THE BIOGENESIS OF CERTAIN ALKALOIDS

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In recent years there have been outstanding advances in the elucidation of the molecular structure of alkaloids. Especially the alkaloids of amaryllidaceae, the aconite and delphinium alkaloids, some steroid alkaloids, and many groups of indole alkaloids have been forced to disclose their secrets. This astonishingly rapid progress has to a large extent been made possible by the development and use of powerful techniques such as chromatography, mass spectrography, X-ray crystal analysis, and nuclear magnetic resonance, to eke out infra-red and ultra-violet spectroscopy.

The chief interest that chemists now perceive in the alkaloid structures is the further opportunity afforded for study of the processes of synthesis in the plant and the new material has given significant help in this direction.

In 1917[1] the author suggested a scheme of biosynthesis of alkaloids based on a comparison of molecular structure. This was amplified at various times in lectures and to some extent in publications[2]. The present contribution surveys some of the verification of predictions, and also corrections, which have been made as a result of experimental work in many laboratories. The most important methods have been the study of biosynthesis in micro-organisms by the use of mutates and, still more directly, the use of isotopic tracers. The latter, usually radioactive, are fed to the plants, the alkaloids being later isolated and degraded in order to identify the site of radioactive atoms.

Although these methods are not without their peculiar pitfalls and though care is required in the design of the experiments and the interpretation of the results, the outcome is a clear proof of the outlines of biogenesis in very many cases. It will be conceded that our speculative ideas played a useful rôle in guiding the selection of experiments which now supersede them.

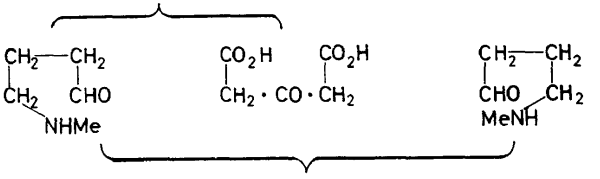
In the pyrrolidine and piperidine groups the predictions from structural relations have been justified, the former stemming from ornithine and the latter from lysine or their respective equivalents[3].

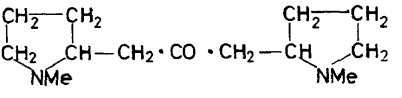
Facile syntheses (*Figure 1*) such as those of hygrine and cuscohygrine[4], tropinone[5], ψ-pelletierine[6] and lobelanine[7], were formerly thought to support the mechanisms proposed. They certainly made the suggestions more plausible. Now we are on firmer ground because the biogenetic pathways in these groups have been confirmed by the radioactive tracer method[8].

Some of the more obvious gaps have been filled by the discovery of new alkaloids. For example, anaferine[9] is the hitherto unknown piperidine analogue of cuscohygrine. On the other hand, the pyridine nucleus of nicotine does not arise from the piperidine ring by dehydrogenation but from nicotinic acid (Leete, Dawson[10]). The type of reaction involved is quite similar to that postulated when lysine was envisaged as a starting point,

but the device used by the tobacco plant is much more elegant than our paper synthesis.

The hydrogen atoms in the pyridine ring subject to isotopic displacement have been identified and the scheme shown in *Figure 2* is deduced from the results.





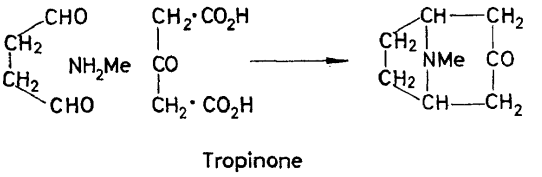


Figure 1

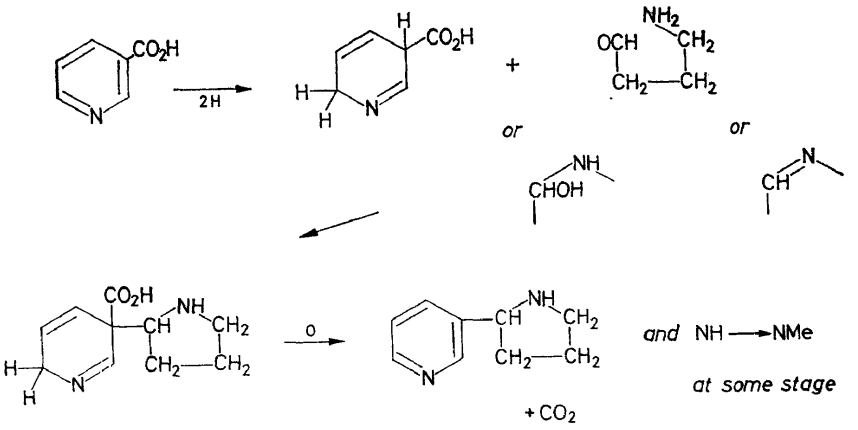


Figure 2

It will be appreciated that the —CH group in the 3-position is activated

not only by attachment to N=CH but also by carboxyl.

The final oxidation recalls that of dihydroflavindine to quindoline (*Figure 3*). This occurs on shaking a cold alkaline solution with air.

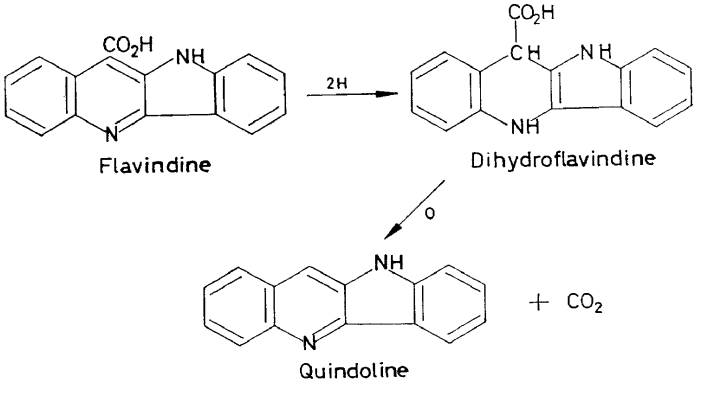


Figure 3

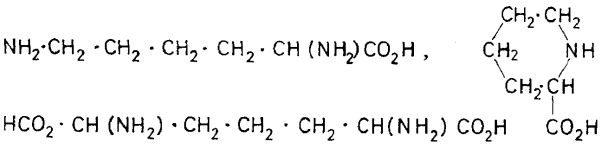
On the other hand the piperidine ring in many alkaloids has been shown to arise from lysine or pentamethylenediamine (*Figure 4*). In the lupinine[11] and sparteine[12] series ingenious syntheses, analoguos to suggested biogenetic routes have been carried out. A paper submitted to the present Symposium by H. R. Schütte (Abstracts of Communications, p. 76) indicates that lupinine is derived from 2 mols. lysine, and sparteine by further implication of 1 mol. lysine.

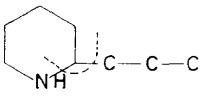
The hypotheses (*Figure 5*) relating to the isoquinoline alkaloids (Winterstein and Trier[13]) with later development by the author[2] have been confirmed in typical examples by tracer experiments. For example, berberine and hydrastine each come from two molecules of tyrosine[14] and not from one of tyrosine and one of a modified prephenic acid in the manner proposed by Wenkert[15].

Figure 6 illustrates the formation of norlaudanosoline and some of the ramifications. It should be unnecessary to emphasize that the stages of such processes as *O*-methylation or methylenation and *N*-methylation are not considered from the speculative angle. They can, of course, be elucidated experimentally in some cases.

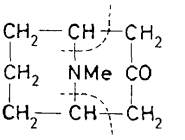
Our theory (*Figure 7*) of thebaine-morphine biogenesis[17], and of the relation of these alkaloids to those of the isoquinoline group, has been brilliantly confirmed by Battersby[18] and also by Leete[19]. Norlaudanosoline, a hypothetical precursor of many isoquinoline alkaloids such as those found in *Papaver somnifera*, has even been found to be convertible into morphine in this opium poppy[20]. The detail must involve removal of an oxygen atom rather than C-migration as previously proposed[21].

Lysine group

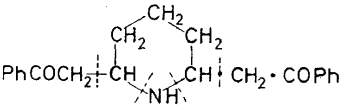




Coniine types



ψ-Pelletierine



Lobelanine

Cuscohygrine: 2 ornithine + 1 acetone

Lobelanine : 1 lysine + 2 acetophenone

Occurrence of A_2B and AB_2 types confirms A and B as structural units

Figure 4

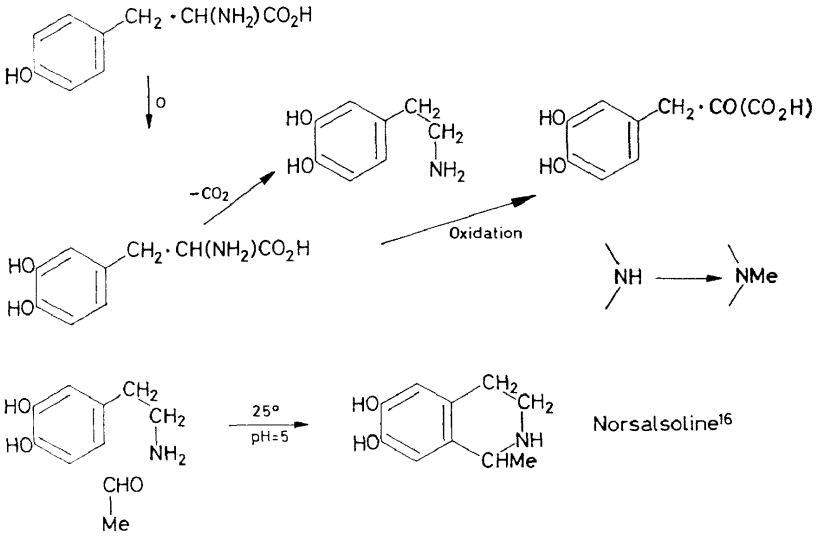


Figure 5 Simple example of the formation of an isoquinoline alkaloid

The author came to the conclusion that the aromatic precursor of most of the isoquinoline alkaloids is probably tyrosine and the correctness of this view has been confirmed in many cases (*e.g.* berberine and morphine). The biogenesis of tyrosine itself (*Figure 8*) has been made clear by B. D. Davis and his colleagues[22] as the result of experiments with mutants of micro-organisms such as *Escherichia coli* and *Neurospora crassa.*

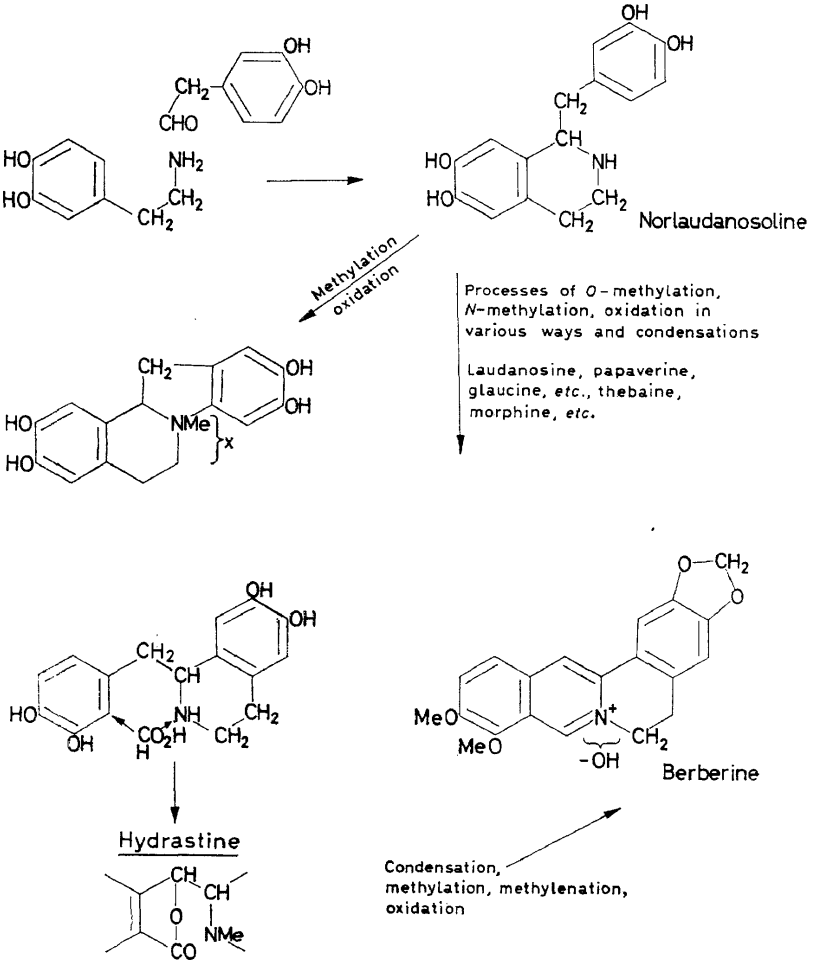
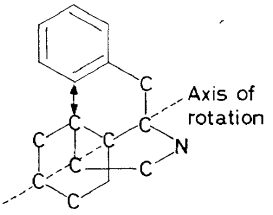


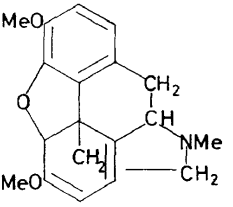
Figure 6

Aromatic nuclei are certainly formed in other ways and one that may be mentioned in passing is the condensation of isopentane units (*ex* mevalonic acid). This, however, is but a special case of the more general " acetate " hypothesis since mevalonic acid is itself derived from acetate.

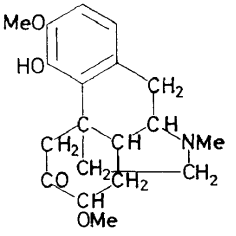
The relative importance of " acetate " and polyketomethylene chains in early stages of phytosynthesis continually increases and is now seen to be significant also in alkaloid biogenesis. Originally put forward by



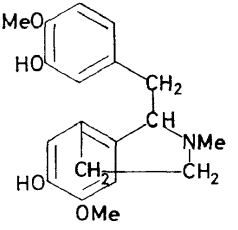
Benzylisoquinoline skeleton with one nucleus rotated round axis shown, indicating position of coupling



Thebaine ; a possible precursor of morphine or codeine

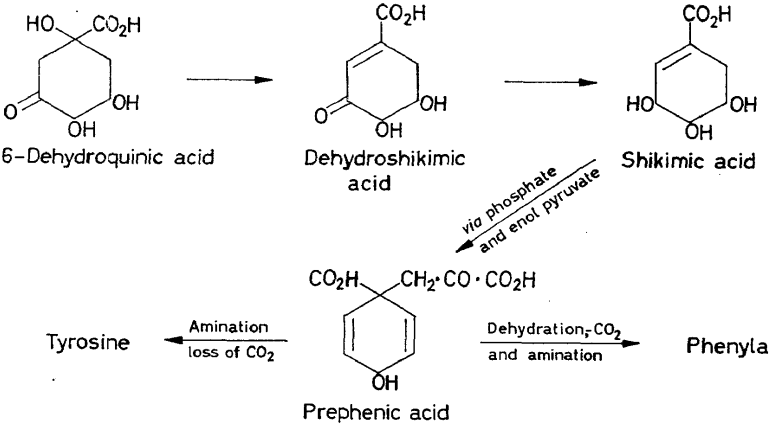


Sinomenine has the appearance of a cyclized protosinomenine but this change has not yet been brought about



Protosinomenine

Figure 7



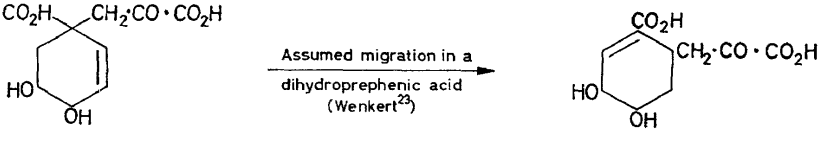


Figure 8

Collie[24] it was supported by elegant synthetic work such as that of Collie himself on diacetylacetone and pyrones, of W. H. Perkin Jr., on the conversion of phenylacetate into polycyclic substances and even, one might think, by Baeyer's conversion of malonic ester into phloroglucinol derivatives. The author developed the theory speculatively and applied it, for example, to orsellinic acid, emodin, hypericin, and the tetracyclic antibiotics[25]. He regarded the (A) nucleus (phloroglucin) of the C_6—C_3—C_6 group (flavanes *etc.*) as derived from acetate whereas the (B) nucleus was supposed to come from tyrosine. This idea has been fully validated. Especially the outstanding isotopic tracer work of Rittenberg[26] in the long-chain acid series, of Cornforth, Bloch, Folkers, and Lynen and their colleagues in the polyisopentanoid fields, and of Birch[27] on mould metabolites and phenolic plant products have demonstrated the rôle of acetate in more and more examples.

Turning to the indole series of alkaloids, very striking advances have been made in recent years. Apart from the betaine hypaphorine, which is fully methylated tryptophan, the indole group of alkaloids was first recognized in the course of investigations of the bases harmine and harmaline[28]. These and also aribine were seen (*Figure 9*) to have the same relation to tryptophan

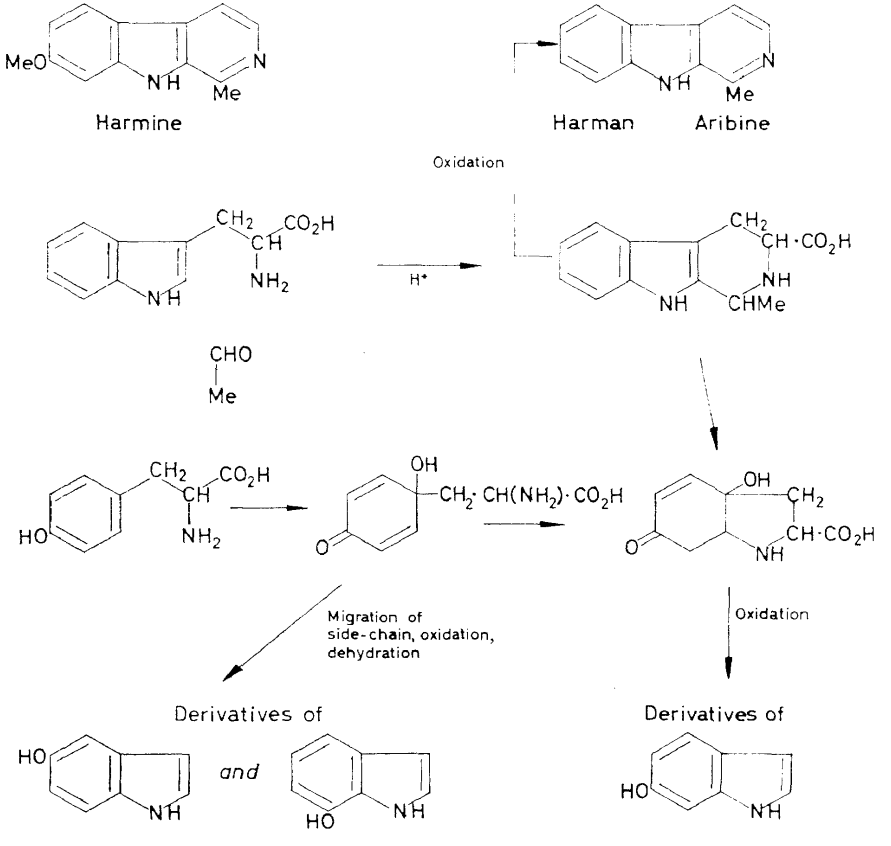
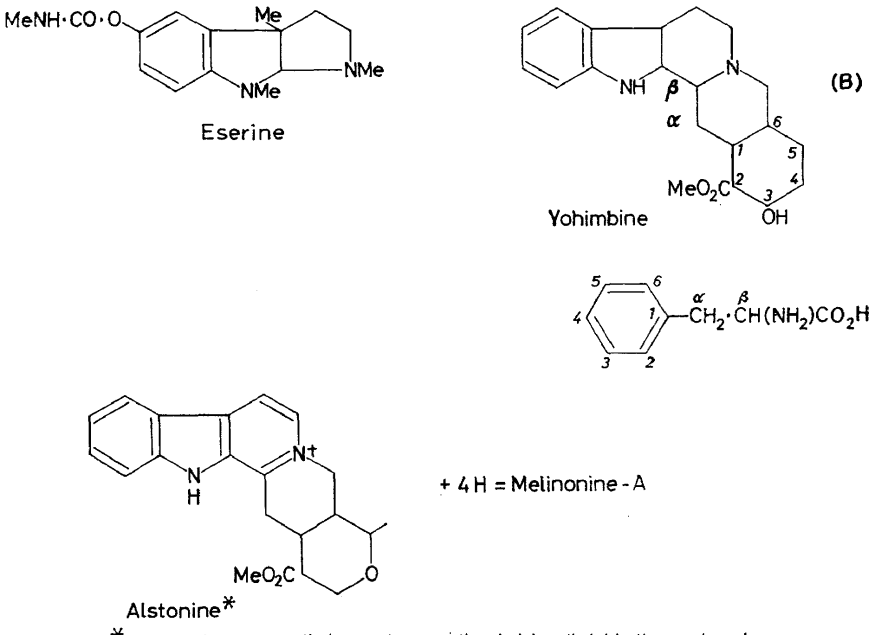


Figure 9

(or a derivative) as the simpler isoquinoline bases, such as salsoline, have to phenylalanine or derivatives thereof[29].

The structure of eserine (physostigmine) was suggested[30] on grounds of biogenetic analogy with corydaline and when the constitution of yohimbine was cleared up after several false starts, Barger (1934)[31] proposed an origin from tryptophan and a phenylalanine derivative (*Figure 10*; here and elsewhere the italicized numbers and α, β refer to the hypothetical precursor,



*In alstonine, corynantheine and many other indole alkaloids the numbered cyclohexane ring is either broken or formed by another biogenetic route

Figure 10

e.g. phenylalanine or a derivative thereof. (B) = berberine bridge). This suggestion could not be developed at that time in adequate detail, chiefly on account of the presence of a carbomethoxy group additional to the phenylalanine moiety. On the other hand, a bridge methylene group in yohimbine was clearly sited in the same position as a corresponding unit in the berberine group of the isoquinoline alkaloids.

It must be interpolated here that the indole nucleus does not always originate from tryptophan. Lycorine is the best example of an alternative process, namely ring closure of a β-phenylethylamine. As shown in *Figure 11*, tyrosine has been proved to be a progenitor of this base[32]. Tyrosine labelled at the asterisked C-atom gave lycorine in which the asterisked carbon was shown to be radioactive, after suitable degradation. Furthermore a *tour de*

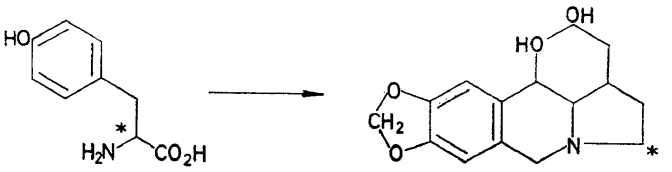
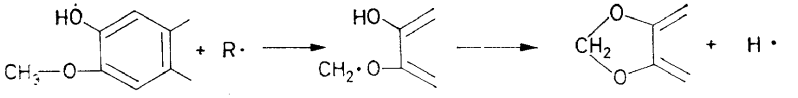


Figure 11

force has been made in that norbelladine has been used as a lycorine precursor[33]. The methylenedioxy group in lycorine may come from formic acid by way of the guajacol group* by a radical reaction:



The subsequent development of the indole group has been dramatic. Following the final elucidation at Oxford of the molecular structure of strychnine and congeners[34], Woodward advanced an ingenious hypothesis[35] that a phenylalanine derivative condensed with tryptophan underwent a ring fission and other changes after which a degradation product of strychnine, known as the Wieland–Gumlich aldehyde[36], could be elaborated by means of acceptable reaction processes (*Figure 12*). This aldehyde has

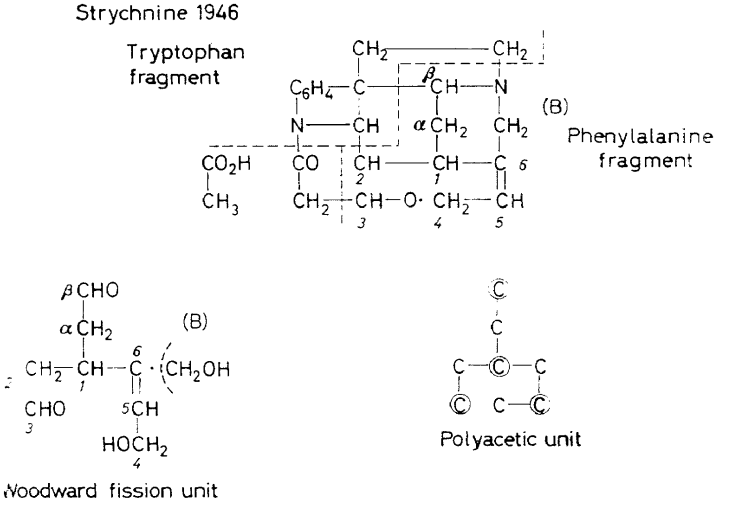


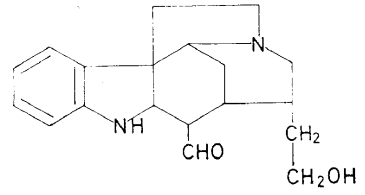
Figure 12

* After the delivery of the lecture Professor D. H. R. Barton kindly informed me that the possible derivation of methylenedioxy from the guajacol MeO— and HO— groups had been previously mentioned by Scribney and Kirkwood (*Nature* **171**, 931 (1953) and also by A. J. Birch and by A. R. Battersby at the Annual Meeting of the Chemical Society (Sheffield, 1962). Definite evidence in favour of these speculations is presented in a forthcoming paper by D. H. R. Barton, G. W. Kirby and J. B. Taylor. The mechanism proposed in the present lecture has not been previously considered so far as the author knows.

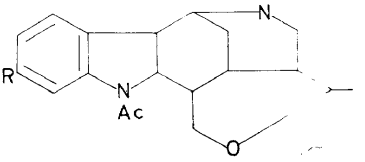
actually been isolated from plant material[37] and its conversion into strychnine requires nothing more than condensation with acetic acid[38].

In view of Leete's work on ajmaline and other alkaloids we can alternatively show the Woodward fission as derived from a polyacetic chain; in *Figure 12* the carbon atoms derived from the carbonyl groups are ringed and it can be seen that the ether oxygen of strychnine is out of step.

The Wieland–Gumlich aldehyde has been found to be related to several of the Curare bases (Karrer[39]). Spermostrychnine and strychnospermine[40] are examples of *Strychnos* bases which do not contain the two carbon atoms (—$CO{\cdot}CH_2$—) attached to N(a) and forming part of a piperidone ring (*Figure 13*).



Wieland-Gumlich aldehyde



R=OMe Strychnospermine
R=H Spermostrychnine

Figure 13

The Woodward fission seemed an inherently improbable event but it has been found possible to assume it in many further cases. For example, the author[41] used it to devise a precise structure for emetine (*Figure 14*). The starting point was a protoberberine which was imagined to be degraded in an aromatic nucleus in exactly the manner of the Woodward fission for strychnine. The intermediate product was then supposed to condense with another molecule of a phenylalanine derivative and then by known reactions (*e.g.* methylation, reduction, decarboxylation) gave a structure for emetine which was almost simultaneously proved to be correct as the final result of a long series of investigations[42]. More remarkable still, Battersby has found the hypothetical intermediate aldehyde among the minor alkaloids of ipecacuanha[43]. On the triacetate-malonate hypothesis the common precursor [with (B)] given at the bottom of *Figure 14* loses one CO_2 from the malonate moiety. Then both ends of a C_5 chain are in an oxidized condition and condense with DOPA with subsequent reduction. Battersby's intermediate results from condensation at one end of the chain only.

A further development of surpassing interest was the proof of the constitution of cinchonamine[44]. It was seen that the structure could be the result of a normal Woodward fission (*Figure 15*). Furthermore, the plausible relation of cinchonamine to cinchonine brought quinine into the indole family.

Many developments, later disclosed, fit into the same pattern. It suffices to mention a few examples, *viz.* corynantheine[45], mavacurine[46], ajmaline[47] and echitamine[48] (*cf. Figure 16*). Nevertheless, these cases involve nothing more than the intermediary of a particular structure which can be assumed to arise from fission of the aromatic nucleus of a phenylalanine derivative.

There is no proof of the origin of this open aldehydic unit from a benzene derivative.

The brilliant work of Davis and his colleagues, already mentioned above, has established the biogenetic sequence leading to phenylalanine, at least in micro-organisms. The intermediates in the process are obviously possible

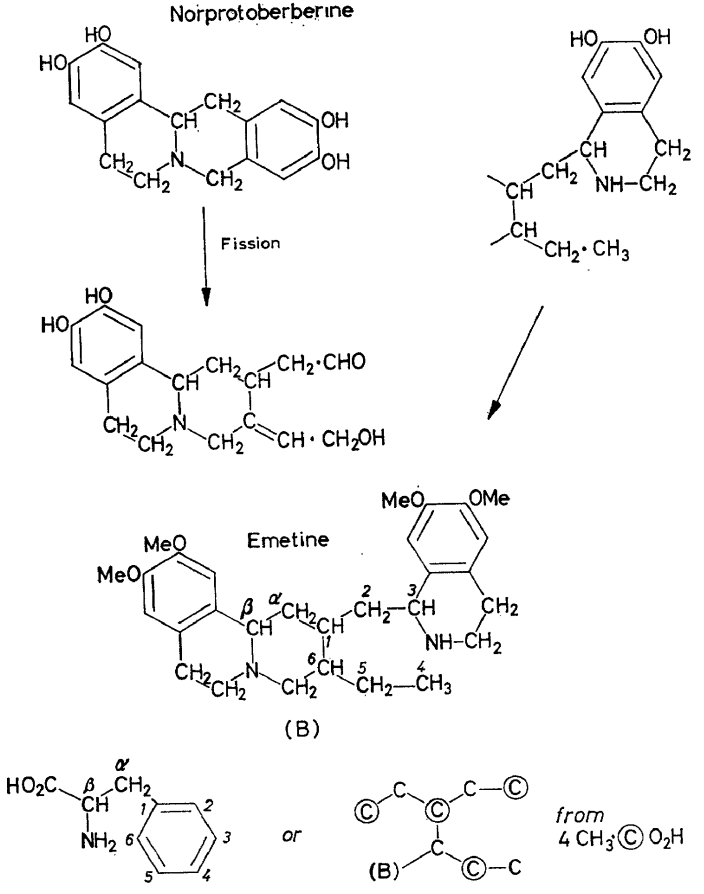


Figure 14

precursors of the aldehyde supposed to be obtained by the Woodward fission (or from a tetra-acetic complex).

Wenkert has advanced in great detail a highly sophisticated theory based on transformations of prephenic acid, though in a recent paper[49] he appears to contemplate also a mevalonic, or at any rate isopentanoid, precursor. Neither view appears likely to gain acceptance in the form so advanced. However, he has drawn attention to occurrence of certain non-nitrogenous substances which are closely similar to the required unit (Woodward fission unit) and which even contain the yohimbine carbonyl

relatively correctly sited (*Figure 17*). The yohimbine CO actually appears as CO_2Me in oleuropeine[50]. A characteristic degradation product of DOPA is also present in the molecule.

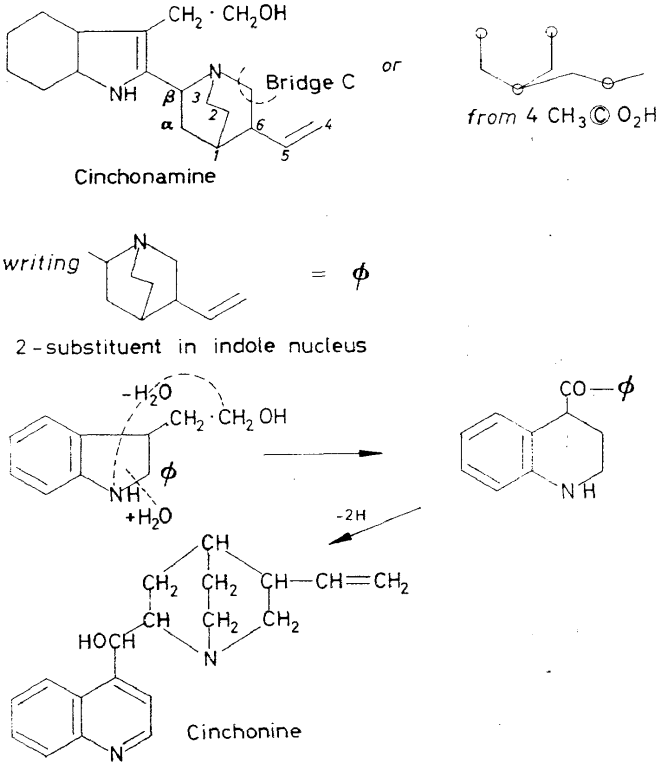


Figure 15

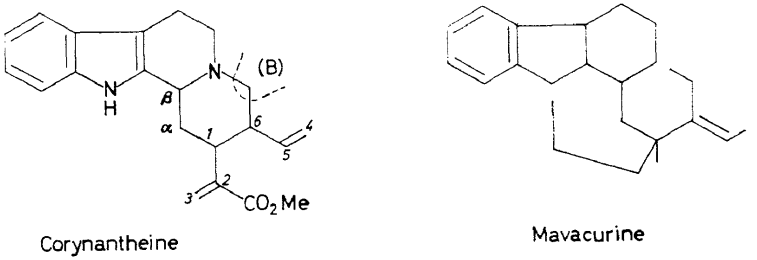


Figure 16

Unfortunately, Wenkert has attempted the extension[52] of his theories into regions where they are certainly inapplicable. An example is the phthalide group of isoquinoline alkaloids; hydrastine for instance comes from two tyrosine molecules.

The whole problem has assumed a new aspect in view of Leete's discovery that the Woodward fission unit (so-called for purposes of identification) hitherto assumed in ajmaline biosynthesis is probably derived from a condensed chain of three acetate units and one malonate unit,

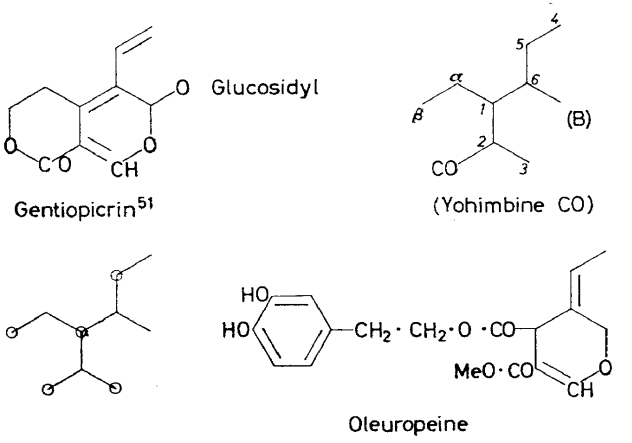


Figure 17

$(CO_2H{\cdot}CH_2{\cdot}C\{:C(CO_2H)_2\}{\cdot}CH_2{\cdot}CO{\cdot}CH_3)$. Two of the carbon atoms have been located as radioactive according to the scheme shown in *Figure 18*.

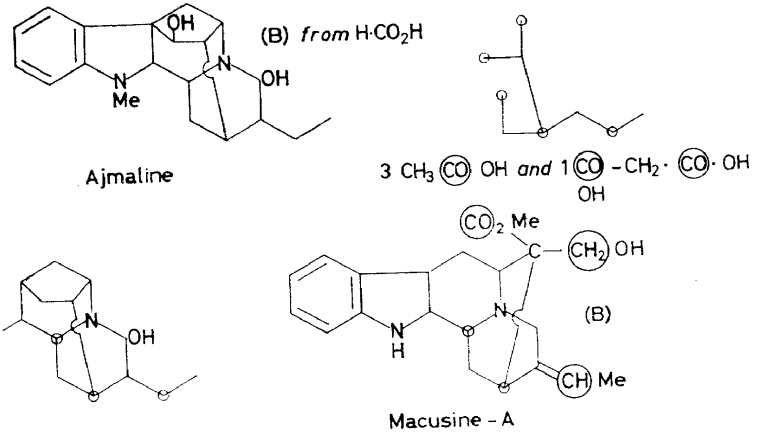


Figure 18

Macusine-A is an alkaloid in the molecule of which the malonate carboxyl is preserved. In ajmaline one carboxyl is presumably lost. Voachalotine (R. H. Martin, private communication) closely resembles macusine-A in skeletal structure (*cf. Figure 19*) in which the carbon atoms derived from the carbonyls of the tri-acetate-malonate chain are ringed.

It is claimed, and probably with justice, that the acetate hypothesis can be applied to the whole of the indole group of alkaloids for which we have hitherto employed the Woodward fission.

Prior to this development, studies of aspidospermine and the *Hunteria* alkaloids (Taylor and colleagues) had disclosed that the berberine bridge

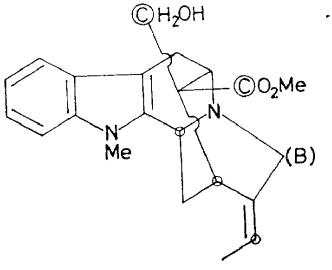
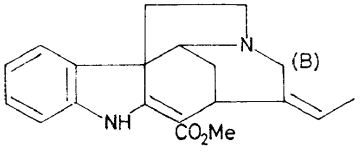


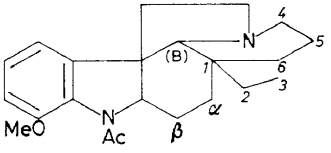
Figure 19

may connect the basic nitrogen atom to that carbon which is joined to the amino-acid chain in a hypothetical phenylalanine precursor[53] (*Figure 20*). This was the first jarring note in the harmony of the Woodward fission applications.



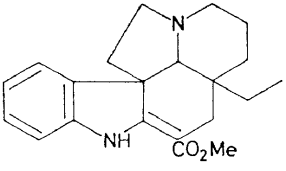
Akuammicine

Clearly related to strychnine; experimentally connected with Wieland–Gumlich aldehyde[55]



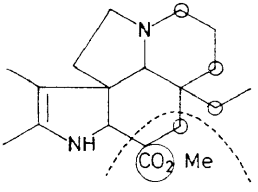
Aspidospermine

The numbering shows a suggestion made by the author[57] on the basis of the Woodward fission; as then pointed out, the system could also be derived from prephenic acid



Vincadifformine[58]

The same skeleton as aspidospermine; the applicability of the acetate hypothesis is shown*



Malonate unit

*In this case an indolenine $\backslash N{=}C\,/$ may attack the methylene of the malonate fragment.

Figure 20

Taylor has effected a most ingenious synthesis of eburmamonine[59] which is based on, and illustrates, the idea of a 1-carbon unit introduced *p*- to a hydroxyl in the phenolic ring (*Figure 21*). Eburmamonine and other *Hunteria* bases contain the same skeleton as aspidospermine.

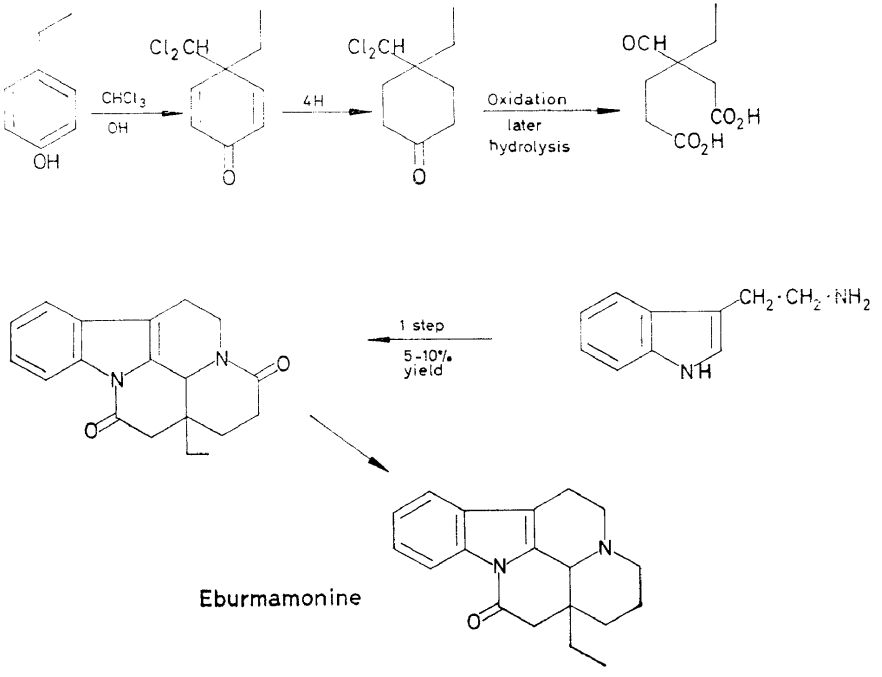


Figure 21

Further alkaloids that can be discussed in connexion with the various ideas on the cryptic unit are ibogaine, vocangine and echitamine. The scheme indicated in *Figure 22* for ibogaine and voacangine appeared satisfactory apart from the unusual position of the 1-carbon unit, the Bridge

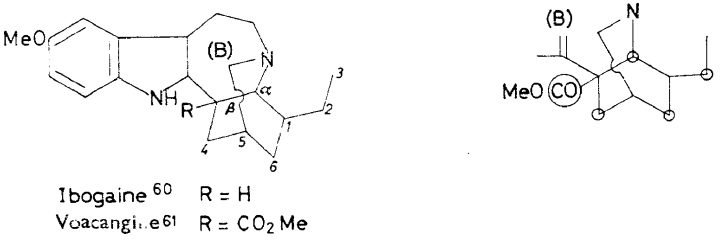


Figure 22

carbon. Also the terminal carbonyl of the phenylpyruvic chain is utilized. *Figure 22* also gives an interpretation in terms of an acetate-malonate chain. In this case the junction with the indole ring is not quite so happily explained.

There are alternative ways of describing the functions of the acetate and malonate groups. Moreover, an intramolecular rearrangement may have occurred.

The remarkable structure of echitamine (*Figure 23*) is best considered on the basis of the acetate-malonate hypothesis; the skeleton applicable is identical with that assumed for ajmaline and macusine-A.

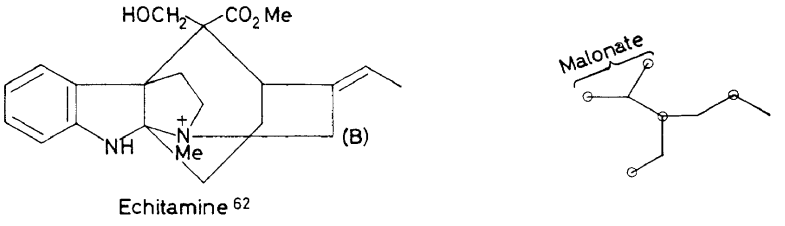


Figure 23

It is perhaps worthwhile to mention that two years ago at Lindau[63] the author hazarded the thought that the aromatic type split in the so-called Woodward fission was not DOPA but a substance having gallic acid orientation of substituents. The idea was to facilitate assumption of a retro-aldol split in a reduced derivative and also to leave open the appearance of oxygen in the strychnine position, that is—O—CH_2·CH_2— instead of the usual —O—CHMe—. It seemed preferable to assume removal of oxygen by reduction rather than to postulate its transference by successive dehydration and hydration of the resulting olefin. At this juncture the "acetate" hypothesis will be generally preferred. It has been contemplated in the present connexion by Battersby, Schlittler and Taylor.

It is significant that one and the same triacetate-malonate chain (I in *Figure 24*) can be regarded as the precursor of gentiopicrin (and similar substances), yohimbine, ajmaline, macusine-A, and voachalotine, as well as of a large number of related alkaloids. For vincadifformine, which also covers aspidospermine and *Hunteria* bases, the skeleton (II in *Figure 24*) is slightly different. In the case of voacangine a Ⓒ—C group in (I) is transposed, giving III (*Figure 24*). A malonate CO then ring closes to C^6 (dotted line).

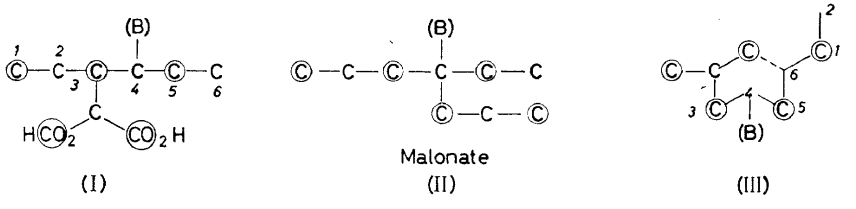
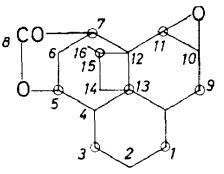


Figure 24

Actually the new chain need not be obtained by migration. It could be constructed *ab initio* in the required manner.

The biogenesis of lycopodium alkaloids has been discussed by Wiesner[64]. He approves and develops an acute suggestion of Conroy[65] that the basic

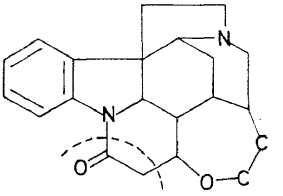
units are two chains of four acetate moieties each. This is illustrated for annotinine in *Figure 25*. The two tetra-acetate chains are indicated, *1–8* and *9–16*. The chemical conformity is remarkable but the lactone carbonyl must be obtained by oxidation of methyl.



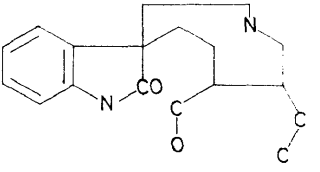
Annotinine

Figure 15

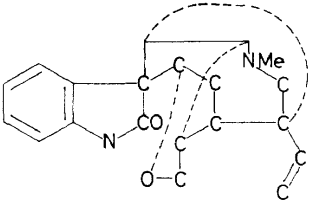
The oxindole alkaloids are doubtless derived from the indoles by processes of molecular rearrangement. The relation of gelsemine[66] to strychnine may be indicated by the breaking of certain bonds and the formation of new ones (*Figure 26*).



Strychnine



Broken and oxidized skeleton



Three new linkages required to reach gelsemine

Figure 26

The topics mentioned illustrate the direction of progress which has been greatly accelerated in the last few years, partly by the manifold applications of isotopic tracer technique but also by the rapid development of physical methods of molecular structural determinations, particularly by means of i.r., N.M.R., and X-ray crystallography. Complementary have been the improved methods of separation of natural products, especially by means of modern versions of chromatography.

There are many more alkaloids and they present many fascinating problems but it is impossible to refer to more of these within the compass of a single lecture.

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