RECENT INVESTIGATIONS ON SOME ALKALOIDS FROM INDIAN PLANTS

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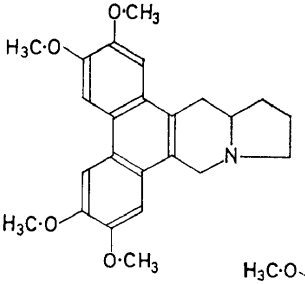
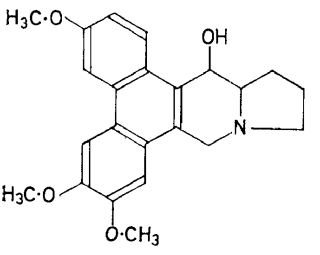
The study of alkaloids constitutes one of the most interesting branches of the chemistry of natural products. India is endowed with a very rich flora, and the ancient Indian system of medicine is largely based on plant remedies. Alkaloids have been isolated from many Indian plants reputed to have medicinal value, but attempts at structure elucidation have not been made in a number of cases. On closer examination, some of these have proved to be identical with alkaloids of known structure, as, for example, " toddaline " with chelerythrine[1], " biflorine " with protopine[2], " umbellatine " with berberine[3], " neprotine " with jatrorrhizine[3], " thalictrine " with magnoflorine[4] and " budrungine " with evodiamine[5]. In some other cases, however, there has been scope for structural investigations, and this paper is concerned with some of the results obtained in these studies.

Tylophora asthmatica Wight et Arn. is a perennial climber growing widely in the plains of India and is particularly abundant in the shrub jungles near Madras. The leaves of this plant have been used as an efficient substitute for ipecacuanha. From this plant Ratnagiriswaran and Venkatachalam[6] isolated two crystalline alkaloids, tylophorine and tylophorinine, which were characterized through a number of derivatives and assigned the molecular formulae $C_{24}H_{27}O_4N$ and $C_{23}H_{27}O_4N$ respectively. As a result of our



(I)



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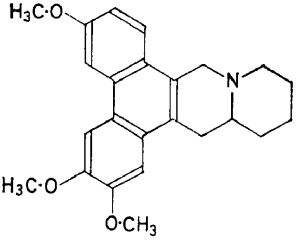


(III)

studies, tylophorine[7] has been shown to have structure (I) and tylophorinine[8] structure (II). The marked similarity of these structures to that of the alkaloid cryptopleurine (III)[9] obtained from *Cryptocarya pleurosperma* is of especial interest, because *Tylophora asthmatica* (Asclepiadaceae) belongs to the Order Tubiflorae of the Metachlamydeae, and is taxonomically far removed from *Cryptocarya pleurosperma* (Lauraceae), which belongs to the Order Ranales of the Archichlamydeae. The structure of cryptopleurine was determined by X-ray crystallography[10], without recourse to chemical studies, and salient features of our degradative studies leading to assignment of structures (I) and (II) to tylophorine and tylophorinine may, therefore, be of some interest.

The major alkaloid tylophorine, for which the correct molecular formula had been assigned by earlier workers, was found to contain four methoxyl groups but no *N*-methyl group. On Hofmann degradation, tylophorinemethine ($C_{25}H_{29}O_4N$) was formed, which on a second Hofmann degradation yielded the basic de-*N*-methyltylophorinemethine ($C_{26}H_{31}O_4N$) and a nitrogen-free product, obviously formed by the replacement of a dimethylamino group by hydroxyl. These results offered conclusive proof that the nitrogen atom in tylophorine was common to two rings.

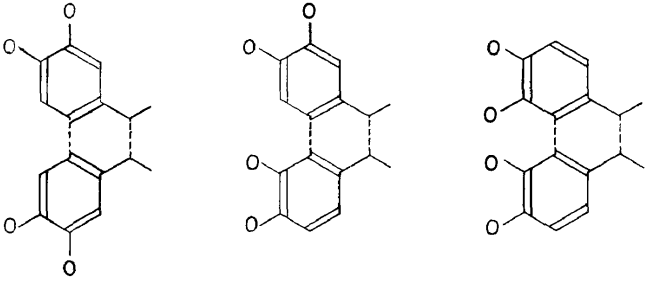
On standing in acid solution, tylophorinemethine, a tertiary base, reverted to a quaternary form, the iodide of which was isolated and found to be identical with racemic tylophorine methiodide. Reversion of a methine to the inactive form of the quaternary salt from which it is derived has been observed in the case of quinolizidine alkaloids of the canadine type[11]. Such a trans-annular interaction is characteristic of eight-, nine- and ten-membered rings[12]. It may, therefore, be concluded that tylophorinemethine has an eight-, nine- or ten-membered ring incorporating the nitrogen atom.

Treatment of tylophorine with cyanogen bromide gave a high yield of a neutral bromocyanamide, which was easily converted into a diethylaminocyanamide on treatment with diethylamine. Since tylophorine has no easily reducible unsaturated bonds, the ready cleavage of a carbon–nitrogen bond indicated[13] the presence of an Ar—C—N— system, and the high reactivity of the bromocyanamide pointed to the presence in it of a $—CH_2Br$ group; hence the partial feature Ar—CH_2—N— should be present in the alkaloid. The bromocyanamide could be converted into a hydroxycyanamide which regenerated tylophorine on acid hydrolysis. The ring opened up by cyanogen bromide should, therefore, be five- or six-membered.

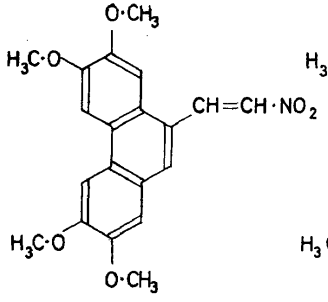
Emde degradation of tylophorine methochloride yielded iso-dihydrohomotylophorine, $C_{25}H_{31}O_4N$. This, on dehydrogenation with palladized charcoal, gave the non-basic detetrahydro-iso-dihydrohomotylophorine, which showed positive pine splinter and Ehrlich tests. That no alteration in ring size had taken place was shown by reduction to the original Emde base. These experiments established the presence of a five-membered nitrogen-containing ring in tylophorine.

The ultra-violet light absorption spectra of tylophorine and the products derived from it by the Hofmann and the Emde degradations were all closely similar to that of phenanthrene. The presence of a phenanthrene ring was proved, and the orientation of the methoxyl groups in the alkaloid established, by the following experiments. iso-Dihydrohomotylophorine-

methine was oxidized with potassium permanganate, and the acidic fraction was esterified with diazomethane to yield a monoester, $C_{21}H_{22}O_6$, and a diester, $C_{22}H_{22}O_8$. Hydrolysis and decarboxylation of the monoester yielded a compound, $C_{19}H_{20}O_4$, corresponding to a tetramethoxymethylphenanthrene. Identification of this compound was rendered possible by a consideration of certain biogenetic aspects. Sir Robert Robinson[14] has suggested that the phenanthrene ring in cryptopleurine could have been



formed from two phenylalanine units. It seemed likely that tylophorine could have resulted from two dihydroxyphenylalanine units (or their equivalent) by coupling in one of three ways. Three of the four tetramethoxymethylphenanthrenes corresponding to these modes of fusion were synthesized, and the decarboxylation product was found to be identical with



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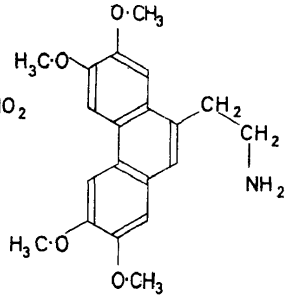

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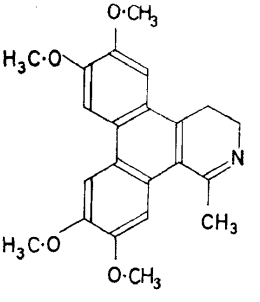

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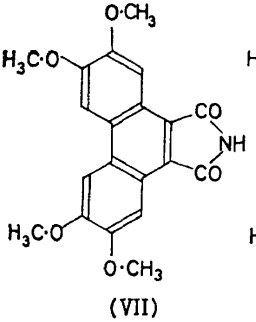

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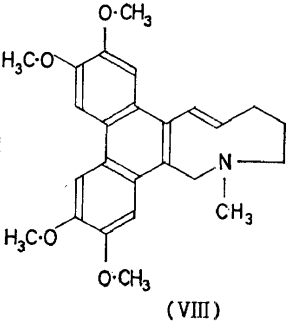

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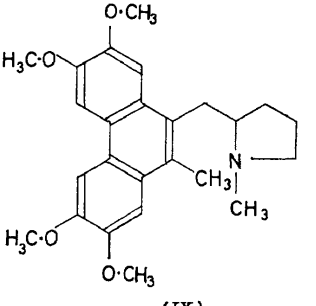
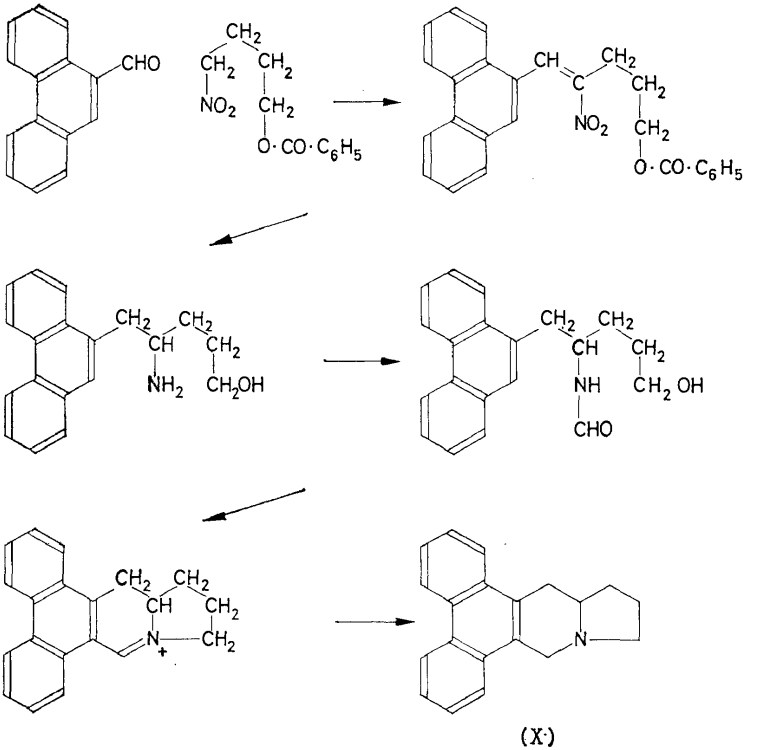


(IX)

2,3,6,7-tetramethoxy-9-methylphenanthrene, thus proving the presence of a phenanthrene ring, the orientation of the methoxyl groups, and one point of attachment of the heterobicyclic system in tylophorine.

The diester, $C_{22}H_{22}O_8$, referred to earlier, could be hydrolysed to a dicarboxylic acid which was readily converted into an anhydride and an imide. The latter was also obtained in poor yield by direct oxidation of tylophorine iso-methohydroxide. Several attempts to synthesize 2,3,6,7-tetramethoxyphenanthrene-9,10-dicarboxylic acid were made, in particular by oxidation of 2,3,6,7-tetramethoxy-9,10-dimethylphenanthrene under a variety of conditions; all these efforts were unsuccessful, however, the starting material being either recovered or totally destroyed. Ultimately, 2,3,6,7-tetramethoxyphenanthrene-9,10-dicarboxylimide was synthesized as follows. Condensation of 2,3,6,7-tetramethoxyphenanthrene-9-aldehyde with nitromethane yielded the corresponding 9-(2′-nitrovinyl)-phenanthrene (IV); this compound was reduced by lithium aluminium hydride to 2,3,6,7-tetramethoxy-9-(2′-aminoethyl)-phenanthrene (V), whose acetyl derivative, on cyclization with phosphorus oxychloride, gave the dihydroisoquinoline (VI). Oxidation of the methiodide of (VI) with potassium permanganate yielded the required imide (VII), which was identical (mixed melting point and infra-red light absorption spectrum) with the oxidation product from tylophorine iso-methohydroxide.

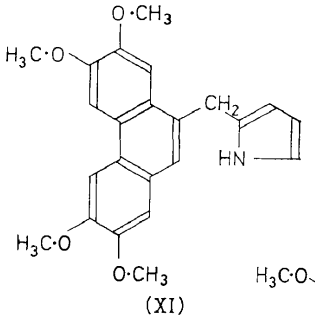
Chart 1. Synthesis of phenanthro-(9,10: 6′,7′)-indolizidine (X)



(X)

On the basis of these results, tylophorine was uniquely formulated as 2,3,6,7-tetramethoxyphenanthro-(9,10: 6′,7′)-indolizidine (I), tylophorinemethine as (VIII), and iso-dihydrohomotylophorine as (IX).

In order to serve as a model for the synthesis of tylophorine, synthesis of the parent ring system, phenanthro-(9,10: 6′,7′)-indolizidine (X), was carried out by the sequence of steps shown in *Chart 1*. However, this method could not be applied to the synthesis of tylophorine itself, since 2,3,6,7-tetramethoxyphenanthrene-9-aldehyde, on condensation with δ-nitrobutyl benzoate, yielded a complex mixture of as yet unidentified products but not the desired nitropentene. Nor could Marchini and Belleau's method[15] for the synthesis of cryptopleurine be applied, since 2,3,6,7-tetramethoxy-9-phenanthrylmethyl chloride failed to condense with proline ester, self-condensation of the latter apparently proceeding much faster than the reaction with the halide. Ultimately, success was achieved by the following route. Treatment of pyrryl magnesium bromide with 2,3,6,7-tetramethoxy-9-phenanthrylmethyl chloride yielded 2-(2,3,6,7-tetramethoxy-9-phenanthrylmethyl)-pyrrole (XI). Reduction in acetic acid solution in the presence of Adams catalyst gave the corresponding pyrrolidine (XII),



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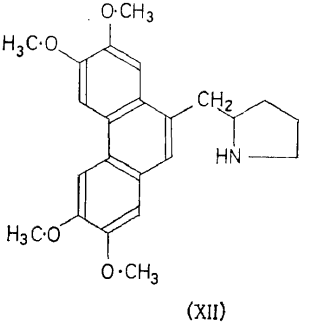

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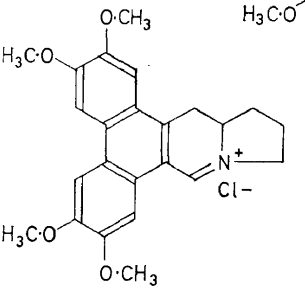


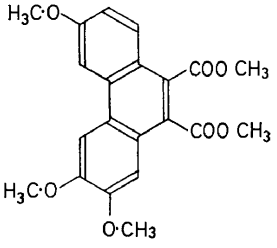
(XIII)

whose *N*-formyl derivative, on cyclization with phosphorus oxychloride, yielded the quaternary chloride (XIII). This was reduced by sodium borohydride to (±)2,3,6,7-tetramethoxyphenanthro-(9,10: 6′,7′)-indolizidine (I). The infra-red light absorption spectrum of the synthetic compound was identical with that of (−)tylophorine in chloroform solution. The synthetic compound was resolved by means of camphor sulphonic acid into (−)tylophorine, m.p.289°(d), $[\alpha]_D^{30}$ − 11·5°, and (+)tylophorine, m.p.289°(d), $[\alpha]_D^{30}$ + 12·25°. The structure (I) assigned to tylophorine was thus proved both by degradation and by synthesis.

The minor alkaloid tylophorinine required elaborate treatment for purification, and, on the basis of analyses of the pure material, the molecular

formula had to be revised to $C_{23}H_{25}O_4N$. The alkaloid contained three methoxyl groups and the infra-red light absorption spectrum showed a weak band at 3·1μ indicating a hydroxyl group. The ultra-violet light absorption spectrum was very similar to that of cryptopleurine, and was unchanged on the addition of alkali, showing that the hydroxyl group was not phenolic. Acetylation yielded an acetate, with infra-red light absorption bands at 5·8 and 8·0μ, confirming the presence of a hydroxyl group.

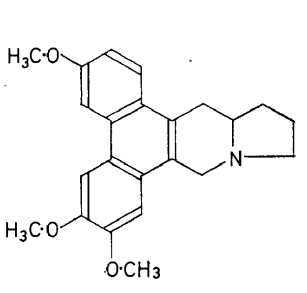
Mild oxidation of tylophorinine methiodide yielded an acid, which was converted into an anhydride under crystallization conditions. Methylation of the acid with diazomethane yielded a diester, $C_{21}H_{20}O_7$, m.p.160–162°, which was identical with dimethyl 2,3,6-trimethoxyphenanthrene-9,10-dicarboxylate (XIV), obtained similarly from cryptopleurine, kindly pre-



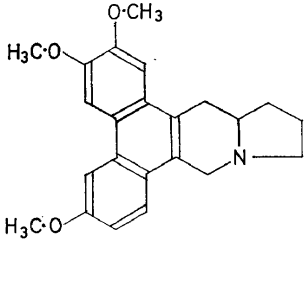
(XIV)

sented to us by Dr Gellert. This established the presence in tylophorinine of a 2,3,6-trimethoxyphenanthrene moiety, to whose 9,10-positions the heterocyclic portion of the molecule was linked. Since less than a gram of material was available, and the Hofmann and Emde degradations gave very poor yields, further work on the lines employed in the case of tylophorine was not possible. However, a definite assignment of structure was made possible through the following experiments. Catalytic hydrogenation of tylophorinine in acetic acid solution in the presence of palladized charcoal and perchloric acid yielded desoxytylophorinine, $C_{23}H_{25}O_3N$.

On the assumption that tylophorinine contained a phenanthro-indolizidine system like tylophorine, two structures, (XV) and (XVI), were possible for desoxytylophorinine. The synthesis of the structure corresponding to (XV) was effected on lines analogous to that employed for tylophorine,



(XV)



(XVI)

starting from 2,3,6-trimethoxy-9-phenanthrylmethyl chloride. The infra-red light absorption spectrum in chloroform solution of the synthetic compound was identical with that of desoxytylophorinine obtained from the natural alkaloid, and both substances gave the same methine, $C_{24}H_{27}O_3N$, m.p.171·5° (identical melting point, mixed melting point, and infra-red light absorption spectra) on Hofmann degradation.

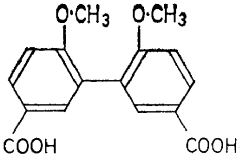
Hydrogenolysis of tylophorinine to desoxytylophorinine under the conditions employed indicated the presence of a benzyl alcohol system. Since tylophorinine does not show the properties of a carbinolamine, the hydroxyl group could be uniquely located and tylophorinine itself assigned structure (II).

Tylophorine and tylophorinine are the only two alkaloids known at present which are phenanthroindolizidines. The Asclepiadaceae are a large family of some 1,800 species, there being a record of 140 species in India alone. Further search in this family may bring to light many more alkaloids of this type.

The Menispermaceae are one of the families of which quite a large number of species has been examined for alkaloids. While protoberberines and aporphines have been isolated from some, the predominant type found in this family is the biscoclaurine type of which more than thirty alkaloids are known at present[16]. In India, there is a record of only eleven genera and eighteen species belonging to the Menispermaceae. The isolation of tiliacorine from *Tiliacora racemosa* Colebr. has been reported by various workers[17], who have recorded for the alkaloid different melting points and analyses. Tiliacorine was isolated by us by a modified procedure and purified by chromatography, and gave analyses corresponding to $C_{34}H_{29}O_3N_2(OCH_3)_3$. The alkaloid was soluble in Claisen's alkali, indicating the presence of a hindered phenolic hydroxyl group. The ultra-violet light absorption spectrum was very similar to that of trilobine and dihydromenisarine (λ_{max} = 295 mμ, log ϵ = 3·91; λ_{min} = 265 mμ, log ϵ = 3·48).

With a mixture of sulphuric and nitric acids, the alkaloid gave the same characteristic blue colour as trilobine, menisarine and isotrilobine, indicating the presence of a dibenzodioxin system[18]. Conventional procedures[16] which were applied in the case of biscoclaurine alkaloids (such as Hofmann degradation followed by ozonolysis, or cleavage with sodium and liquid ammonia) failed to yield any useful result. However, direct oxidation studies were fruitful, and made it possible to assign a structure to tiliacorine[19, 20].

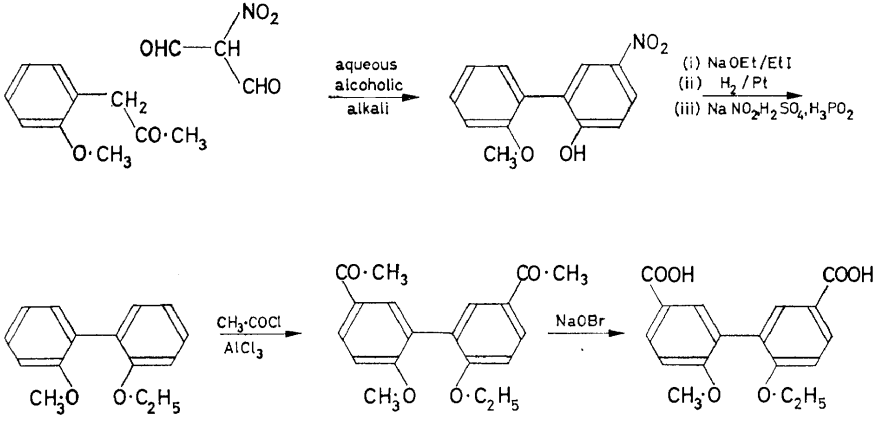
Oxidation of *O*-methyltiliacorine dimethiodide with potassium permanganate yielded an acid, $C_{16}H_{14}O_6$, which gave a dimethyl ester, $C_{18}H_{18}O_6$. This was surprising, since all known biscoclaurine alkaloids containing a dibenzodioxin system yield only 2-methoxydiphenyl ether 4′,5-dicarboxylic acid, $C_{15}H_{12}O_6$. The acid, $C_{16}H_{14}O_6$, contained two methoxyl groups, and could not have been a dimethoxydiphenyl ether dicarboxylic acid which would have had the formula $C_{16}H_{14}O_7$. Decarboxylation of the acid, $C_{16}H_{14}O_6$, yielded a compound, $C_{14}H_{14}O_2$. The ultra-violet light absorption spectrum and the formula of this substance suggested that it could be 2,2′-dimethoxydiphenyl, and this was confirmed by comparison with an



(XVII)

authentic sample. If tiliacorine is a biscoclaurine type alkaloid, the point of attachment of the diphenyl to the rest of the molecule should be through the 5- and 5′- positions. Consequently, the acid, $C_{16}H_{14}O_6$, should be 2,2′-dimethoxy-5,5′-dicarboxydiphenyl (XVII), and this was confirmed by direct comparison of the acid and its dimethyl ester with authentic specimens[19].

Chart 2. Synthesis of 2-methoxy-2′-ethoxy-5,5′-dicarboxydiphenyl

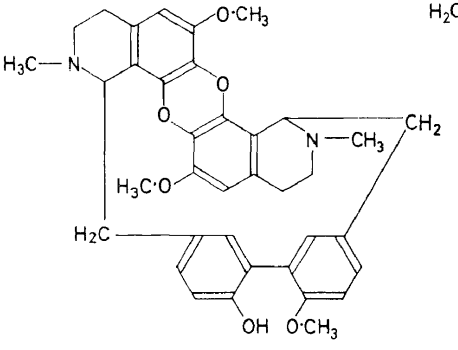


The isolation of 2,2′-dimethoxy-5,5′-dicarboxydiphenyl clearly indicates that tiliacorine is derived from two molecules of coclaurine, the carboxyl groups at the 5,5′-positions labelling the points of attachment of the diphenyl system to the two isoquinoline moieties. Tiliacorine is thus revealed as a new type of biscoclaurine alkaloid in which the benzyl residues of the two coclaurine units are linked directly, and not through oxygen as is the case in all instances recorded so far. Numerous examples of such a phenol coupling are known, the aporphines being a familiar example[21]. The surprising thing, therefore, is not the direct coupling between the two benzyl moieties observed in tiliacorine, but that such a type has not been encountered so far, although the chemical examination of over fifty species of Menispermaceae and Magnoliaceae is on record.

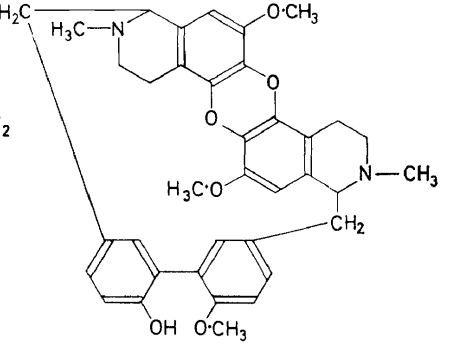
Oxidation of tiliacorine dimethiodide itself yielded 4-methoxyisophthalic acid. This indicated the location of the phenolic hydroxyl group in the diphenyl unit, and this assignment was confirmed by the formation of 2-methoxy-2′-ethoxy-5,5′-dicarboxydiphenyl on oxidation of *O*-ethyltiliacorine dimethiodide[20]. An authentic specimen of this acid was synthesized by a novel method, illustrated in *Chart 2*, which utilized nitromalonaldehyde,

in a manner similar to that used by Hill and Hale many years ago for the synthesis of *p*-nitrophenol derivates[22].

Analytical results are in agreement with the presence in tiliacorine of a dibenzodioxin ring, which was indicated by the colour reaction, and also with the location of two of the methoxyl groups in this unit. With these considerations in mind, and on the basis of the Faltis theory[23], tiliacorine could almost certainly be formulated as (XVIII). The alternative structure (XIX), involving the 5,6-positions of the isoquinoline moieties, is of a type that has not been encountered in Nature so far.

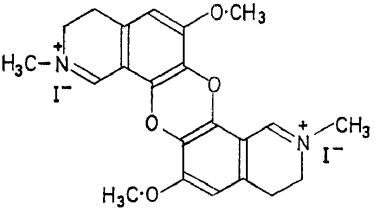


(XVIII)



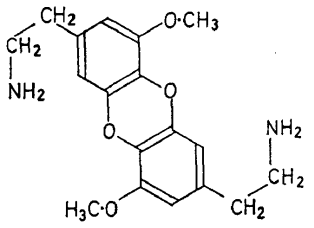
(XIX)

It was necessary to degrade tiliacorine to an identifiable dibenzodioxin derivative, so that the presence of this ring system in the alkaloid, and the orientation of the substituents suggested in structure (XVIII), could be unequivocally established. With this object, tiliacorine was oxidized with manganese dioxide–sulphuric acid[24] to yield a compound which was isolated as the quaternary iodide, $C_{22}H_{24}O_4N_2I_2$, and which can be formulated as (XX) on the basis of structure (XVIII) for tiliacorine. Since



(XX)

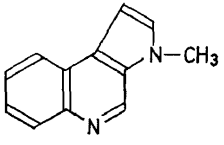
the oxidation with manganese dioxide gives very poor yields, further degradation based on the oxidation product has not been feasible. It is hoped that it will be possible to prove structure (XX) for the quaternary iodide by synthesis. The amine (XXI), has been synthesized, and this is expected to lead not only to the quaternary iodide (XX), but ultimately to the synthesis of the alkaloid itself.



(XXI)

The Apocyanaceae are a large family rich in alkaloid-bearing plants, as is seen from the fact that no less than two hundred of the thousand and more alkaloids known at present have been obtained from plants belonging to this family[25]. Though steroidal alkaloids have been found in certain genera, the majority of Apocyanaceous plants so far investigated yield indole alkaloids of greater or lesser complexity. The presence of alkaloidal material in *Alstonia scholaris*, a tall graceful tree growing all over India, has been known for nearly a century, but it was through the work of Goodson and Henry[26] that reliable data were first provided. These authors isolated the principal alkaloid, echitamine, as its " hydrochloride ", and characterized it by preparation of several derivatives. They showed that it contained a carbomethoxy group, and, by means of colour reactions on the alkali-fusion products, demonstrated the presence of an indole nucleus. Recently, echitamine has aroused considerable interest[27a–e], and, while it is not possible to outline all the work carried out by the different groups of investigators, salient features can be summarized.

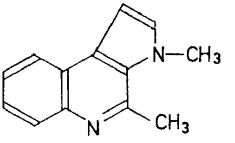
The alkaloid was easily recognized to be a dihydroindole derivative from its ultra-violet light absorption spectrum. The presence of an allyl quaternary ammonium system was established by reduction of echitamine chloride to a tertiary base, originally formulated by us as $C_{22}H_{28}O_3N_2$, but later shown to be $C_{21}H_{26}O_3N_2$ by Conroy *et al.*[27d]. The tertiary base gave an N_a-acetyl* derivative (colour reaction, infra-red and ultra-violet spectra), showing the presence of an $—N_aH$ group. Selenium dehydrogenation of the tertiary base yielded 1′-methylpyrrolo-(2′,3′:3,4)quinoline (XXII),



(XXII)

whole identity, surmised on the basis of its analysis and ultra-violet light absorption spectrum, was confirmed by comparison with an authentic specimen obtained by silver acetate oxidation of calycanthine. On zinc dust distillation of what was presumably the same tertiary base, Birch, Hodson and Smith obtained 1′,2-dimethylpyrrolo-(2′,3′:3,4)quinoline (XXIII).

* The nitrogen atoms in the molecule are designated N_a and N_b.

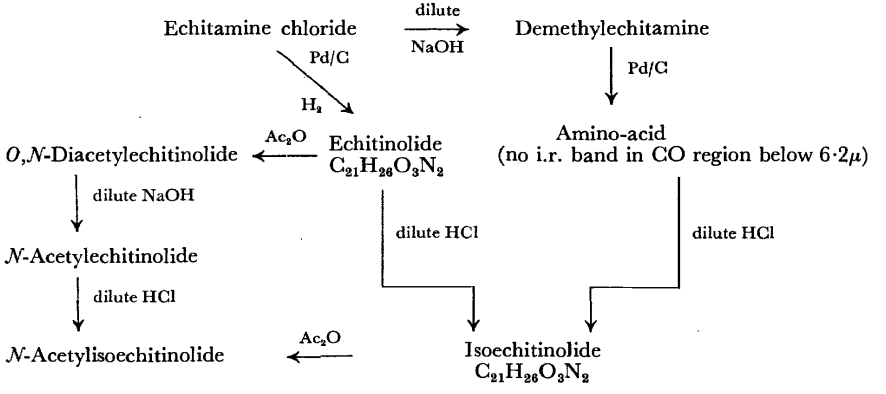


(XXIII)

In our attempts to formulate a structure for echitamine, we were largely guided by the work of Hodson and Smith[28] on the ultra-violet light absorption characteristics of dihydroindoles in neutral and in acid solution. When these observations were taken into account, the ultra-violet light absorption characteristics of echitamine and several products derived from it appeared to indicate the presence of an N_a—C—N_b system. Although the tertiary base, $C_{21}H_{26}O_3N_2$, obtained on reduction of echitamine chloride, did not undergo the reductive cleavage characteristic of eserine-like compounds, its methiodide underwent ring opening on treatment with cold 2N alkali to yield a compound, $C_{22}H_{30}O_4N_2$, which could be deoxygenated to a second tertiary base, $C_{22}H_{30}O_3N_2$. Any structure proposed for echitamine will not be acceptable unless it is capable of explaining these results*.

Some other experimental work having a bearing on the structure of echitamine carried out in our laboratory is shown in *Chart 3.* In order to avoid confusion, the terms " echitinolide " and " isoechitinolide ", suggested by Conroy *et al.*, have been adopted.

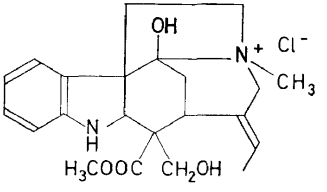
Chart 3. Synthesis of echitinolide, isoechitinolide, and their acetyl derivatives from echitamine



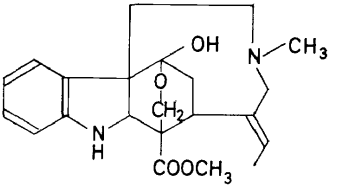
It was obvious that isoechitinolide must be a lactone, since it was obtained from demethylechitamine. The third oxygen atom must be present as an ether, since the compound was recovered unchanged after refluxing with sodium borohydride in methanol solution, and since it did not contain a

* See p. 437.

hydroxyl group, as shown by the absence of active hydrogen in *N*-acetyl-isoechitinolide. Furthermore, isoechitinolide did not also contain the double bond originally present in echitinolide, since its *N*-acetyl derivative was recovered after treatment with sodium periodate–osmium tetroxide. These results could not be satisfactorily explained on the basis of our original presumption that the reduction product of echitamine chloride was an ester. Indeed, we discovered that our " dihydroechitamine " was a lactone, since Zeisel determination showed no methoxyl group, and it should really be formulated as $C_{21}H_{26}O_3N_2$. At this stage, a paper by Conroy *et al.* appeared in which it was recognized that the initial product of reduction of echitamine is so consistituted as to lose spontaneously a molecule of methanol with the formation of a lactone. These authors also clearly established the presence of a $HOCH_2—\underset{|}{\overset{|}{C}}—COOCH_3$ moiety, and suggested the structure (XXIV) for echitamine chloride and (XXV) for echitamine



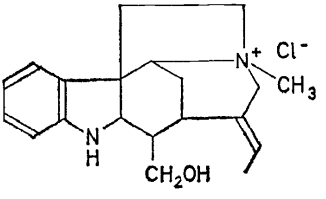
(XXIV)



(XXV)

base. The formation of alloechitamine, with the properties described for it, is not compatible with alternative structures. The sequence of reactions starting with echitinolide methiodide referred to earlier is also satisfactorily explained, since the system O—C—N present in echitinolide might be expected to simulate the behaviour of the N—C—N system present in eserine-like compounds.

Conclusive proof of the structure (XXIV) suggested for echitamine chloride could be provided by correlation with some compound of established structure, *e.g.* the alcohol (XXVI), obtained from the Wieland–Gumlich aldehyde[29].

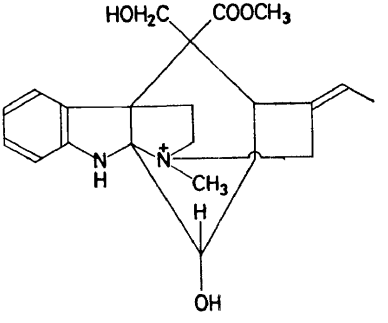


(XXVI)

In a recent survey[30], it has been estimated that hardly 2 per cent of the 191,000 species of flowering plants has been examined for alkaloids. The alkaloid chemist need never be at a loss for interesting problems, and there will always be enough around to beguile his wits.

Note added in proof

Professor J. M. Robertson and co-workers have solved the structure of echitamine by the X-ray method working on crystals of echitamine bromide methanol solvate[31]. *This structure (XXVII) has been confirmed independently by the X-ray investigations of crystals of echitamine chloride and iodide*[32].



(XXVII)

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