

CHAPTER II

HISTORICAL



1. Distribution

Natural sources of indole alkaloids are not only found in plants but also in animals, for example bufotenine (5-hydroxy-N, N-dimethyl tryptamine) occurs in the skin of certain toads and the biogenic amine serotonin (5-hydroxy-tryptamine) is present in minute amounts in the central nervous tissue of warm blooded animal. (25)

The simple indole derivatives are rather widely distributed amongst the dicotyledons; whereas the more complex indole alkaloids are frequent in the Metachlamydeous families Apocynaceae, Strychnaceae, Convolvulaceae and Rubiaceae, they occur also in fungi (*Claviceps* spp.). (25) Indoles have been recognised since the early years of present century. Recently their appearance in Rubiaceae has been reported. The more complicated structure of indole alkaloids occur in Subfamily Cinchonoideae, which has been a very rich source of this type of compounds. They are distributed in the following genera:- (36,37,45,48,56,67)

Adina, Anthocephalus, Cephalanthus, Cinchona, Corynanthe, Mitragyna, Nauclea, Pseudocinchona and *Uncaria*

The more complicated types of indole alkaloids are divided as follows

1.1 Iridoid carboline glycosides

The alkaloids in the form of glycoside combination (glyco-alkaloids) are found in *Holarrhena* spp. (Apocynaceae), *Solanum* spp. (Solanaceae) and *Veratrum* spp. (Liliaceae) but the aglycone part of these groups are steroidal nuclei. (34,35)

Recently the indole-glycosidic-alkaloids have been reported, the occurrence of these alkaloids are mostly in the Naucleaeae.

The occurrence of Iridoid carboline glycosides

Botanical source	Alkaloid	Reference
<i>Adina cordifolia</i> Hook. F. (Rubiaceae)	Cordifoline	36
	Deoxycordifoline	68
<i>Adina rubescens</i> Hemsl. (Rubiaceae)	Rubenine	37
	Rubescine	44
	Deoxycordifoline lactam	39
	5-oxostrictosidine	40
	Macrolidine	38
	Vincoside lactam	43
	3 α , 5 α -deoxycordifoline	41
	3 β , 5 α -tetrahydroxy cordifoline lactam	41
10 β -D-glucosyloxy vincoside lactam	42	

Botanical source	Alkaloid	Reference
<i>Anthocephalus cadamba</i> Miq. (Rubiaceae)	Cadambine	45
	3 α -dihydrocadambine	45
	3 β -dihydrocadambine	47
	3 α -isodihydrocadambine	46
	3 β -isodihydrocadambine	47
	Strictosidine (Isovincoside)	47
<i>Nauclea diderrichii</i> Merr. (Rubiaceae)	3 α -dihydrocadambine	48
<i>Nauclea latifolia</i> Smith. (Rubiaceae)	Isovincoside lactam	70
<i>Rhazya stricta</i> Decaisne. (Apocynaceae)	Strictosidine (Isovincoside)	26
<i>Rhazya orientalis</i> A. Dc.	Strictosidine (Isovincoside)	24
	5 α -carboxystrictosidine	68
<i>Strychnos decussata</i> (Pappe) Gil. (Strychnaceae)	Strychnos Base (Unnamed)	49

Botanical source	Alkaloid	Reference
<i>Vinca rosea</i> (L.) Reichb.f. (Apocynaceae)	Vincoside	31
	Isovincoside (Strictosidine)	31
<i>Vinca minor</i> L. (Apocynaceae)	Vincoside	69

1.2 Pyridino-carboline alkaloids

The pyridino-carboline alkaloids, as the name indicated, contain both carboline and pyridine nuclei. The analogues of these alkaloids are angustine and angustidine which have recently been isolated from *Strychnos angustiflora* Benth.⁽⁵¹⁾ and many species of African and Asian *Strychnos* (Strychnaceae).⁽⁵²⁾

The occurrence of these alkaloids in the Naucleaeae are shown as follows :

The occurrence of Pyridino-carboline alkaloids

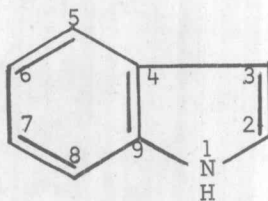
Botanical source	Alkaloid	Reference
<i>Anthocephalus cadamba</i> Miq.	Cadamine	50
	Isocadamine	50

Botanical source	Alkaloid	Reference
<i>Mitragyna javanica</i> Korth et Valeton	Angustine	52
<i>Mitragyna parvifolia</i> (Roxb.) Korth.	Angustine	52
<i>Nauclea coadunata</i> Roxb. ex Smith.	Angustine	52
<i>Nauclea diderrichii</i> Merr.	Naucledine	56
	Nauclelerine	56
	Nauclechine	56
	Nauclexine	56
	Naucleonine	57
	Naucleonidine	57
<i>Nauclea latifolia</i> Smith.	Nauclefine	54
	Naucletine	54
	Naufoline	55
	Decarbomethoxynauclechine	55
<i>Nauclea parva</i> Merr.	Parvine (Nauclefine)	53
<i>Uncaria bernaysii</i> F. Muell.	Angustine	52

Botanical source	Alkaloid	Reference
<i>Uncaria guianensis</i> Aubl. (<i>U. tomentosa</i> DC.)	Angustine	52
<i>Uncaria homomalla</i> Miq.	Angustine	52
	Angustoline	52
	Angustidine	52
<i>Uncaria rhynchophylla</i> Miq.	Angustine	52
	Angustoline	52
	Angustidine	52

2. Chemical nature of indole alkaloids

When a pyrrole ring is condensed with a benzene ring, the resulting compound is indole.



Indole (Benzopyrrole)

An indole ring with a methyl group substituted at C-3 is called skatole. Both indole and skatole have a very foul odour

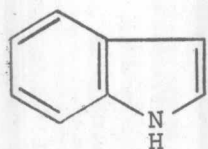
and are responsible for much of the bad smell of our solid wastes, or feces. The word "Skatole", in fact, comes from the Greek word meaning "feces". (19)

These two compounds are formed in the intestines by the action of bacteria and the amino acid involved in this action is tryptophan. Tryptophan has the indole ring in its side-chain and is odourless. It is one of the amino acids that we must have in our diet. Bacteria always manage to get some of the tryptophan molecules and form indole and skatole. These compounds are useless to the body and are not absorbed. They are just eliminated with the feces. (19)

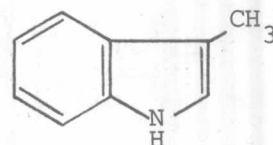
Out of tryptophan, the body makes an important compound which has only been studied recently. Put a hydroxyl group on the indole ring of tryptophan and remove the carboxyl group out of the molecule and the resulting compound is known as serotonin. (19)

Serotonin is found chiefly in the brain, nerves and apparently has something to do with the working way of brain cells. Normally, it is quickly broken down by an enzyme called amine oxidase. Certain known chemicals will interfere with the working of amine oxidase and will cause serotonin to pile up in the brain. This results in all sorts of mental quirks. Hallucinations and temporary mental disorders can be produced. (19)

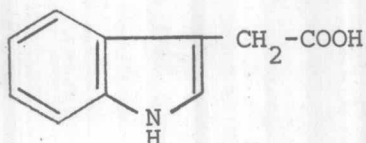
It has also been discovered that some drugs work along these lines in the opposite direction. They calm tensions and fears and therefore are known as tranquilizers. They have become



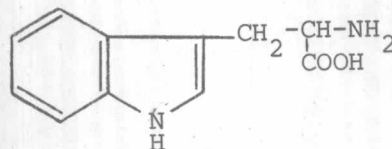
Indole



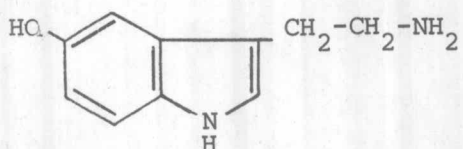
Skatole



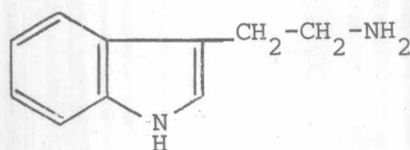
Indole-3-acetic acid (IAA)



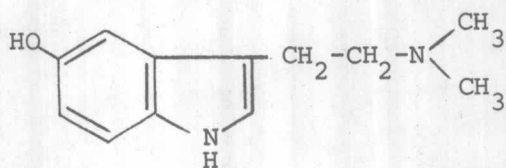
Tryptophan



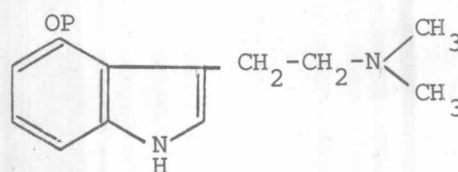
Serotonin



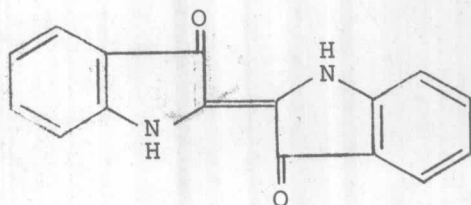
Tryptamine



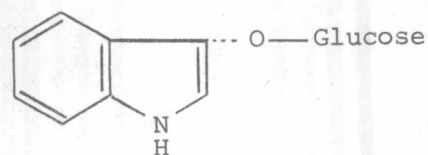
Bufotenine



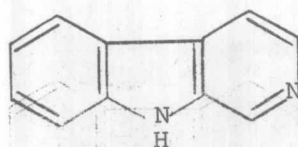
Psilocybine



Indigo



Indican



Carboline

Figure II Some naturally occurring simple indole compounds

quite popular in the last few years. (19)

Two indole rings joined together at the carbon atom next to the nitrogen atom make up a molecule of a deep blue substance called indigo. The name "indigo" comes from "indicus", the old Latin name for "India" since it was from India that the ancient Romans got the substance. From indigo, by the way, comes the name "indole". (19)

By far the most important plant indole is an indole-3-acetic acid (IAA), the naturally occurring growth regulator of universal occurrence in the plant kingdom. (20)

Indole, the index compound of the group, occurs in plants, probably as a breakdown product from tryptophan. It occurs in the distilled oil obtained from jasmine flowers (*Jasminum sambac* Ait.) by enfleurage, and together with skatole in the decaying wood of *Celtis reticulosa* Miq., *C. cinnamomoea* Linn. (21) Numerous other occurrences of indole have been reported but since indole is not an alkaloid, this is not given here in detail.

Many psychoactive plants owe their activity to chemical structures containing an indole nucleus. This nucleus is evident in the synthesis of Lysergic acid diethylamide (LSD) and in such well known compounds as yohimbine, reserpine and physostigmine alkaloids. It is because of the presence of indole alkaloids that many of the most striking hallucinogenic plants owe their biodynamic activity. (25)

There are about 600 alkaloids with an indole nucleus or a nucleus very close to an indole group in their molecules. This

group of alkaloids includes some of which are widely used such as the strychnos alkaloids, corynanthe alkaloids and rauwolfia alkaloids.

These alkaloids are derivatives of indole nucleus. The various groups of them will be classified according to the position of the substituents and the degree of substitution in the pyrrole part of the indole nucleus.

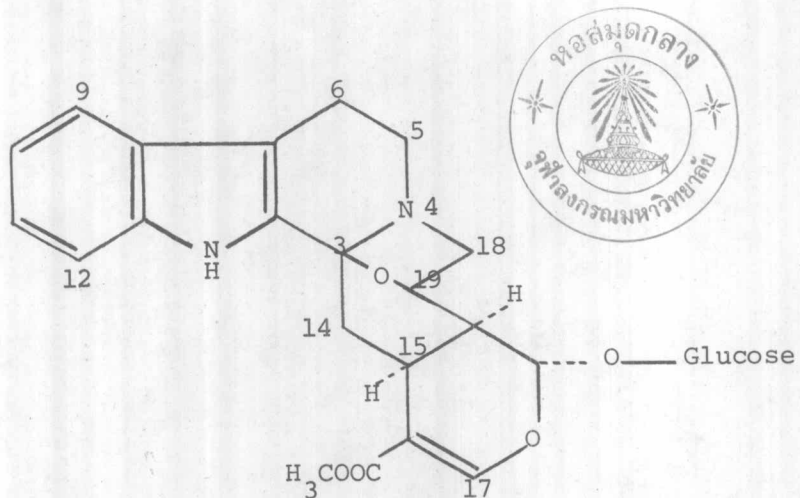
It is extremely difficult to classify indole alkaloids because of their chemical complexity. Of the more than twenty classes of indole alkaloids, those involved in hallucinogenic plants may be placed in four categories :

- a) lysergic acid derivatives (the ergoline alkaloids),
- b) tryptamine (N, N-dimethyltryptamine, psilocybine),
- c) the carboline (harmine), and
- d) the iboga alkaloids (ibogamine).⁽²⁵⁾

It is believed that indole alkaloids arise from tryptophan and a monoterpenoid moiety.⁽²²⁾ Tryptamine is recognised as possible intermediates in the biogenetic pathway to the harmine type (β -carboline) alkaloids on one hand and many of the more complicated indole type on the other.

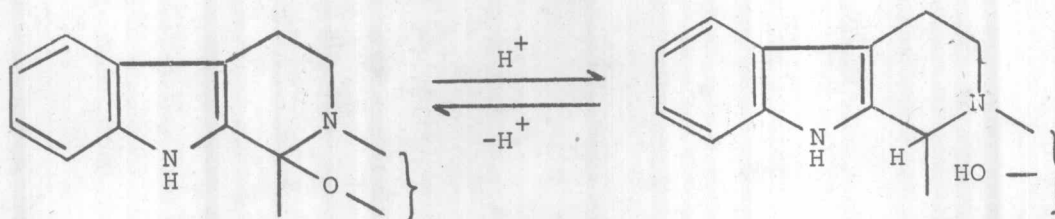
3. Chemical nature of *Anthocephalus* alkaloids

The pentacyclic indole heteroyohimbine type glycosidic alkaloids are widely distributed in the Naucleaeae. Heteroyohimbinoïd glycoside skeleton comprising of carboline unit joins with

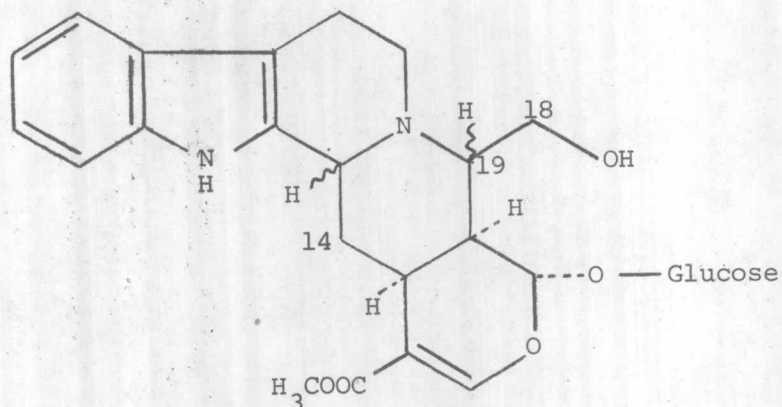


Cadambine

Reduction of cadambine with NaBH_4 in acetic acid afforded 3β -dihydrocadambine and this indicates that cadambine is derived from 3β precursor.



b) Six membered ring D, isodihydrocadambine has two stereoisomeric forms i.e. $\text{C}(3)\text{-H } \alpha$ and β



Isodihydrocadambine C(3)-H - α
- β

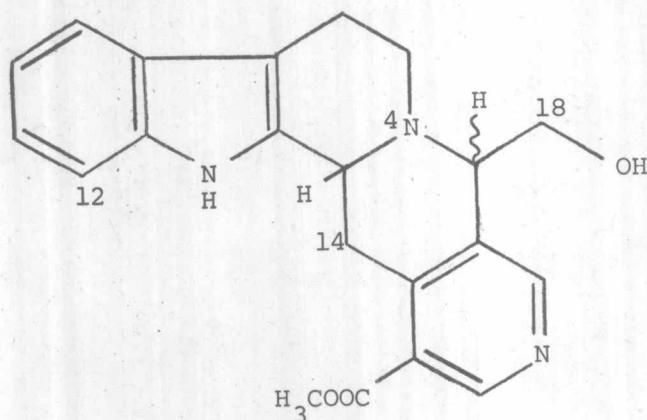
Structurally corresponding to heteroyohimbine type can be judged that configurations of 3α -dihydrocadambine, 3α -isodihydrocadambine are *allo* and 3β -dihydrocadambine, 3β -isodihydrocadambine are *epiallo*.⁽⁸⁴⁾

	C(3)-H	C(20)-H	C(15)-H
3α -dihydrocadambine	α	α	α
3α -isodihydrocadambine	α	α	α
3β -dihydrocadambine	β	α	α
3β -isodihydrocadambine	β	α	α

In view of non-glycosidic alkaloids, less polar constituents cadamine and isocadamine also occur in *Anthocephalus*.⁽⁵⁰⁾

Both alkaloids presumably occurring as the alcohols have the unusual N(4)-C(19) bond and are thus structurally analogous to isodihydrocadambine (3β) since there are several precedents for the formation of pyridine from glycosidic dihydropyran rings. The striking difference is in the stereochemistry of C(3) which shows that they are derived from a 3β precursor rather than 3α and hence

constitute the first vincoside derivatives to be found in the plant. (50)



Cadamine, isocadamine C(19)-H remains undetermined

4. Biogenesis

Knowledge on the biosynthesis of alkaloids in recent years has helped a great deal in unifying the alkaloids of apparently different skeletal patterns into common groups on the basis of their precursors, and from their biosynthesis it is also possible to have the informations in the genetic level in plant organisms. Since the sequence of biogenetic steps reflect the evolutionary history of the plant world, genetic information would be useful for classification of taxa. In recent years, intensive research in this field is being pursued in different parts of the world using experimental verification on the modes of application of radioactive tracer techniques. The biosynthesis of indolic base involves a concerted process comprising :

- a) biosynthesis of tryptophan or its decarboxylation product tryptamine,
- b) biosynthesis of non-tryptophan, i.e. C₉-C₁₀ residues, and
- c) appropriate condensation of the products from a) and b) to build up the indole alkaloids. (26)

4.1 Formation of tryptamine

Robinson had originally suggested that the two nitrogens and the aromatic portion of all of the then known indole alkaloids originate from tryptophan via its decarboxylation product, tryptamine. (29)

Tryptophan is known to originate in plant cells from shikimic acid-5-phosphate. (27)

This route, often called the shikimic acid pathway, involves the condensation of phosphoenolpyruvate and 4-carbon sugar erythrose-4-phosphate which is derived from pentose phosphate pathway. The product of this reaction is converted to shikimic acid. Phosphorylation of shikimic acid yields 5-phosphoshikimic acid. (27)

The amino acid tryptophan is derived from anthranilic acid, 5-phosphoribosyl-1-pyrophosphate and serine as outlined in Figure III.

By means of a coupled reaction the carboxyl group is then cleaved and the pyrrole ring is linked to the former carbon atom 1 of the anthranilic acid molecule. The enzyme catalyzing this cyclisation causes elimination of a hydroxyl ion from carbon atom 2

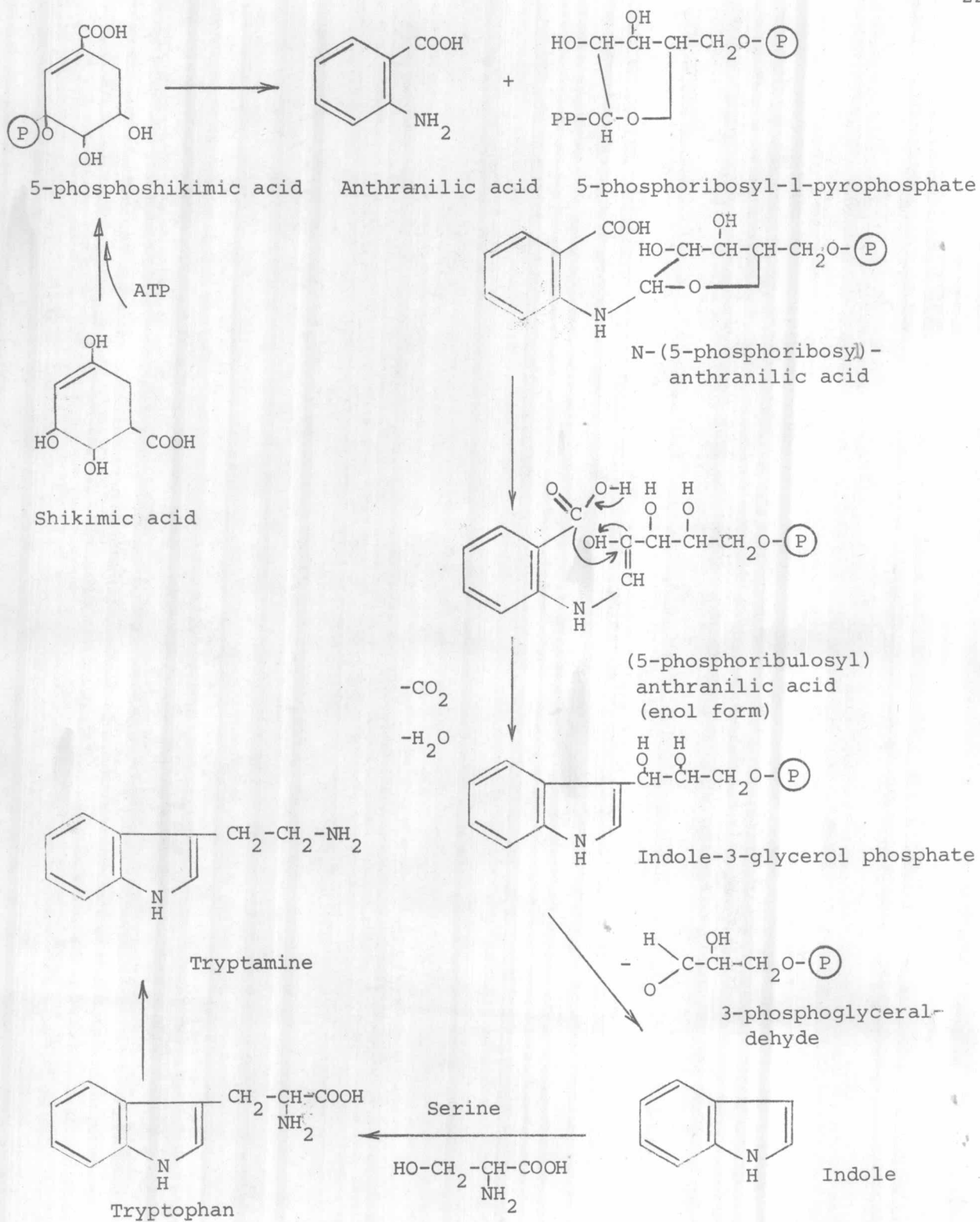


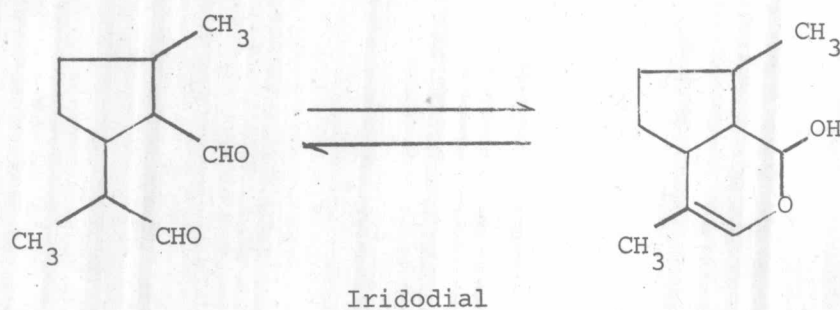
Figure III Formation of Tryptamine (27)

of the enol form of ribulose. Spontaneous ring closure then occurs with subsequent elimination of carbon dioxide and a proton.

Indole-3-glycerol phosphate formed in this manner is broken down in the next reaction step to indole and 3-phosphoglyceraldehyde. Indole then reacts with serine in the presence of the enzyme tryptophan synthetase, with the elimination of water and formation of tryptophan. (27)

4.2 Formation of non-tryptamine residue (iridoid compound)

Iridoid compounds are cyclic monoterpenes structurally derived from iridodial.



Iridodial, as well as substances of similar structures, occurs in the defensive secretions of the ants of the *Iridomyrmex* sp. and is named after these organisms. The iridoid compounds were formerly known as pseudo-indicans since a few of them polymerise in the presence of acids and oxygen to blue coloured substances and thus behave like indican, which under similar condition produces the blue dye indigo. (28)

Iridoid substances are especially widespread in higher plants. They may be divided into compounds of the loganin group

which possesses ten carbon atoms and those of the aucubin group with nine carbon atoms. (28)

During the "boom" of indole alkaloid chemistry in the last 15 years, an enormous experimental glossary on the structure and chemistry of these natural products has been accumulated. This quickly brought to the conclusion that the non-tryptophan derived part of the overwhelming majority of the indole alkaloids is a ten or a nine carbon unit. Several authors exercised their chemical imagination in order to formulate a general biogenetic hypothesis explaining the origin of the nine or ten carbon portion of these alkaloids. (29)

By this time it was known, as the result of numerous feeding experiments, that the C_9-C_{10} components of the indole alkaloids were derived by way of the acetate-mevalonate pathway through an iridoid skeleton, which were incorporated into indole alkaloids through condensation with tryptamine. Since the non-tryptophan aliphatic C_9-C_{10} units can be incorporated in three basic forms, their incorporation can result in three basic classes of indole alkaloids e.g. corynanthe, iboga and aspidosperma skeletons. (30)

After some of these hypothesis had been invalidated by feeding experiments, investigations carried out principally by Arigoni, Battersby, Scott and their groups (33) provided a well documented insight into the biosynthesis of these alkaloids. The major achievement of their research has been the unambiguous establishment of the terpenoid origin of the nine or ten carbon

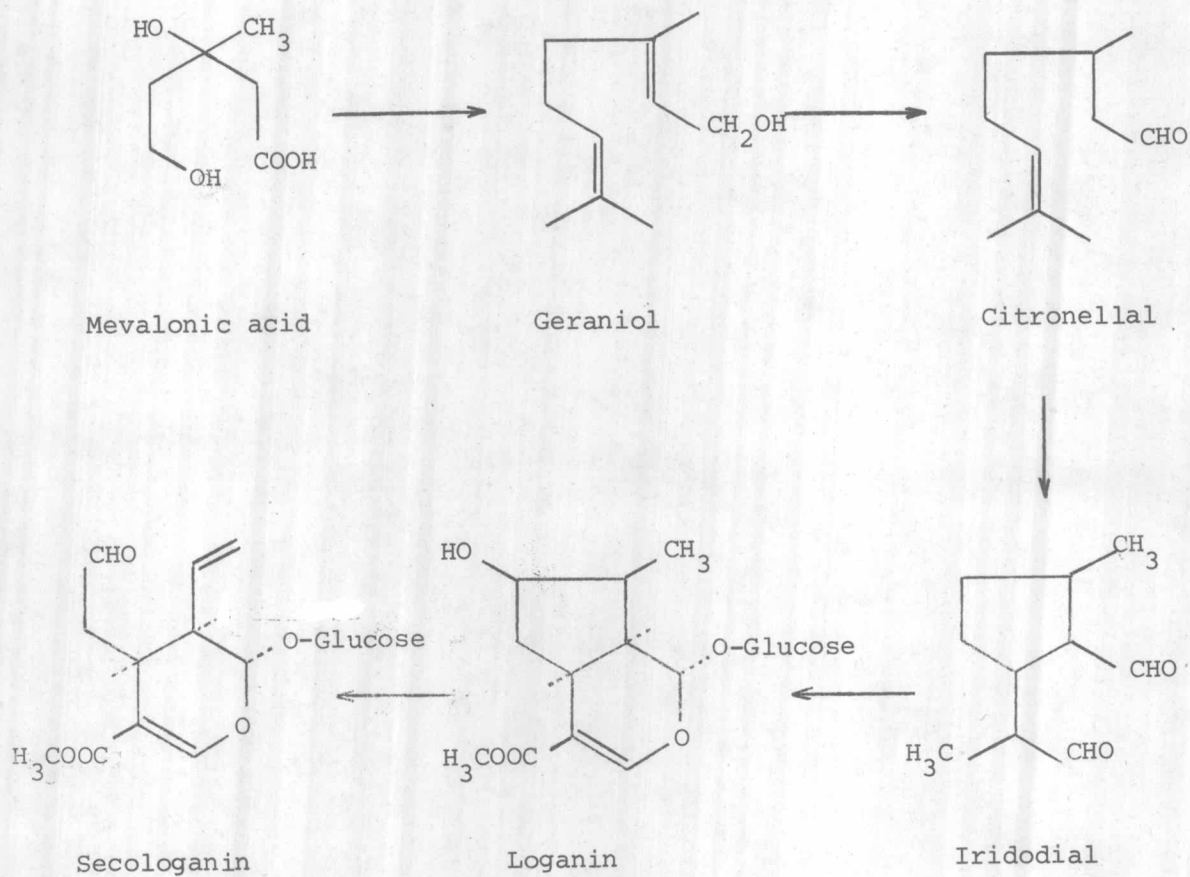
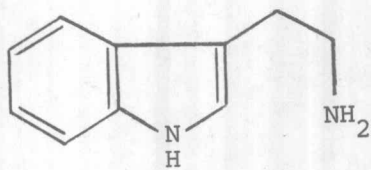
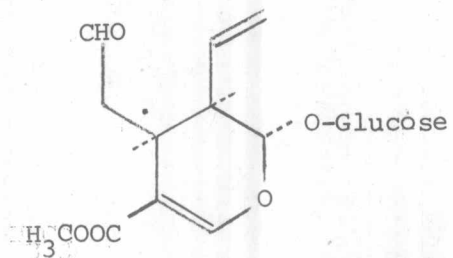


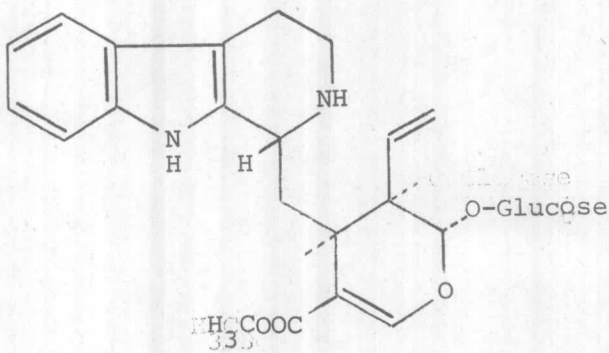
Figure IV Monoterpene hypothesis showing the formation of non-tryptophan residue⁽²⁹⁾



Tryptamine



Secologanin



Vincoside

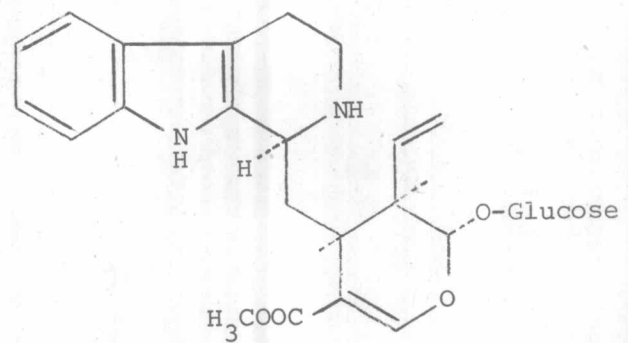
Isovincoside
(Strictosidine)

Figure V Initial step in the biosynthesis of indole alkaloids (31)

moiety. First hypothesis was postulated by Thomas and Wenkert.^(76,77) It was shown that this part of the indole alkaloids is derived from two moles of mevalonate by way of cyclisation of geraniol → Iridodial → loganin → secologanin as outline in Figure IV.

4.3 Formation of indole alkaloids

When tryptamine reacts with secologanin at pH 4.5, two bases are formed, the major product, vincoside and the minor product isovincoside (Strictosidine).⁽³¹⁾ (See Figure V)

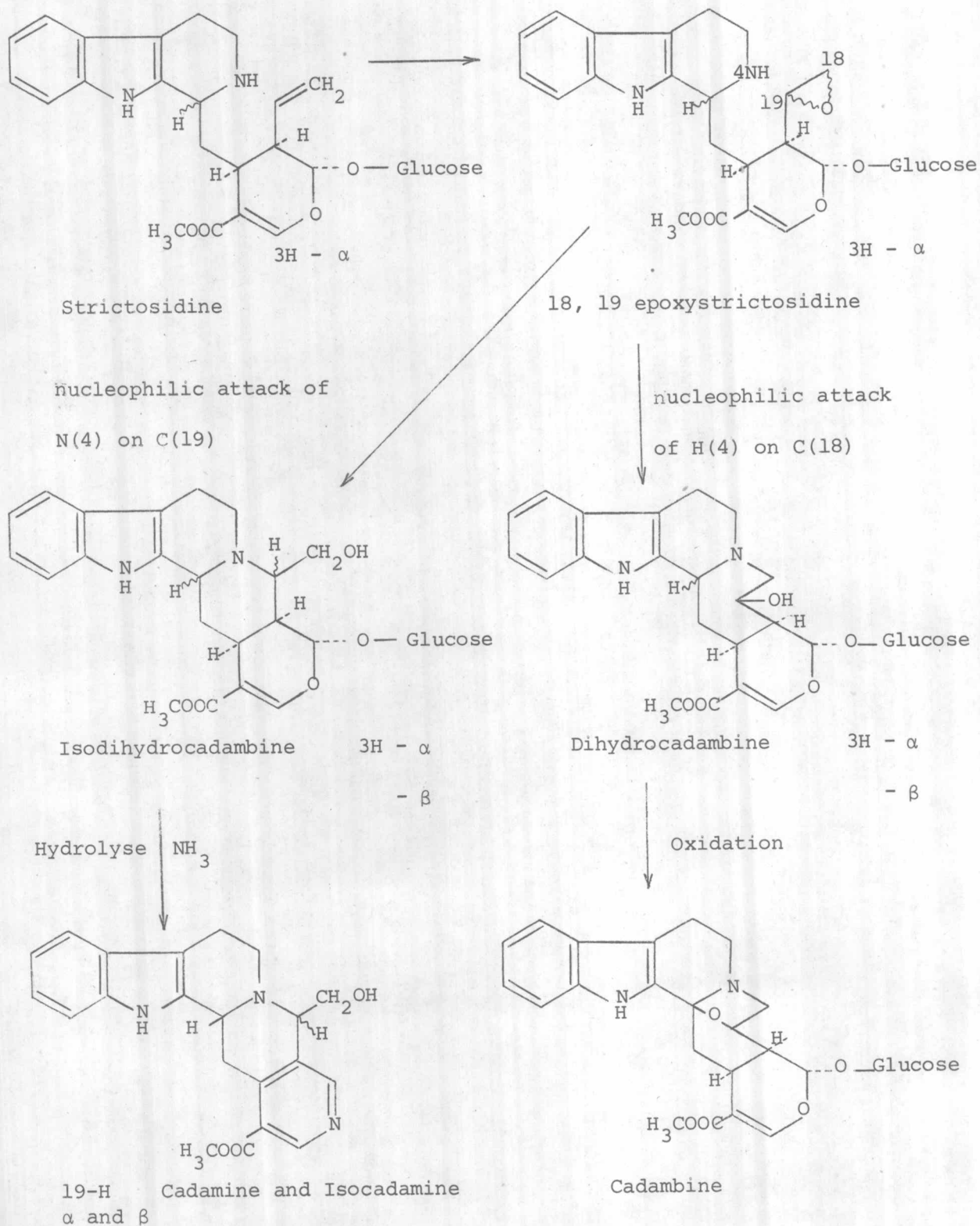
Loganin, secologanin and vincoside fulfill the condition for being true precursors of the various classes of indole alkaloids.⁽²⁹⁾

4.4 Biogenesis of *Anthocephalus* alkaloids

There is ample evidence to expect that *Anthocephalus* alkaloids are derived from tryptophan or tryptamine and a terpenoid component which in the final pre-alkaloidal stage is represented by secologanin.

It is clear that a minimal chemical modification of an oxidation involves transforming the vinyl group of strictosidine to an 18, 19-epoxystictosidine equivalent,⁽⁵⁷⁾ probably after the initial condensation forming strictosidine (isovincoside),⁽⁴⁶⁾ and reaction of this unit with nucleophilic attack of N(4) on C(18) can lead to the hydroxylated seven-membered ring of dihydrocadambine. A further oxidation of dihydrocadambine would form cadambine.⁽⁴⁶⁾

Reduction of cadambine with NaBH_4 in acetic acid provided

Figure VI Biogenesis of *Anthocephalus* alkaloids

3 β -dihydrocadambine. (47)

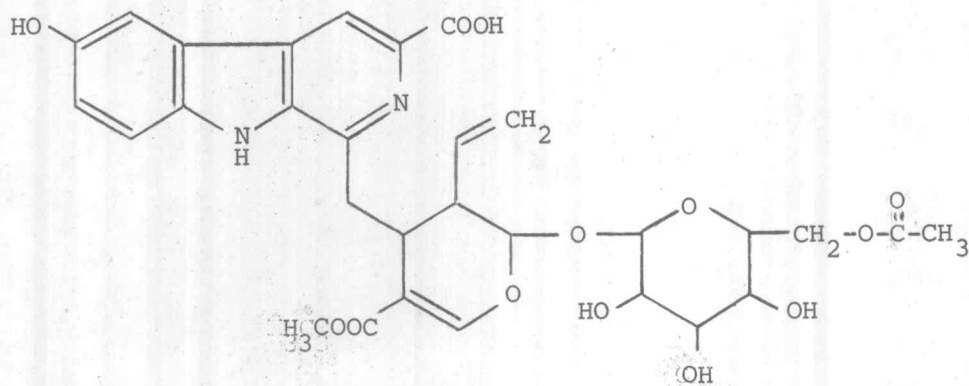
An obvious modification of 18, 19-epoxystrictosidine on nucleophilic attack of N(4) on C(19) would lead to isodihydrocadambine.

Hydrolysis of isodihydrocadambine lead to a key intermediate, which gives rise to cadamine or isocadamine after the reaction with ammonia. (50)

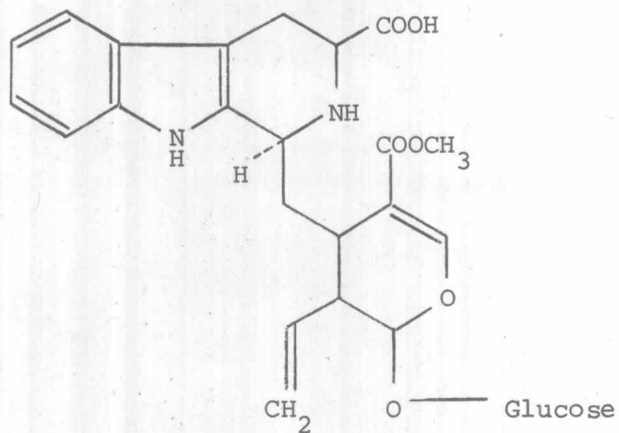
Anthocephalus alkaloids has thus provided only cyclised derivatives of strictosidine (isovincoside) with novel N(4) C(18) and C(19) bonds. Interestingly neither traces of vincoside nor its more stable lactam could be found even though strictosidine is present. (47) It is presumed that these alkaloids derived from strictosidine (isovincoside) rather than vincoside.

5. Structures related to *Anthocephalus* alkaloids isolated from other botanical sources.

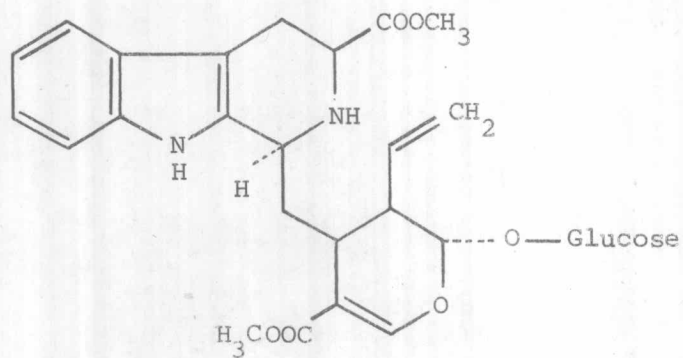
5.1 Iridoid carboline



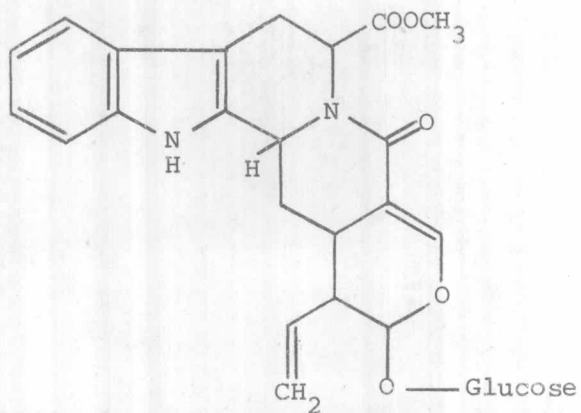
Cordifoline (36)



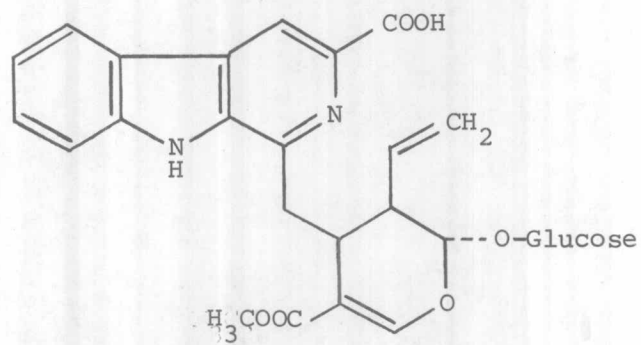
5 α -carboxystrictosidine (68)



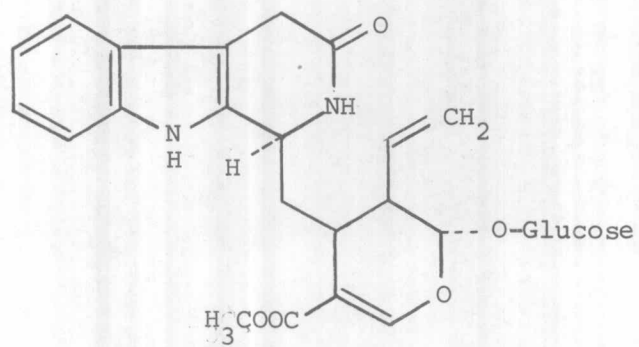
3 α , 5 α Deoxycordifoline (41)



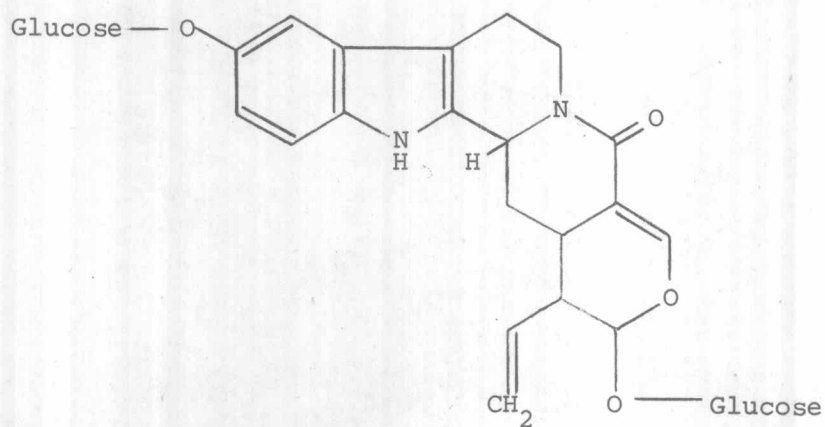
3 β , 5 α tetrahydrodeoxy cordifoline lactam (41)



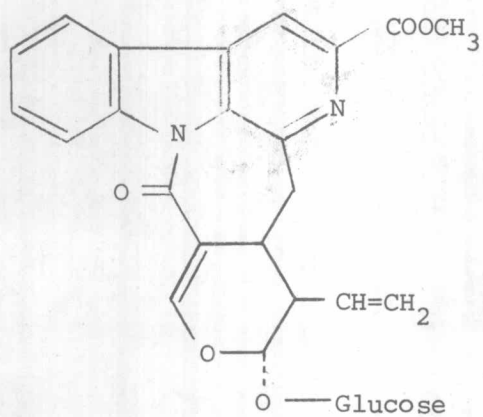
Deoxycordifoline (68)



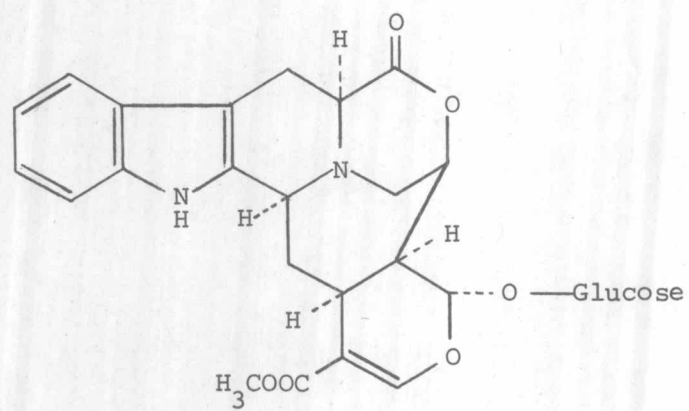
5-oxostrictosidine (40)



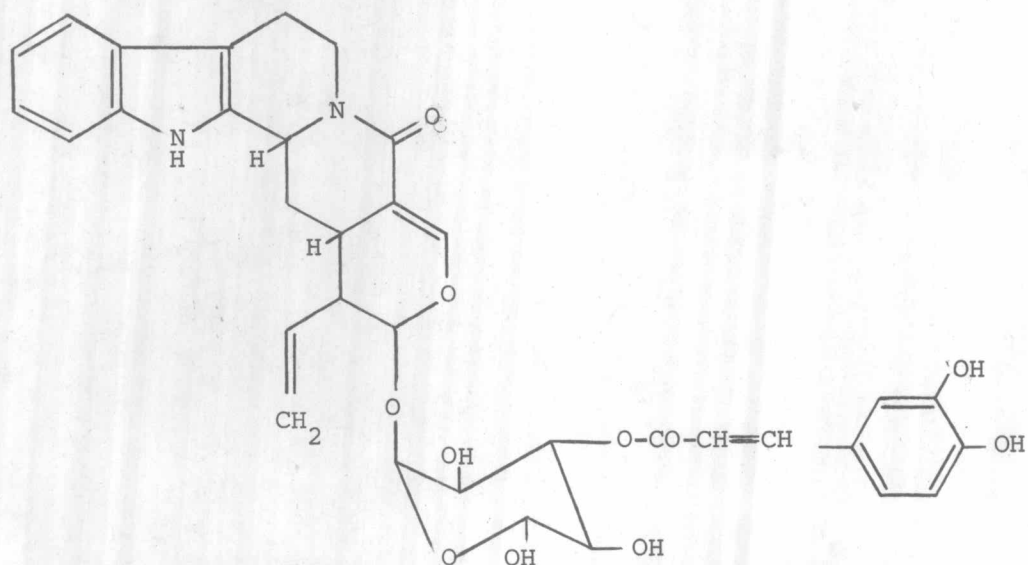
10 β-D glucosyloxyvincoside lactam (42)



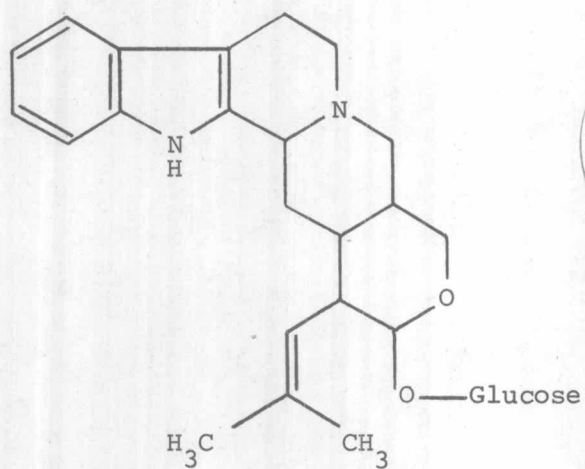
Deoxycordifoline lactam (39)



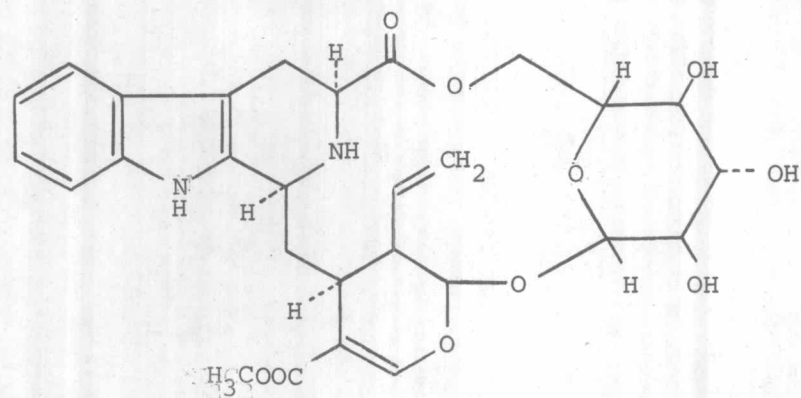
Rubenine (37)



Rubescine (44)

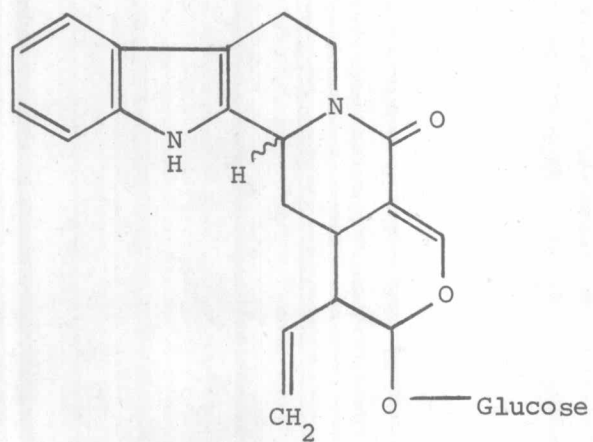


Strychnos Base (49)



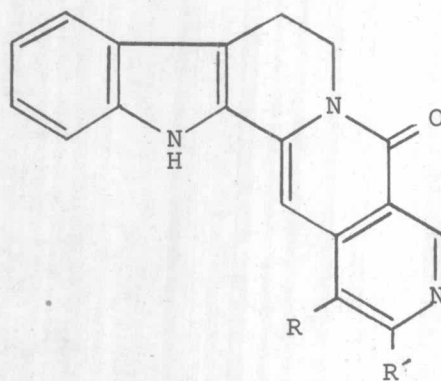
Macrolidone (38)

I15964528



Isovincoside lactam⁽⁷⁰⁾ C(3)H- α

Vincoside lactam⁽⁴³⁾ C(3)H- β

5.2 Pyridino carboline

Angustine, $R = -CH = CH_2$; $R' = H$ ⁽⁵²⁾

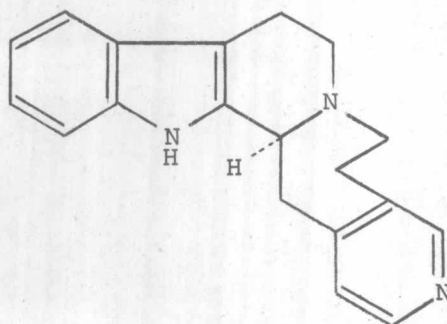
Angustidine, $R = H$; $R' = -CH_3$ ⁽⁵²⁾

Angustoline, $R = -CH(OH)CH_3$; $R' = H$ ⁽⁵²⁾

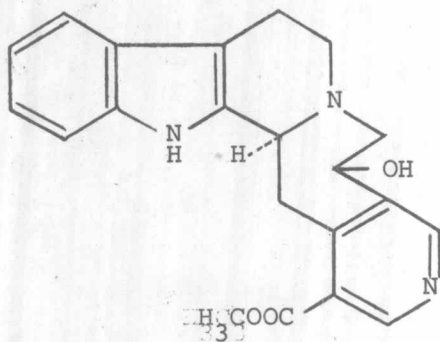
Nauchetine, $R = -CO-CH_3$; $R' = H$ ⁽⁵⁴⁾

Nauclefine, $R = H$; $R' = H$ ^(53,54)

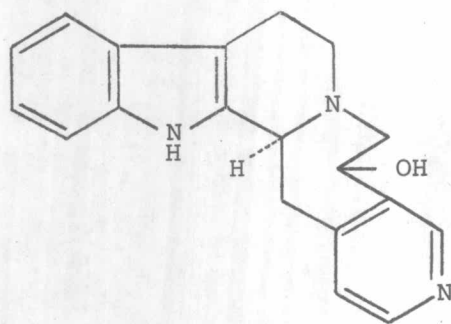
(Parvine)



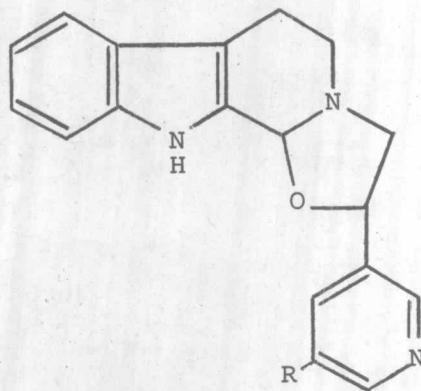
Naufoline ⁽⁵⁵⁾



Nauclechine (56)

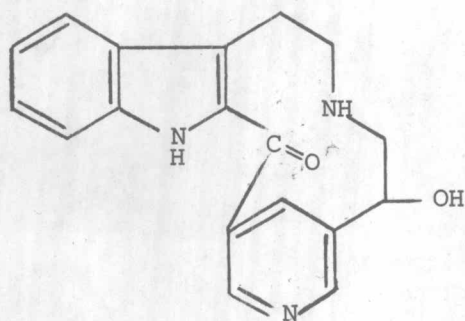


Decarbomethoxynauclechine (55)

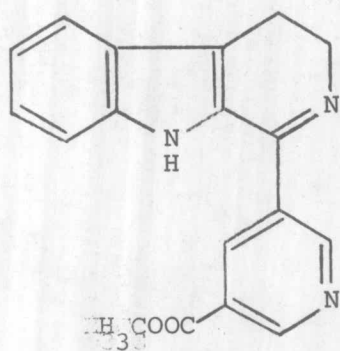


Naucleonine R = H ⁽⁵⁷⁾

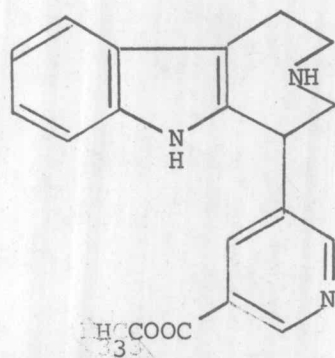
Naucleonidine R = CO₂CH₃ ⁽⁵⁷⁾



Nauclexine ⁽⁵⁶⁾



Naucledine (56)



Nauclederine (56)