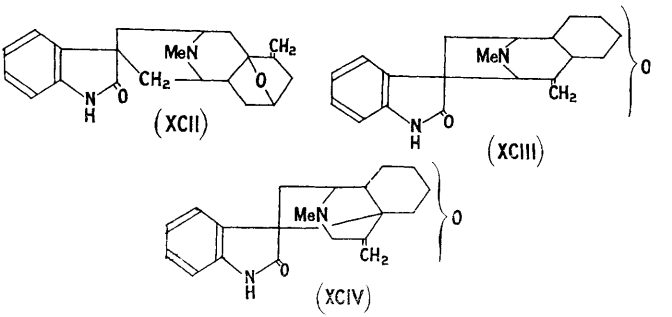
[68] Henry, *J.*, 1932, 2759 ; Millson, Robinson, and Thomas, *Experientia*, 1953, **9**, 89 ; Robinson and Thomas, *J.*, 1954, 3522.

[69] (*a*) Wormley, *Amer. J. Pharm.*, 1870, **42**, 1 ; (*b*) Gerrard, *Pharm. J.*, 1883, **13**, 641 ; *Jahresber.*, 1883, 1353 ; Chou, *Chinese J. Physiol.*, 1931, **5**, 345 (*Chem. Abs.*, 1932, **26**, 806) ; Chou, Wang, and Cheng, *ibid.*, 1936, **10**, 79 (*Chem. Abs.*, 1936, **30**, 4270).

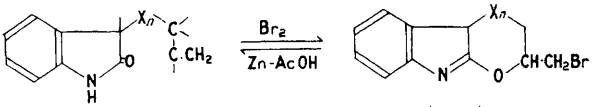
* This alkaloid, also known as vincamajoridine, has recently been isolated, together with reserpinine, from *Vinca major* L.[67]

and gelseverine, are well established. Chinese *Gelsemium* species also contain several alkaloids, but, with the exception of gelsemine, obtained from *G. elegans* (Gardn.) Benth., they do not appear to have been related to those extracted from the North American varieties.[69]

Gelsemine, $C_{20}H_{22}O_2N_2$, is the principal alkaloid of this series, and has been studied in recent years by several groups of workers. One of its nitrogen atoms is contained in a tertiary basic group, while the other is inert. Reduction of gelsemine with lithium aluminium hydride results in elimination of one oxygen atom with the formation of a dihydroindole base. This behaviour is characteristic of 3 : 3-disubstituted oxindoles, and the presence



of this grouping was confirmed by comparison of the ultraviolet spectra of gelsemine and 3 : 3-dimethylindole, and the colour reactions of gelsemine and strychnine. The second, inert oxygen atom is presumed to be present in an ether link, and the alkaloid was readily proved to contain a terminal double bond. The formula (XCII) was deduced from these results by



(XCV)
(X = C, N or O; n = 0, 1, or 2)

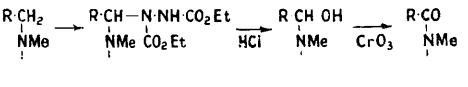
(XCVI)

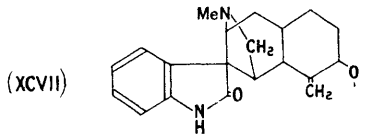
Gibson and Robinson, but the alternative formulæ (XCIII) and (XCIV) were preferred by Goutarel, Janot, Prelog, Sneeden, and Taylor, who interpreted the results of a series of transformations on gelsemine as indicating the presence of the grouping (XCV). For example, reaction with bromine led to a cyclic derivative, formulated as (XCVI), and the reverse process was achieved by reduction with zinc and acid.[70] These conclusions of Goutarel *et al.* were challenged by Jones and Stevens,[71a] who doubted

[70] Chu and Chou, *J. Amer. Chem. Soc.*, 1940, **62**, 1955 ; Marion, *Canad. J. Res.*, 1943, **21**, *B*, 247 ; Kates and Marion, *J. Amer. Chem. Soc.*, 1950, **72**, 2308 ; *Canad. J. Chem.*, 1951, **29**, 37 ; Gibson and Robinson, *Chem. and Ind.*, 1951, 93 ; Goutarel, Janot, Prelog, Sneeden, and Taylor, *Helv. Chim. Acta*, 1951, **34**, 1139 ; Goutarel, Janot, Prelog, and Sneeden, *ibid.*, p. 1962 ; Prelog, Patrick, and Witkop, *ibid.*, 1952, **35**, 640 ; Habgood, Marion, and Schwarz, *ibid.*, p. 638.

[71a] Jones and Stevens, *J.*, 1953, 2344.

whether gelsemine is an allylamine, since Hofmann degradation of dihydrogelsemine did not proceed normally, as expected for a substance possessing the partial structure (·NMe·CH·CHMe·). The first positive evidence against the formulæ (XCII—XCIV) was provided by Habgood and Marion,[71b] who demonstrated that gelsemine contains a methylene group adjacent to the basic nitrogen atom. Reaction of dihydrogelsemine with diethylazodicarboxylate gave a product which behaved as a carbinolamine. Oxidation of this gave an amide, the infrared spectrum of which suggested that it probably contained a five-membered lactam ring. Habgood and Marion interpreted this evidence by the following partial formulæ, and proposed for gelsemine the constitution (XCVII), which can be derived biogenetically from tryptamine and tyrosine.

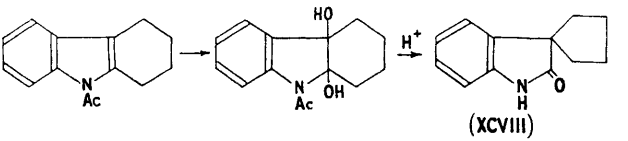




(XCVII)

The minor alkaloids of *G. sempervirens* are probably also oxindole derivatives, but little is known about them. Oxindole alkaloids also occur in other botanical species, *e.g.*, mitraphylline, formosanine, and rhynchophylline in *Ourouparia formosana* Matsumura et Hayata.[72]

Although the formula of gelsemine is not known with certainty, the presence of the 3 : 3-disubstituted oxindole chromophore is well established. This grouping presumably arises *in vivo* by oxidation and rearrangement of indole derivatives, a process which is also feasible *in vitro, e.g.*, the conversion



(XCVIII)

of 9-acetylhexahydro-10 : 11-dihydroxycarbazole, by means of acid, into a spirocyclic oxindole derivative (XCVIII). The reverse process was attempted with gelsemine, by Witkop and Patrick, since the tetrahydrocarboline obtained should be easier to study than gelsemine, but so far without success.[73]

[71b] Habgood and Marion, *Canad. J. Chem.*, 1955, **33**, 604.

[72] Chou, *Chinese J. Physiol.*, 1931, **5**, 131 (*Chem. Abs.*, 1931, **25**, 4085); Raymond-Hamet, *Compt. rend.*, 1950, **230**, 1405; Janot, Goutarel, and Friedrich, *Ann. pharm. franç.*, 1951, **9**, 305; Schwarz and Marion, *Canad. J. Chem.*, 1953, **31**, 958; *J. Amer. Chem. Soc.*, 1953, **75**, 4372; Cook, Gailey, and Loudon, *Chem. and Ind.*, 1953, 640.

[73] Plant and Robinson, *Nature*, 1950, **165**, 36; Witkop, *J. Amer. Chem. Soc.*, 1950, **72**, 614; Perkin and Plant; *J.*, 1923, **123**, 676.

Alkaloids of Calabash Curare.—The highly toxic constituents of gourd or calabash curare from various sources in South America have been investigated by Wieland and his collaborators, and more extensively in recent years by Karrer and his associates. More than thirty alkaloids have so far been isolated by precipitation and separation of the reineckates, or by chromatographic techniques.[74] They are all quaternary salts, and a study of their ultraviolet spectra has shown that they all contain the indole ring system, either as such, or in various reduced or oxidised-reduced forms.[75] Except with fluorocurine and mavacurine, also isolated from Venezuelan *Strychnos toxifera*, very little progress has been made in the elucidation of the structures of these alkaloids. Chemical studies have been hampered by the difficulty of isolating the pure alkaloids in large quantity. No doubt the problem would be simplified if the samples of curare consisted of extracts from one botanical species, instead of a mixture of several species. Another disadvantage is that the composition of the curare varies according to its source. Included in this group are the alkaloids of *Strychnos toxifera* and *S. mitscherlichii*, which are possible constituents of some samples of curare.

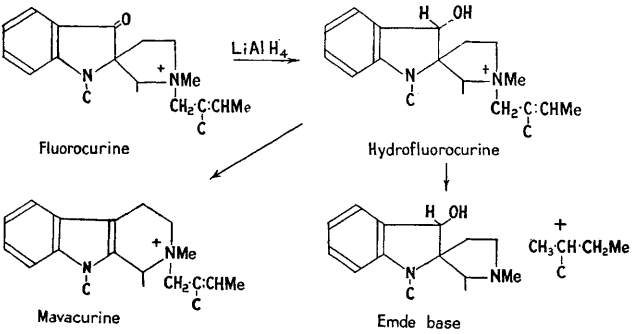
Fluorocurine, $C_{20}H_{25}O_2N_2^+$, contains one methylimino-, one *C*-methyl, and one acetylatable hydroxyl group, and there is a double bond in the molecule. The ultraviolet spectrum closely resembles that of a 1 : 2 : 2-trisubstituted indoxyl, and it is probable that the alkaloid contains this grouping. Reduction of fluorocurine with lithium aluminium hydride yields hydrofluorocurine, which is converted by sulphuric acid into the trisubstituted indole, mavacurine, $C_{20}H_{25}ON_2^+$, by loss of water. The quaternary nitrogen atom is the one which bears the methyl group, since thermal decomposition of fluorocurine chloride gives norfluorocurine, which is reconverted into the alkaloid by methyl chloride. Similarly, normavacurine yields mavacurine. The indoxyl-nitrogen atom is probably bound in another ring, since there is no imino-group in the molecule, and the position of the *C*-methyl group excludes the possibility of an *N*-ethyl group. Selenium dehydrogenation of mavacurine gave a base, which was not completely identified, but was very probably an *N*-substituted β-carboline derivative.

The position of the double bond in these alkaloids was demonstrated by ozonolysis and Kuhn–Roth oxidation which gave, respectively, acetaldehyde and acetic acid. Further, chromic acid oxidation of dihydrofluorocurine gave a significant amount of propionic acid, confirming the presence of an ethylidene group, $CH_3{\cdot}CH{:}$. Catalytic reduction of hydrofluorocurine chloride ($C_{20}H_{27}O_2N_2Cl$) yielded a tertiary base, $C_{20}H_{30}O_2N_2$, which contained two *C*-methyl groups and probably arose by reduction of the double bond and simultaneous Emde reduction. This product gave a mixture of acetic

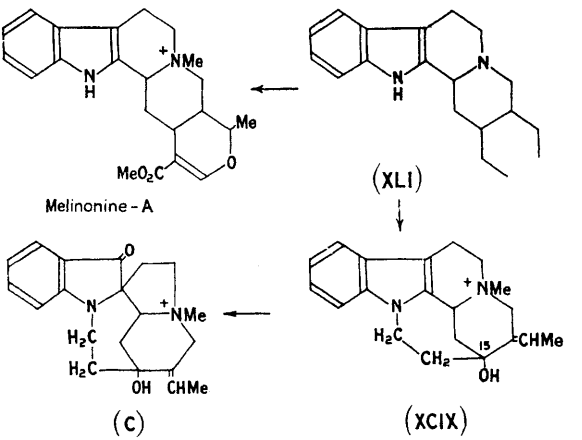
[74] Karrer and Schmid, *Helv. Chim. Acta*, 1946, **29**, 1853 ; 1947, **30**, 1162, 2081 ; 1950, **33**, 512 ; Schmid, Kebrle, and Karrer, *ibid.*, 1952, **35**, 1864 ; Kebrle, Schmid, Waser, and Karrer, *ibid.*, 1953, **36**, 345 ; Asmis, Bächli, Giesbrecht, Kebrle, Schmid, and Karrer, *ibid.*, 1954, **37**, 1968 ; Giesbrecht, Meyer, Bächli, Schmid, and Karrer, *ibid.*, p. 1974 ; Asmis, Schmid, and Karrer, *ibid.*, p. 1983 ; Wieland, Bähr, and Witkop, *Annalen*, 1941, **547**, 173 ; Wieland and Merz, *Chem. Ber.*, 1952, **85**, 731.

[75] Kebrle, Schmid, Waser, and Karrer, *Helv. Chim. Acta*, 1953, **36**, 102.

and α-methylbutyric acid on oxidation. Hence, the abovet ransformations can be accommodated in the annexed partial formulæ :



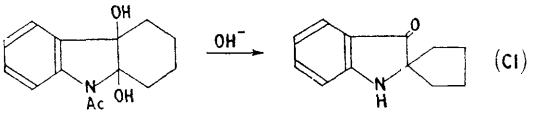
Since the infrared spectrum suggests the presence of an *ortho*-disubstituted benzene derivative, it is clear that the two remaining carbon atoms and the hydroxyl group must be situated in the alicyclic portion of the molecule, and further, since the indoxyl group and the double bond are the only centres of unsaturation, the alkaloids must be pentacyclic. Mavacurine and melinonine-A occur together in *Strychnos melinoniana*, and hence it is possible that they are related biogenetically. The formula for mavacurine can therefore be expanded to (XCIX), and it only remains to justify the position



of the hydroxyl group. Mavacurine is not a carbinolamine, and Karrer and his co-workers are of the opinion that the most likely position is at $C_{(15)}$. If this formula represents mavacurine, fluorocurine must be (C), and may be formed *in vivo* from the former by oxidation and rearrangement.[76] This

[76] Bickel, Giesbrecht, Kebrle, Schmid, and Karrer, *Helv. Chim. Acta*, 1954, **37**, 553 ; Bickel, Schmid, and Karrer, *ibid.*, 1955, **38**, 649 ; for summaries see : Karrer, *Nature*, 1955, **176**, 277 ; Karrer and Schmid, *Angew. Chem.*, 1955, **67**, 361.

parallels the known rearrangement of 9-acetylhexahydro-10 : 11-dihydroxycarbazole in alkaline solution to a spirocyclic indoxyl (CI).[73]



(CI)

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