

## CHAPTER II

HISTORICAL1. Alkaloids isolated from species of UncariaUncaria bernaysii F. Muell. (from New Guinea)

Plant Part	Alkaloid	Reference
Leaf	Akuammigine, Tetrahydroalstonine, Isopteropodine, Pteropodine, Speciophylline, Uncarine F, Isopteropodine N-oxide, Pteropodine N-oxide, Speciophylline N-oxide, Uncarine F N-oxide.	(15)
Stem	Indole and oxindole alkaloids as in leaf	(15)
Dried flower	Angustine	(16)

Uncaria ferrea DC. (from New Guinea)

Plant Part	Alkaloid	Reference
Leaf	Isopteropodine , Pteropodine , Speciophylline , Uncarine F .	(17) , (18)

Uncaria formosana Matsamura et Hayata.

Plant Part	Alkaloid	Reference
Stem	Formosanine (Uncarine B)	(11) , (19) , (20)

Uncaria gambier Roxb. (Ourouparia gambir Baillon)

Plant Part	Alkaloid	Reference
Leaf	Dihydrocorynantheine	(21)
	Gambirine	(22)
	Roxburghine A, B, C, D, and E	(23)
	Isorhynchophylline	(22)
	Rhynchophylline	(22)
	Rotundifoline	(22)
Stem	Dihydrocorynantheine	(23)
	Roxburghine D and E	(23)
	Tetrahydroalstonine	(23)
	Isorhynchophylline	(23)
	Rhynchophylline	(23)
	Rotundifoline	(23)
Gambir*	Gambirtannine	(22)
	Dihydrocorygambirtannine	(22)
	Oxogambirtannine	(24)

\* Gambir (or Gambier) is a tanning material, produced by evaporation of the aqueous extract of partially fermented leaves and stems of a Rubiaceae Uncaria gambier Roxb. (Ourouparia gambir Baillon), a tree growing in South-East Asia. (24)

Uncaria gambir (Hunt) Roxb.

Plant Part	Alkaloid	Reference
Stem	Gambirdine, Isogambirdine, Mitrephylline.	(21)

Uncaria guianensis Aubl. (Uncaria tomentosa DC.) from Dutch Guiana

Plant Part	Alkaloid	Reference
Leaf	Angustine	(26)
	Rhynchophylline	(25)
Stem	Angustine	(16)
	Rhynchophylline	(25)
Flowers	Angustine	(16)

Uncaria hamomalla Miq.

Plant Part	Alkaloid	Reference
Leaf	Angustine, Angustoline, Angustidine.	(16)

Uncaria kawakamii Hayata (Ourouparia kawakamii Hayata)

Plant Part	Alkaloid	Reference
Root	Uncarine A	(11), (26)
	Uncarine B (Formosanine)	(27)
	Mitraphylline	(28)
	Rhynchophylline	(28)
Bark and Stem	Oxindole alkaloids as in root	(28)

Uncaria longiflora (Poir.) Merr. (from Pulau Laut, Borneo)

Plant Part	Alkaloid	Reference
Leaf	Isomitraphylline, Mitraphylline, Isopteropodine, Pteropodine, Speciophylline, Uncarine F, Isomitraphylline N-oxide, Mitraphylline N-oxide, Isopteropodine N-oxide, Pteropodine N-oxide, Speciophylline N-oxide.	(15)

Uncaria macrophylla Wall.

(from Assam; Indo-china; Kwangtung, China; Yunnan, China)

Plant Part	Alkaloid	Reference
Leaf	Corynoxine, Corynoxine B, Isorhynchophylline, Rhynchophylline.	(15)

Uncaria pteropoda Miq. (from Malaya)

Plant Part	Alkaloid	Reference
Root	Isopteropodine, Pteropodine.	(29), (32)
Bark and Stem	Oxindole alkaloids as in root	(29), (32)

Uncaria rhynchophylla Miq.(Ourouparia rhynchophylla Matsamura and Hayata)

Plant Part	Alkaloid	Reference
Leaf	Angustine, Angustoline, Angustidine.	(16)
Tendrill	Isorhynchophylline, Rhynchophylline.	(11), (30)
Stem	Oxindole alkaloids as in tendrill	(11), (30)
-	Hirsutine, Hirsuteine, Corynantheine, Dihydrocorynantheine, Rhynchophylline, Isorhynchophylline, Corynoxetine, Isocorynoxetine.	(31)

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2. Other indole and oxindole alkaloids similar in structure to the Uncaria alkaloids, isolated from the other botanical source.

2.1 Indole alkaloids

Alkaloid	Botanical source	Reference
Akuammigine	<u>Picrasma nitida</u> Stapf. Th. et H. Durand	(56), (57)
	<u>Mitragyna parvifolia</u> (Roxb.) Korth.	(33)-(39)
Akuammigine N-oxide	<u>Mitragyna parvifolia</u> (Roxb.) Korth.	(33)-(39)
Corynantheine	<u>Corynanthe yohimbe</u> K. Schum.	(42)
	<u>Mitragyna parvifolia</u> (Roxb.) Korth.	(37), (38)
	<u>Pseudocinchona africana</u> Aug. Chev.	(43)
Dihydrocorynantheine	<u>Corynanthe yohimbe</u> K. Schum.	(40), (41)
	<u>Mitragyna parvifolia</u> (Roxb.) Korth.	(33)-(39)
	<u>Pseudocinchona africana</u> Aug. Chev.	(43)
Hirsutine	<u>Mitragyna hirsuta</u> Havil.	(44)-(46)
	<u>M. parvifolia</u> (Roxb.) Korth.	(33)-(39)
Hirsuteine	<u>Mitragyna hirsuta</u> Havil.	(44)-(46)
	<u>M. parvifolia</u> (Roxb.) Korth.	(37), (38)



Alkaloid	Botanical source	Reference
Tetrahydro- alstonine	<u>Alstonia constricta</u> F. Muell.	(47)
	<u>Mitragyna parvifolia</u> (Roxb.) Korth.	(33)-(39)
	<u>Rauvolfia ligustrina</u> Roem. et Schult.	(48)
	<u>R. sellowi</u> Muell. - Arg.	(49)
	<u>Vinca lancea</u> (Boj. ex A.DC.) K.Schum.	(50)
	<u>V. major</u> L.	(51)
	<u>V. rosea</u> (L.) Reichb.f.	(52), (53)
Angustine	<u>Mitragyna javanica</u> Koord. et Valetton	(16), (54)
	<u>M. parvifolia</u> (Roxb.) Korth.	(16), (35)
	<u>Nauclea coadunata</u> Roxb. ex J.E.Smith. ( <u>Sarcocephalus coadunata</u> Roxb. ex J.E. Smith Druce)	(16)
	<u>Strychnos angolensis</u> Gilg.	(16)
	<u>S. angustiflora</u> Benth.	(16), (55)
	<u>S. borneensis</u> Ijenh.	(16)
	<u>S. camptoneura</u> Gilg. et Busse.	(16)
	<u>S. floribunda</u> Gilg.	(16)
	<u>S. ledermannii</u> Gilg. et Bened.	(16)
	<u>S. minor</u> Dennst.	(16)
	<u>S. odorata</u> A. Chev.	(16)
	<u>S. ovata</u> A.W. Hill	(16)
	<u>S. potatarum</u> L.f.	(16)
<u>S. samba</u> Duvign.	(16)	

Alkaloid	Botanical Source	Reference
Angustine	<u>Strychnos schefferi</u> Gilg.	(16)
	<u>S. trichoneura</u> Leeuwenberg.	(16)
	<u>S. umbellata</u> (Lour.) Merr.	(16)
	<u>S. usambarensis</u> Gilg.	(16)
	<u>S. vanprukii</u> Craib (= <u>S. aenea</u> A.W. Hill and L. Wray Jr. s.n.; = <u>S. quadrangularis</u> A.W. Hill.)	(16)
	<u>S. xantha</u> Leeuwenberg.	(16)
	<u>S. angustiflora</u> Benth.	(16)
	<u>S. borneensis</u> Leenh.	(16)
	<u>S. minor</u> Dennst.	(16)
	<u>S. odorata</u> A. Chev.	(16)
	<u>S. ovata</u> A.W. Hill	(16)
	<u>S. samba</u> Duvign	(16)
	<u>S. schefferi</u> Gilg.	(16)
	<u>S. trichoneura</u> Leeuwenberg	(16)
	<u>S. umbellata</u> (Lour.) Merr.	(16)
	<u>S. vanprukii</u> Craib. (= <u>S. aenea</u> A.W. Hill et L. Wray Jr. s.n.; = <u>S. quadrangularis</u> A.W. Hill.)	(16)
	<u>S. xantha</u> Leeuwenberg	(16)
	<u>S. anglolensis</u> Gilg.	(16)
	<u>S. angustiflora</u> Benth.	(16)

Alkaloid	Botanical source	Reference
Angustidine	<u>Strychnos borneensis</u> Leenh.	(16)
	<u>S. minor</u> Dennst.	(16)
	<u>S. odorata</u> A. Chev.	(16)
	<u>S. ovata</u> A.W. Hill	(16)
	<u>S. samba</u> Duvign	(16)
	<u>S. schefferi</u> Gilg.	(16)
	<u>S. trichoneura</u> Leeuwenberg	(16)
	<u>S. umbellata</u> (Lour.) Merr.	(16)
	<u>S. vanprukii</u> Craib (= <u>S. aenea</u> A.W. Hill et L. Wray Jr. s.n. & = <u>S. quadrangularis</u> A.W. Hill	(16)
	<u>S. xantha</u> Leeuwenberg	(16)

2.2 Oxindole alkaloids

Alkaloid	Botanical source	Reference
Isomitraphyl- line	<u>Mitragyna hirsuta</u> Havil.	(44)-(46)
	<u>M. javanica</u> Koord et Valetton	(54)
	<u>M. parvifolia</u> (Roxb.) Korth.	(33)-(39)
	<u>M. speciosa</u> Korth.	(58)-(64)
	<u>M. tubulosa</u> Havil.	(65)
Mitraphylline	<u>Mitragyna hirsuta</u> Havil.	(44)-(46)
	<u>M. javanica</u> Koord et Valetton.	(54)
	<u>M. parvifolia</u> (Roxb.) Korth.	(33)-(39)
	<u>M. rotundifolia</u> (Roxb.) O. Kuntze.	(66)
	<u>M. rubrostipulacea</u> (Roxb.) O.Kuntze.	(67)-(70)
	<u>M. speciosa</u> Korth.	(58)-(64)
	<u>M. stipulosa</u> (DC.) O. Kuntze.	(71), (72)
	<u>M. tubulosa</u> Havil.	(65)
Isopteropodine	<u>Mitragyna parvifolia</u> (Roxb.) Korth.	(33)-(39)
Pteropodine	<u>Mitragyna parvifolia</u> (Roxb.) Korth.	(33)-(39)
Speciophylline	<u>Mitragyna inermis</u> (Willd.) O.Kuntze.	(70), (73)-(75)
	<u>M. parvifolia</u> (Roxb.) Korth.	(33)-(39)
	<u>M. speciosa</u> Korth.	(58)-(64)

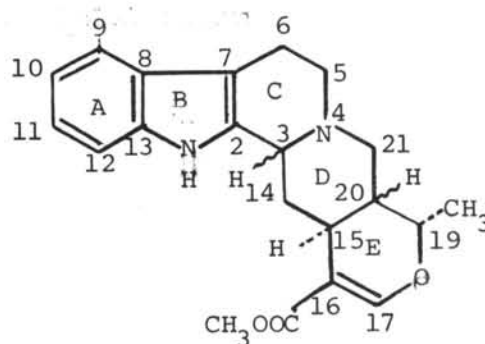
Alkaloid	Botanical source	Reference
Speciophylline N-oxide	<u>Mitragyna parvifolia</u> (Roxb.) Korth.	(33)-(39)
Uncarine F	<u>Mitragyna inermis</u> (Willd.) O. Kuntze. <u>M. parvifolia</u> (Roxb.) Korth.	(70), (73)-(75) (33)-(39)
Uncarine F N-oxide	<u>Mitragyna parvifolia</u> (Roxb.) Korth.	(33)-(39)
Corynoxine	<u>Pseudocinchona africana</u> Aug. Chev.	(15), (77)
Corynoxine	<u>Pseudocinchona africana</u> Aug. Chev. <u>Mitragyna hirsuta</u> Havil. <u>M. parvifolia</u> (Roxb.) Korth.	(77) (44)-(46) (35), (37)-(39)
Isorhyncho- phylline	<u>Mitragyna ciliata</u> Aubrev. et Pellgr. <u>M. hirsuta</u> Havil. <u>M. inermis</u> (Willd.) O. Kuntze. <u>M. parvifolia</u> (Roxb.) Korth. <u>M. rotundifolia</u> (Roxb.) O. Kuntze. <u>M. rubrostipulacea</u> (Roxb.) O. Kuntze. <u>M. stipulosa</u> (DC.) O. Kuntze. <u>M. tubulosa</u> Havil.	(70), (72), (78) (44)-(46) (70), (73)-(75) (33)-(39) (33), (79) (61), (67), (80)- (82) (71), (72) (65), (61)
Isorhyncho- phylline N-oxide	<u>Mitragyna inermis</u> (Willd.) O. Kuntze. <u>M. rotundifolia</u> (Roxb.) O. Kuntze.	(70), (73)-(75) (33), (79)

Alkaloid	Botanical source	Reference
Rhyncho- phylline	<u>Mitragyna ciliata</u> Aubrev.et Pellgr.	(70), (72), (78)
	<u>M. hirsuta</u> Havil.	(44)-(46)
	<u>M. inermis</u> (Willd.) O. Kuntze.	(70), (73)-(75)
	<u>M. parvifolia</u> (Roxb.) Korth.	(33)-(39)
	<u>M. rotundifolia</u> (Roxb.) O. Kuntze.	(33), (79)
	<u>M. rubrostipulacea</u> (Roxb.) O.Kuntze.	(61), (67), (80)-(82)
	<u>M. speciosa</u> Korth.	(58)-(64)
	<u>M. tubulosa</u> Havil.	(65)
Rhyncho- phylline N-oxide Rotundifoline	<u>Mitragyna inermis</u> (Willd.) O.Kuntze.	(70), (73)-(75)
	<u>Mitragyna ciliata</u> Aubrev.et Pellgr.	(70), (72), (78)
	<u>M. inermis</u> (Willd.) O. Kuntze.	(70), (73)-(75)
	<u>M. parvifolia</u> (Roxb.) Korth.	(33)-(39)
	<u>M. rubrostipulacea</u> (Roxb.) O.Kuntze.	(61), (67), (80)-(82)
	<u>M. speciosa</u> Korth.	(58)-(64)
	<u>M. stipulosa</u> (DC.) O. Kuntze.	(71), (72)
	<u>M. tubulosa</u> Havil.	(65)

3. Basic structure of indole alkaloids from species of Uncaria.

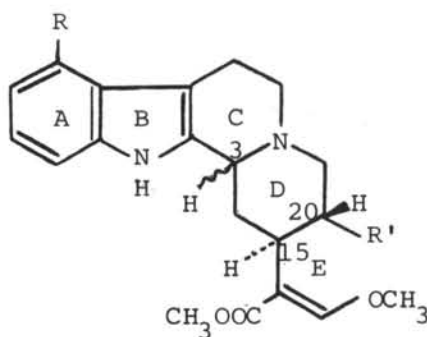
3.1 Closed E ring

Akuammigine and Tetrahydroalstonine (83)



3.2 Open E ring

Dihydrocorynantheine, Gambirine, Corynantheine,  
Hirsutine and Hirsuteine (31, 84, 85, 91)



Dihydrocorynantheine and Hirsutine,  $R = H$  ;  $R' = -CH_2CH_3$

Gambirine ,  $R = OH$ ;  $R' = -CH_2CH_3$

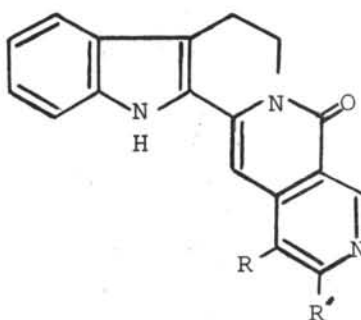
Corynantheine and Hirsuteine ,  $R = H$  ;  $R' = CH=CH_2$

### 3.3 Other indole alkaloids

#### Angustine, Angustoline and Angustidine <sup>(16)</sup>

Three pyridino - indole - quinolizidinone alkaloids, angustine, angustoline and angustidine have been identified in extracts from species of Mitragyna, Nauclea, Uncaria (Rubiaceae) and from African and Asian species of Strychnos (Loganiaceae). These alkaloids have recently been isolated from Strychnos angustiflora Benth. <sup>(55)</sup>

These alkaloids have the following basic structure :



Angustine,  $R = -CH = CH_2$ ;  $R' = H$

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

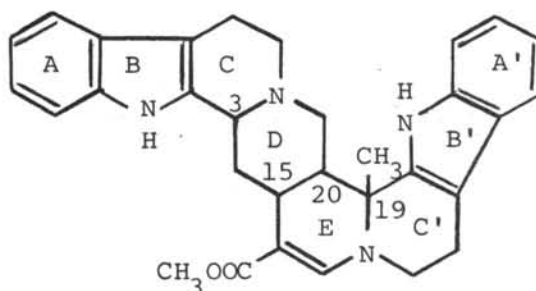
Angustidine,  $R = H$ ;  $R' = -CH_3$

#### Roxburghine A, B, C, D, and E

Roxburghine A, B, C, D, and E new diastereoisomeric indole alkaloids isolated from the leaves of Uncaria gambier Roxb. are reported by Merlini, Mondelli, Nasini and Hesse. <sup>(86)</sup>  
Roxburghines D and F are also present in the stems of



Uncaria gambier Roxb. together with tetrahydroalstonine and dihydrocorynantheine. (23)



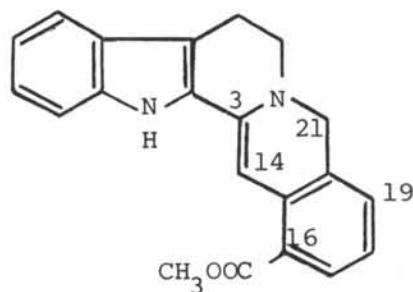
Roxburghines

It must be noted that the skeleton of ABCDE rings in the roxburghines is the same as that of heteroyohimbines. The four asymmetric centers in both alkaloid types are equivalent (C-3, C-15, C-19, C-20). (23)

Gambirtannine, Dihydrogambirtannine, Oxogambirtannine and Neooxygambirtannine. (24, 84)

In 1966 Merlini, Mondelli, Nasini and Hess reported the presence in Uncaria gambier Roxb., of three new indole alkaloids, namely gambirtannine, dihydrogambirtannine and oxogambirtannine. All of these three indole alkaloids were extracted from gambir and neooxygambirtannine was obtained during the workup of the extract. (24)

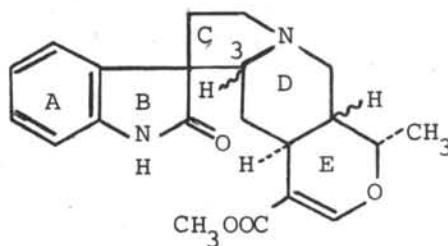
These alkaloids have the following basic structure :



4. Basic structure of oxindole alkaloids from species of Uncaria

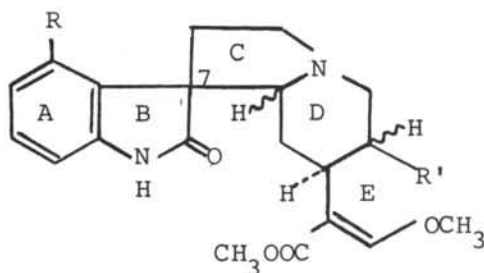
4.1 Closed E ring

Isomitraphylline, Mitraphylline, Uncarine A (Isoformosanine), Uncarine B (Formosanine), Isopteropodine, Pteropodine, Speciophylline and Uncarine F. (86)



4.2 Open E ring

Corynoxine, Corynoxine B, Isorhynchophylline, Rhynchophylline, Isocorynoxine, Corynoxine and Rotundifoline. (31, 77, 90)



Corynoxine, Corynoxine B, Isorhynchophylline and Rhynchophylline  $R = H$ ;  $R' = CH_2CH_3$

Isocorynoxine and Corynoxine  $R = H$ ;  $R' = CH=CH_2$

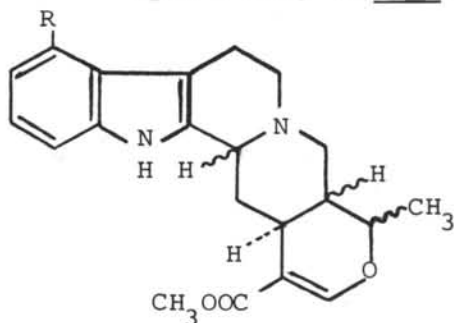
Rotundifoline  $R = OH$ ;  $R' = CH_2CH_3$

##### 5. Configuration of indole alkaloids

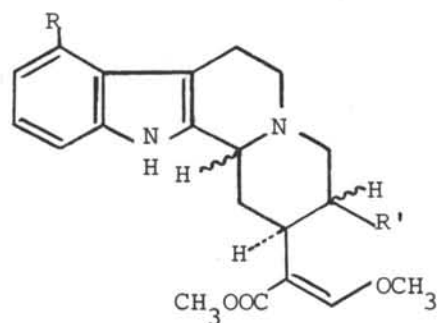
There are two types of heteroyohimbine alkaloids depending upon the nature of ring E.

Closed E ring

Open E ring (E seco)



Closed E ring



Open E ring (E seco)

Since all naturally occurring known heteroyohimbine alkaloids possess a C(15)-H $\alpha$  configuration and have asymmetric centres at C(3)

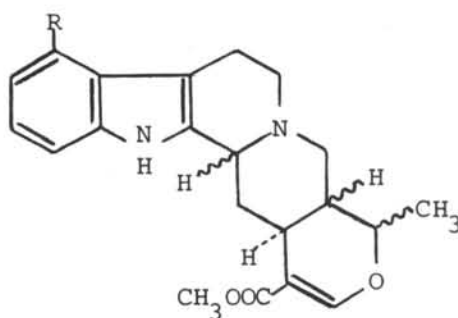
and C(20), thus there are four possible configuration as follows :<sup>(83)</sup>

Configuration	C(3)-H	C(20)-H
<u>allo</u>	$\alpha$	$\alpha$
<u>normal</u>	$\alpha$	$\beta$
<u>epiallo</u>	$\beta$	$\alpha$
<u>pseudo</u>	$\beta$	$\beta$

Besides the closed E ring alkaloids possess a further asymmetric centre at C(19), (i.e. CH<sub>3</sub>  $\alpha$  or  $\beta$ ), so that eight isomers are possible. The E seco alkaloids may show geometric isomerisation because of the double bond between C(16) and C(17) though all the alkaloids of known absolute configuration possess a C(17)-H cis to the C(16) ester group. The aromatic substitution have been found to occur at C(9)-R, the group being either a methoxy or hydroxy group.<sup>(35, b)</sup>

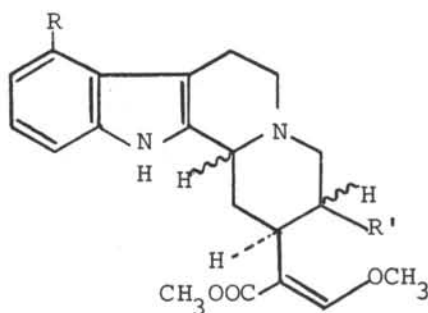
In the E seco alkaloids R' may be either -CH<sub>2</sub>.CH<sub>3</sub> or -CH=CH<sub>2</sub>. When the alkaloids present in individual species are considered in terms of their configuration and D/E ring structure it will be seen that where indole and oxindole alkaloids are present together the D/E ring system is identical in both.<sup>(39, b)</sup>

5.1 Configuration of closed E ring indole alkaloids from species of Uncaria



R	Configuration	Alkaloid	Reference
H	<u>allo</u>	Tetrahydroalstonine	(15), (23)
	<u>normal</u>	-	
	<u>epiallo</u>	Akuammigine	(15)
	<u>pseudo</u>	-	
OH	Has not yet been found	-	
OCH <sub>3</sub>	Has not yet been found	-	

5.2 Configuration of open E ring indole alkaloids from species of Uncaria



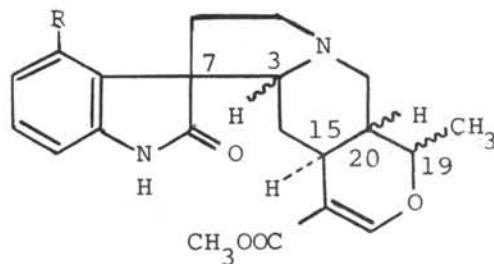
R	Configuration	C(20)-CH <sub>2</sub> .CH <sub>3</sub>	C(20)-CH=CH <sub>2</sub>	Reference
H	<u>allo</u>	-	-	-
	<u>normal</u>	Dihydrocorynantheine	Corynantheine	(23), (31)
	<u>epiallo</u>	-	-	
	<u>pseudo</u>	Hirsutine	Hirsuteine	(31)
OH	<u>allo</u>	-	-	
	<u>normal</u>	Gambirine	-	(22)
	<u>epiallo</u>	-	-	
	<u>pseudo</u>	-	-	
OCH <sub>3</sub>	Has not yet been found			

## 6. Configuration of oxindole alkaloids.

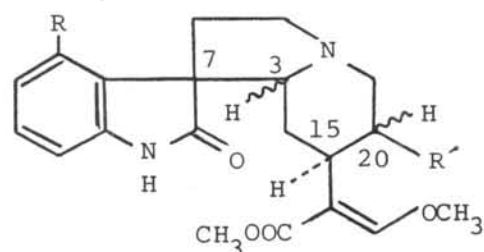
There are two types of oxindole alkaloids depending upon the nature of ring E.

Closed E ring

Open E ring (E seco)



Closed E ring



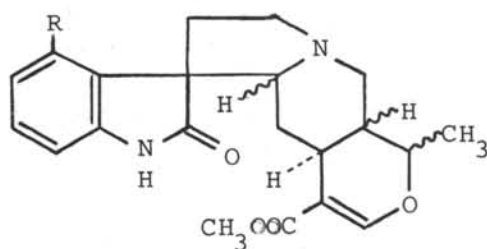
Open E ring

Similar to the heteroyohimbine alkaloids the same four configurations are possible (allo, normal, epiallo and pseudo).

In addition, the oxindole alkaloids have asymmetric centre at C(7), thus, eight configurations may exist either as an A or B series alkaloid by isomerisation about the spiro carbon C(7). A and B oxindole alkaloids are classified according to the position of the lactam carbonyl group relative to the plane of the C ring. Those alkaloids in which the lactam carbonyl lies below the plane of the C ring being termed the A series and those in which the lactam carbonyl lies above the plane of C ring being termed the B series. Further, in both types of oxindole alkaloids the lone pair of electrons on N(4) may either be on the same side of the C(7) as the lactam carbonyl group or on

the opposite side, the former are known as syn and the latter as anti alkaloids. (35 b, 36)

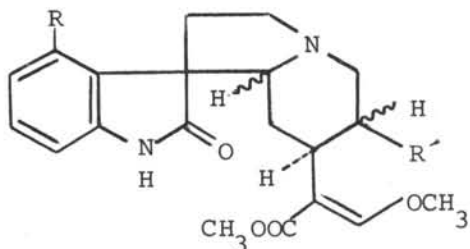
6.1 Configuration of closed E ring oxindole alkaloids from species of Uncaria



R	Configuration	C(7)	C(19)- CH <sub>3</sub>	Oxindole (CO/N4)	Alkaloid	Reference
H	<u>allo</u>	A	$\alpha$	<u>anti</u>	Isopteropodine (Uncarine C)	(15), (17), (18)
		B	$\alpha$	<u>syn</u>	Pteropodine (Uncarine E)	(15), (17), (18)
	<u>normal</u>	A	$\alpha$	<u>anti</u>	Isomitraphylline	(15)
		B	$\alpha$	<u>syn</u>	Mitraphylline	(28), (15)
		A	$\beta$	<u>anti</u>	Uncarine A (Isoformosanine)	(11)
		B	$\beta$	<u>syn</u>	Uncarine B (Formosanine)	(11), (19), (20), (27)
	<u>epiallo</u>	A	$\alpha$	<u>syn</u>	Speciophylline (Uncarine D)	(15), (17), (18)
		B	$\alpha$	<u>anti</u>	Uncarine F	(15), (17), (18)
OH	Has not yet been found					
OCH <sub>3</sub>	Has not yet been found					



6.2 Configuration of open E ring oxindole alkaloids from species of Uncaria.



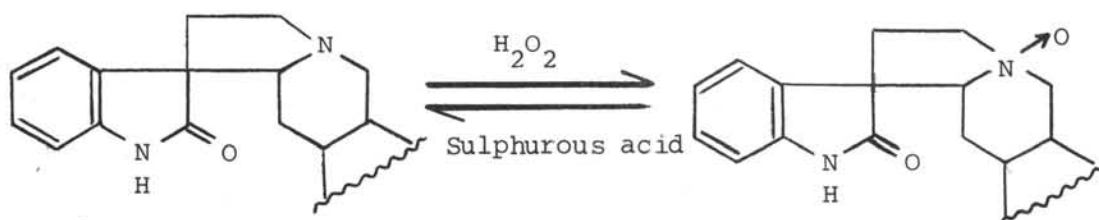
R	Configuration	Series	C(20)-CH <sub>2</sub> -CH <sub>3</sub>	C(20)-CH=CH <sub>2</sub>	Reference
H	<u>allo</u>	A	Corynoxine	-	(15)
		B	Corynoxine B	-	(15)
	<u>normal</u>	A	Isorhyncho- phylline	Isocory- noxine	(22), (31)
		B	Rhyncho- phylline	Corynoxine	(22), (25), (31)
	<u>epiallo</u>	A	-	-	
		B	-	-	
OH	<u>allo</u>	A	-	-	
		B	-	-	
	<u>normal</u>	A	Rotundifoline	-	(22)
		B	-	-	
	<u>epiallo</u>	A	-	-	
		B	-	-	
OCH <sub>3</sub>	Has not yet been found				

It should be noted that no pseudo oxindole alkaloids have been isolated and this confirms the view of Trager et al. that they are unable to exist. (101)

## 7. Alkaloid N-oxides

Shellard, Phillipson, and Sarpong (1971) prepared the N-oxides of isorhynchophylline and rhynchophylline by treating an ethanolic solution of the alkaloid with  $H_2O_2$  overnight, followed by heating on a boiling water bath for 30 minutes.<sup>(75)</sup> Shellard and Rungsiyakul (1973) have also used this as one of the methods to prepare the N-oxide of ciliaphylline.<sup>(65)</sup>

The N-oxides are readily reconverted to the parent alkaloids by the reduction with sulphurous acid.<sup>(75)</sup>



Naturally occurring alkaloid N-oxides are known for several types of alkaloids pyrrolizidine, quinolizidine and piperidine bases. Their roles in plant metabolism are not known although several theories have been advanced for some specific alkaloids.<sup>(93)</sup> N-oxides of indole alkaloids akuammigine and tetrahydroalstonine have been reported to be present in Uncaria species<sup>(94)</sup> and N-oxides of the oxindole alkaloids isorhynchophylline, rhynchophylline, rhynchociline & ciliaphylline in species of Mitragyna.<sup>(65, 75)</sup>

Phillipson and Hemingway (1973) had earlier reported the isolation of the N-oxides of the closed E ring oxindole alkaloids isopteropodine, pteropodine, speciophylline and uncarine F from the leaves of Uncaria bernaysii F. Muell.<sup>(15 a)</sup> More recently they have isolated the N-oxides of isomitraphylline and mitraphylline from the leaves of Uncaria longiflora (Poir.) Merr.<sup>(15 b)</sup>

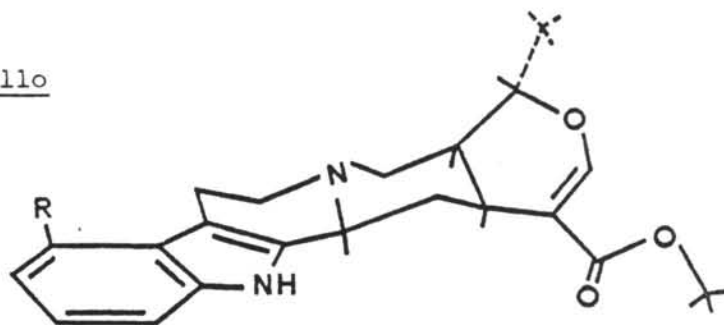
Other possibilities are that the N-oxides may play some part in the interconversion of the isomers or that the reversible oxidation of the tertiary base to the N-oxides is essential to some metabolic process in the plant.<sup>(15 a)</sup>

#### 8. Preferred conformations

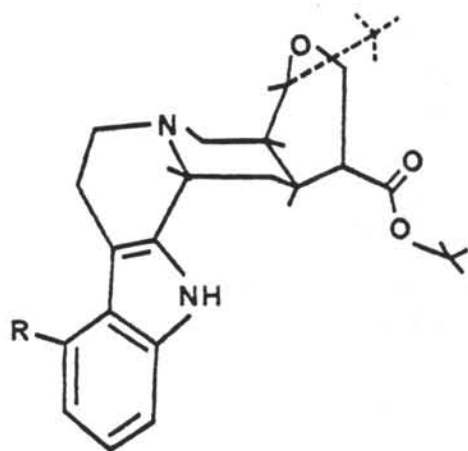
There are in fact four basic stereochemical arrangements or configurations, namely, allo, epiallo, normal and pseudo. Each of these may have the C(19)-CH<sub>3</sub> group  $\alpha$  or  $\beta$ .<sup>(95)</sup>

Wenkert and Bringi (1959) pointed out that in indole and oxindole alkaloids has an  $\alpha$ -orientation.<sup>(96)</sup>

The preferred conformation of the indole and oxindole alkaloids from Uncaria species were established as follows :

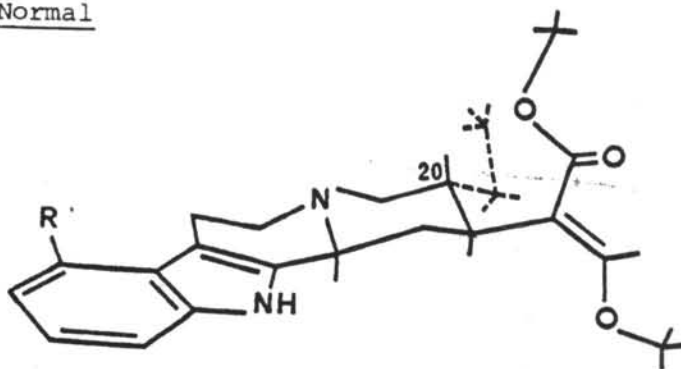
8.1 Indole alkaloids8.1.1 Closed E ringAllo

R = H, Tetrahydroalstonine

1Epiallo

R = H, Akuammigine

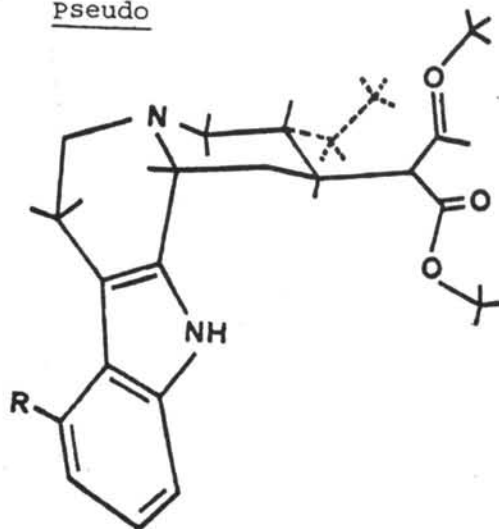
2

8.1.2 Open E ringNormal3

R = H, Dihydrocorynantheine

R = OH, Gambirine

R = H, C (20) Et = Vinyl, Corynantheine

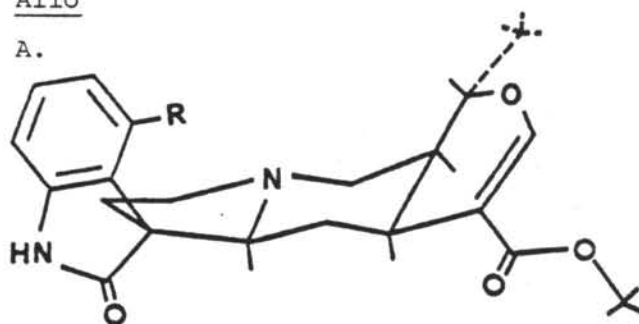
Pseudo4

R = H, Hirsutine

R = H and C (20) Et = Vinyl, Hirsuteine

8.2 Oxindole alkaloids8.2.1 Closed E ring (C (19) - H  $\alpha$ )Allo

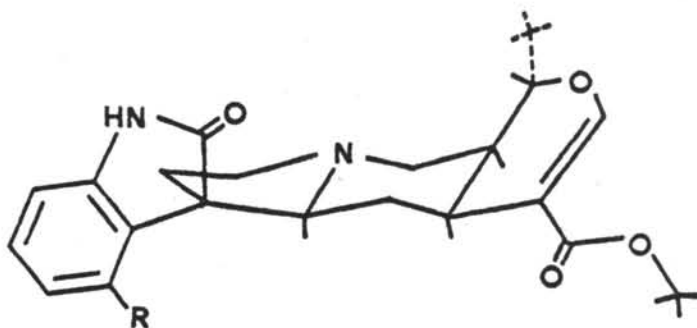
A.

5

R = H, Isopteropodine

Allo

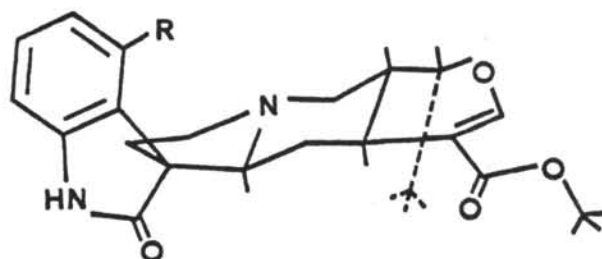
B.

6

R = H, Pteropodine

Normal

A.

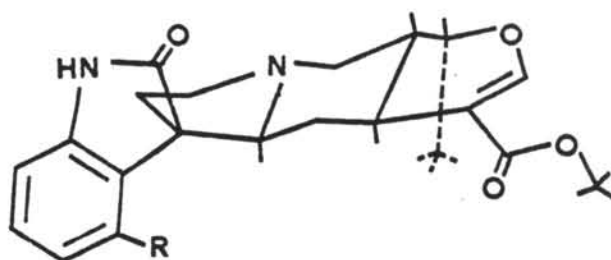


7

R = H, Isomitraphylline

Normal

B.

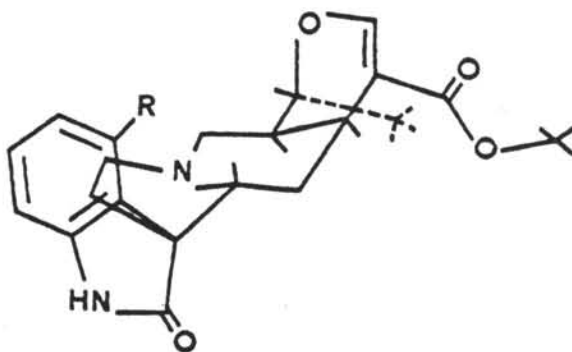


8

R = H, Mitraphylline

Epiallo

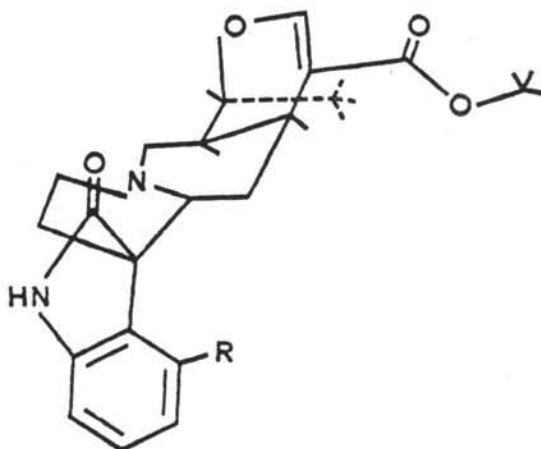
A.

9

R = H, Speciophylline

Epiallo

B.

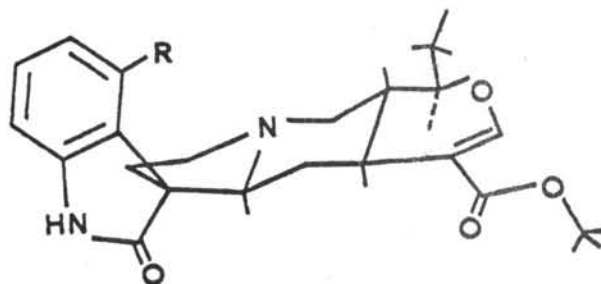
10

R = H, Uncarine F

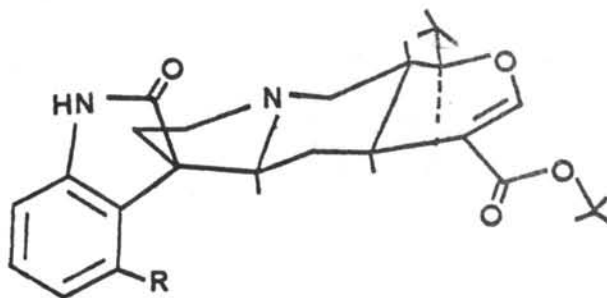


8.2.2 Closed E ring (C (19) - H  $\beta$ )Normal

A.

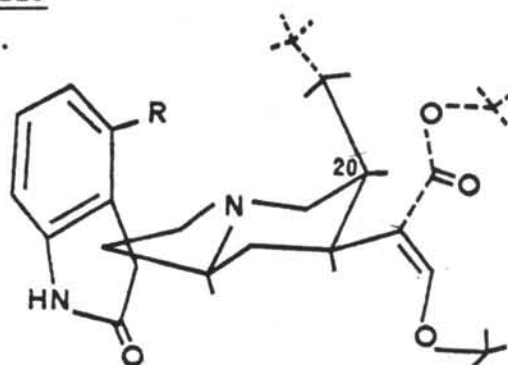
11R = H, Uncarine A  
(Isoformosanine)Normal

B.

12R = H, Uncarine B  
(Formosanine)

8.2.3 Open E ringAllo

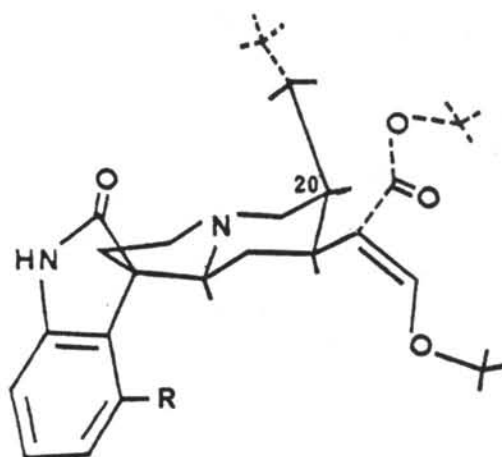
A.

13

R = H, Corynoxine

Allo

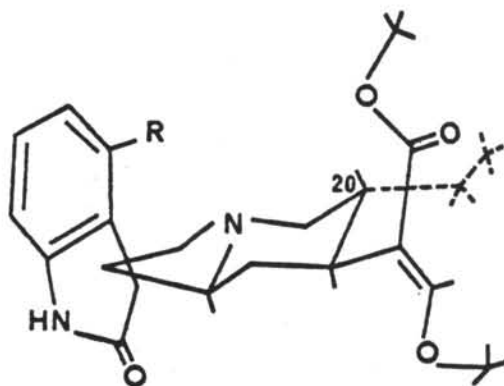
B.

14

R = H, Corynoxine B

Normal

A.

15

R = H, Isorhynchophylline

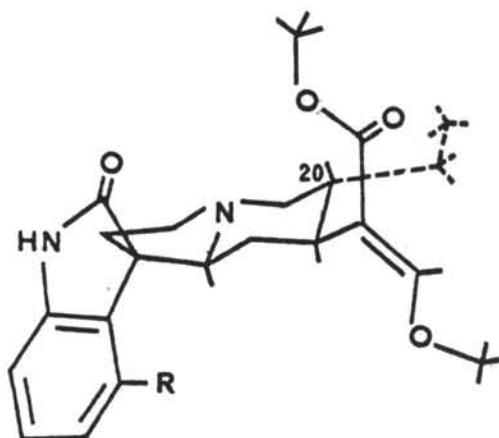
R = OH, Rotundifoline

R = H and C (20) Et = Vinyl -

isocorynoxine

Normal

B.

16

R = H, Rhynchophylline

R = OH, Isorotundifoline

R = H and C (20) Et = Vinyl -

corynoxine

## 9. Biogenesis

### 9.1 Indole alkaloids

Many workers have reported and argued about the results of the investigations, then proposed hypotheses concerning the biogenesis of indole alkaloids since early 1900's.<sup>(91)</sup>

It was accepted that tryptamine provided the  $\beta$ -carboline portion of the indole alkaloids. Tryptophan, from which tryptamine is derived, is biosynthesised from shikimic acid, having anthranilic acid as an intermediate<sup>(113, 114)</sup> (Figure I).

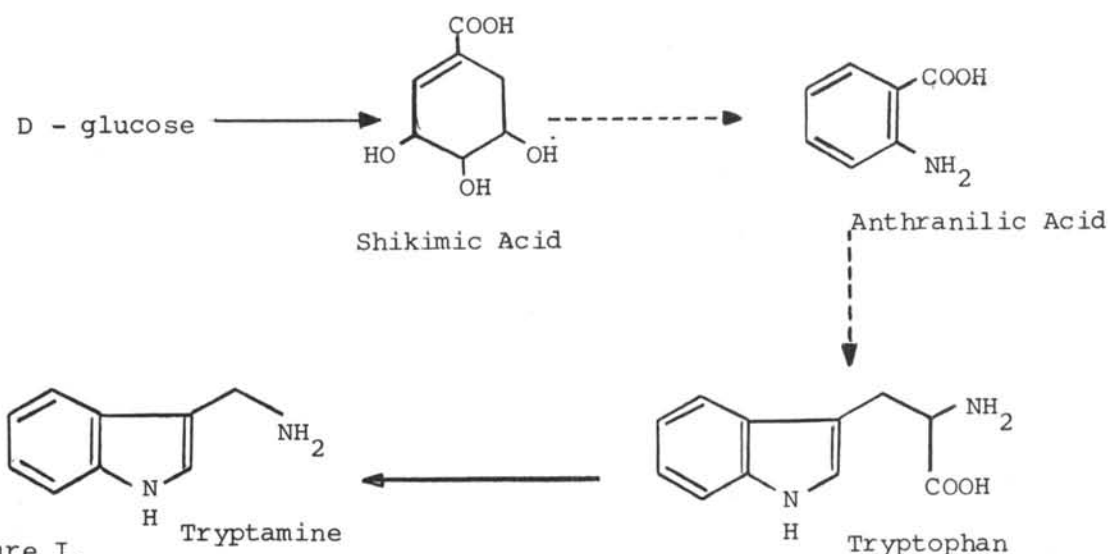
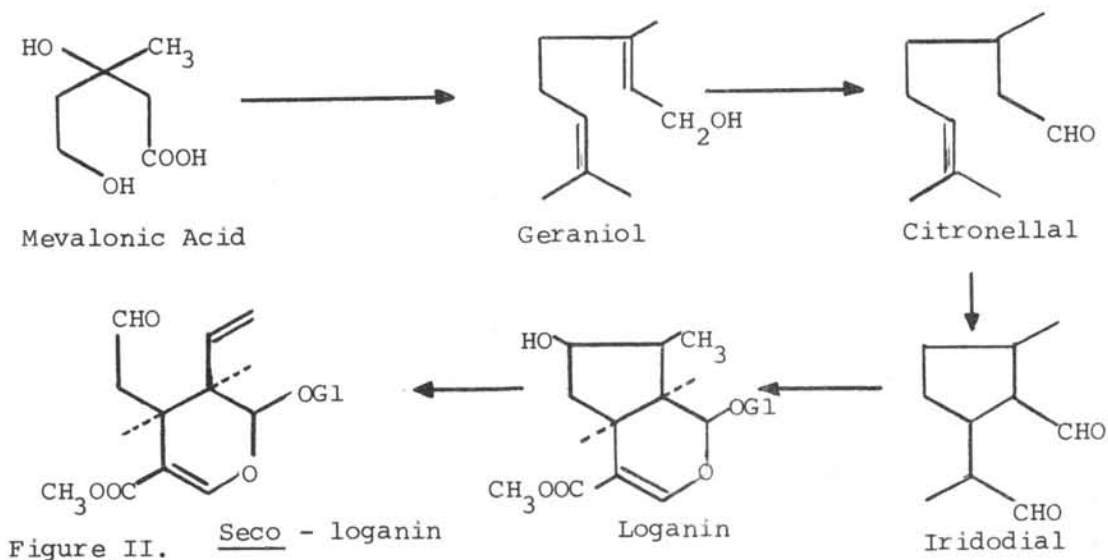


Figure I.

The tryptamine formed then condenses with a  $C_{9-10}$  unit to give the corresponding indole alkaloids. Several different hypotheses had been postulated but now have been abandoned following the establishment of one theory by the use of radioactive tracer experiments. The theory was independently suggested by Thomas<sup>(97)</sup> and Wenkert<sup>(115)</sup> and confirmed by many other investigators.<sup>(91)</sup> Following from this

Battersby et al.<sup>(116)</sup> pointed out that it was seco - loganin that reacts with the tryptamine. They also proposed a pathway of seco - loganin from mevalonic acid, having geraniol, citronellal, irridodial and loganin as intermediates (Figure II).



Battersby et al.<sup>(117)</sup> found that vincoside and another intermediate are in the pathway from the reaction of tryptamine and seco - loganin to form indole alkaloids. Blackstock et al.<sup>(106)</sup> have recently shown that vincoside has the C(3)-H  $\beta$  configuration. This was also reported by De Silva et al.<sup>(111)</sup>

The biogenesis pathway to the indole alkaloids can therefore be represented as shown below<sup>(91)</sup> (Figure III).

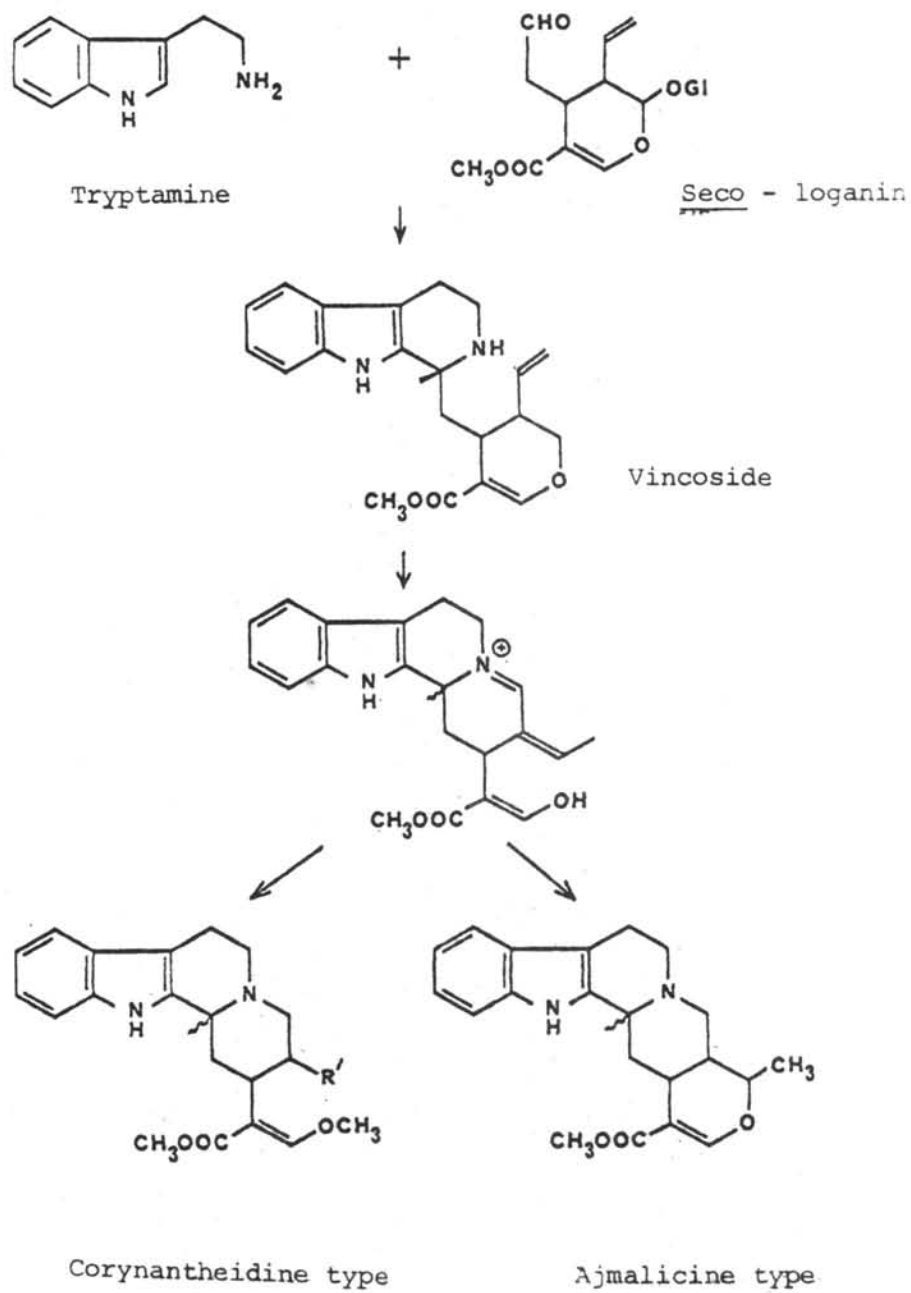


Figure III

## 9.2 Oxindole alkaloids

Jackson and Smith,<sup>(99)</sup> with the knowledge of C<sub>9-10</sub> unit, have pointed out that the condensation between tryptamine and the C<sub>9-10</sub> unit is more likely to be  $\beta$  condensation than an  $\alpha$  condition as proposed by Woodward<sup>(98)</sup> on the ground that the latter intermediate is far less stable than the former intermediate.

They stated that tryptamine reacts with C<sub>9-10</sub> unit to give a Schiff's base. This compound then undergoes cyclisation at either an  $\alpha$  or  $\beta$  position of the indole nucleus to give the  $\beta$ -carboline or the spiro-indolenine, respectively. They also pointed out that the  $\beta$ -condensation is more favoured because the intermediate produced (spiro-indolenine) does not necessitate a re-arrangement of the  $\pi$  electron system of the benzene ring which would be the case with an  $\alpha$  condensation.

The spiro-indolenine can readily either isomerise in mild acid condensation to give the  $\beta$ -carboline and hence indole alkaloids, or oxidise to give oxindole alkaloids<sup>(99)</sup> (Figure IV).

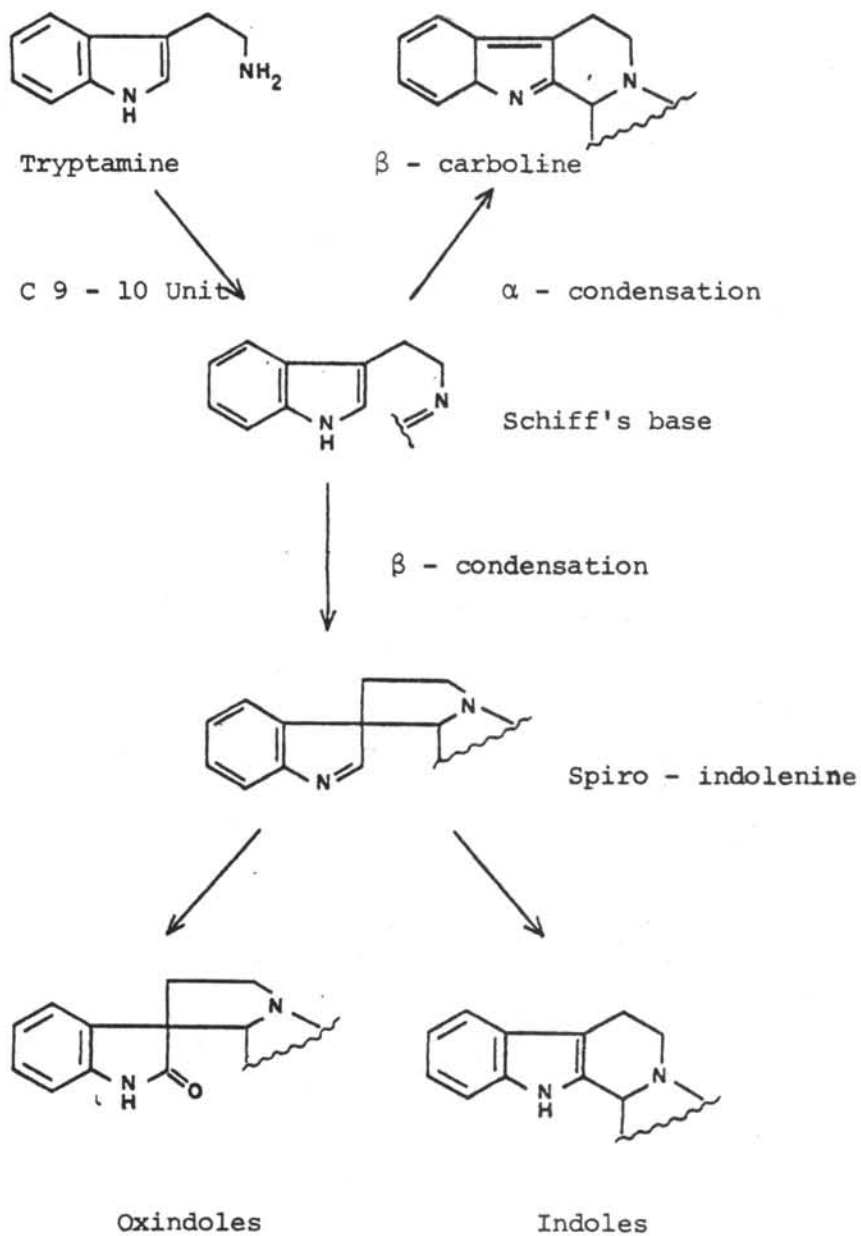


Figure IV

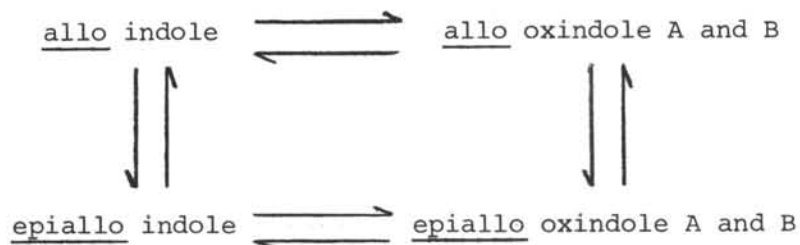


## 10. Biogenesis of the Uncaria alkaloids

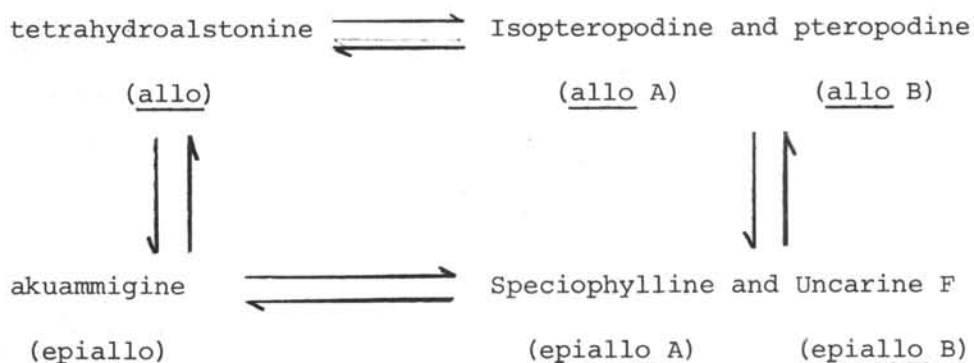
Four interconvertible stereoisomeric pentacyclic oxindole alkaloids have been reported to be present in the leaves of Uncaria bernaysii F. Muell.<sup>(15 a)</sup> These four isomers have been established as, isopteropodine (uncarine E, epiallo A), pteropodine (uncarine C, allo B), speciophylline (uncarine D, epiallo A), and uncarine F (epiallo B).<sup>(15 a)</sup>

The two indole alkaloids tetrahydroalstonine (allo) and akuammigine (epiallo) found as minor alkaloids in the Uncaria bernaysii F. Muell. leaves and stems extracts, possess D and E ring system which are identical in structure to the major oxindole alkaloids isolated. A similar situation exists for Uncaria rhynchophylla Miq. when the E-seco indole and oxindole alkaloids, isolated also have identical D/E ring systems.<sup>(31)</sup> Pentacyclic oxindole and indole alkaloids with common D/E ring systems are also found to occur together in several species of the related genus Mitragyna. Since heteroyohimbine alkaloids are readily converted chemically into the corresponding oxindole alkaloids it has been postulated that heteroyohimbines are synthesised in the plant and converted into oxindole alkaloids.<sup>(33)</sup> Recently, pteropodine and isopteropodine have been converted into tetrahydroalstonine and akuammigine<sup>(31)</sup> and it is possible that oxindole alkaloids may be converted to indole alkaloids within the plant. Furthermore, tetrahydroalstonine and akuammigine are readily interconvertible chemically as are isopteropodine, pteropodine, speciophylline and uncarine F.<sup>(15 a)</sup> Hence, the following

relationships may be possible within Uncaria bernaysii F. Muell. and in species of Mitragyna. (15 a)



The alkaloidal sequence of Uncaria bernaysii F. Muell. is :



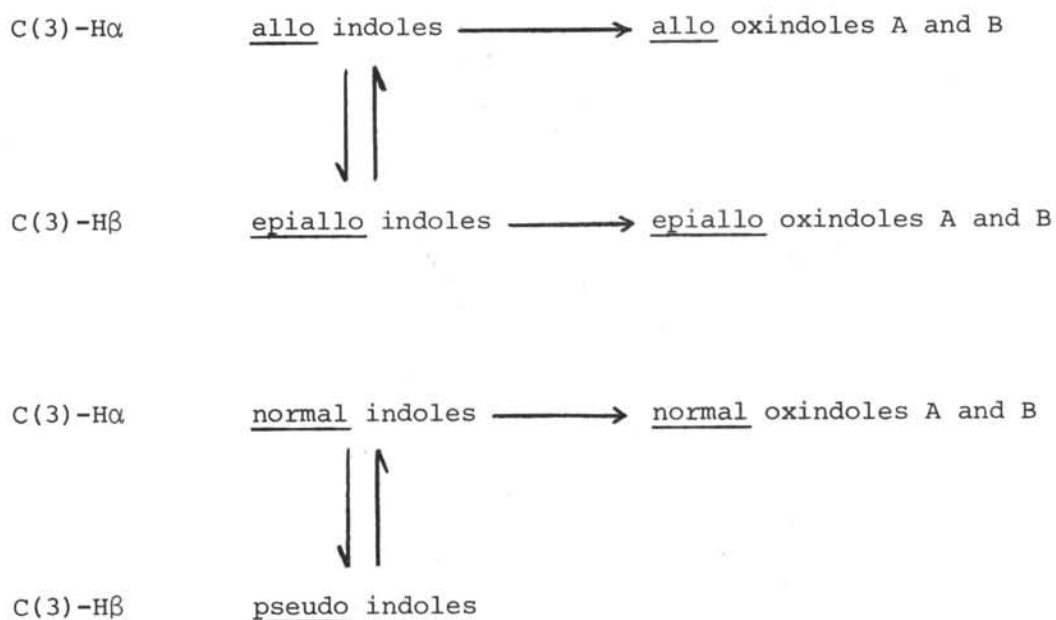
It was observed by Shellard, Phillipson and Gupta (1969) that when both indole and oxindole alkaloids occurred in Mitragyna species, the D/E ring systems were identical in both types of alkaloids. (35 b) Furthermore, with the exception of Mitragyna speciosa Korth. the indole alkaloids present in the largest quantity are the thermodynamically less stable configurations, i.e. epiallo and pseudo. This gave rise to the possibility that there was a well defined biogenetic link between the formation of the indole and oxindole alkaloids and a hypothesis was put forward by Shellard, Phillipson and Gupta (1969) (35 b) that :

a) the plant synthesised the thermodynamically more stable indole alkaloids according to the scheme suggested by Battersby and Hall (1969) for the biogenesis of indole alkaloids,

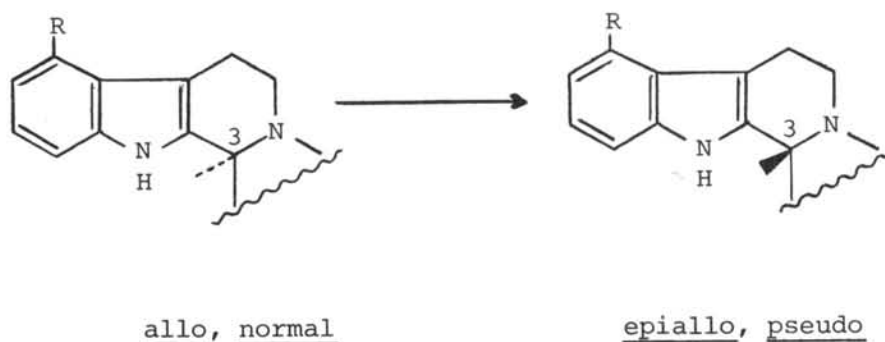
b) these alkaloids then isomerised into the corresponding thermodynamically less stable configuration, and

c) all the indole alkaloids were then converted to the corresponding oxindole alkaloids. (39 b)

It should be noted that no pseudo oxindole alkaloids have been isolated and this confirms the view of Trager et al. (1968) that they are unable to exist. (101) These two hypotheses can thus be summarised as follows : (39 b)



In terms of configuration, the isomerisation of the indole alkaloids involves the conversion of C(3)-H $\alpha$  to C(3)-H $\beta$ .<sup>(39 b)</sup>

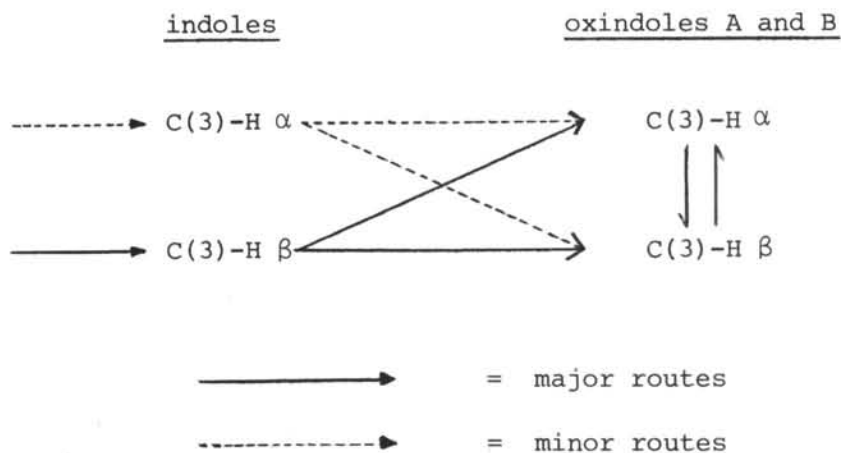


The indole transformation involves the conversion of C(3)-H $\alpha$  to C(3)-H $\beta$  but this was achieved in vitro by Wenkert and Roychoudhuri.<sup>(102, 103)</sup> The in vitro conversion of indole alkaloids to the corresponding oxindoles was carried out by Finch and Taylor<sup>(86)</sup> and Shavel and Zinnes.<sup>(104)</sup> Since then these conversions have been repeated with most of the *Mitragyna* indole alkaloids.<sup>(105)</sup>

However, in some of the plants examined, the allo and normal indole alkaloids could not be detected. Nevertheless, the speculative hypothesis required them to be present even if only in small quantities; so Shellard et al. examined leaves, stem bark and roots collected at monthly intervals from the same trees [*Mitragyna parvifolia* (Roxb.) Korth.] over a long period of time. The alkaloids were found in trace amounts in the very young leaves. With *Mitragyna* species, there is no seasonal leaf-fall; after some time the leaves fall and a short time afterwards new leaves appear.<sup>(105)</sup>

However, in one of the geographical variants of Mitragyna parvifolia (Roxb.) Korth. although ajmalicine could not be found, 3-isoajmalicine is present and the thought that in this species, mitraphylline could not be obtained from 3-isoajmalicine was shown to be correct by in vitro and in vivo experiments.<sup>(36, 37, 38)</sup> Other feeding experiments showed that mitraphylline is obtained from ajmalicine but the unexpected observation was that there is no interconversion between the two related indole alkaloids. Later work using <sup>14</sup>C-labelled indole alkaloids also showed that there is no interconversion between the allo and epiallo indole alkaloids though each type of alkaloid would give rise to both allo and epiallo oxindole alkaloids.<sup>(105)</sup>

It was, therefore, considered more likely that the C(3)-H $\alpha$  and C(3)-H $\beta$  indole alkaloids were separately synthesised from a precursor but that the epiallo and pseudo indole alkaloids were the dominant ones and offered the main pathway to the oxindole alkaloids. This modification of the hypothesis later becomes more rational with Blackstock's revelation in 1971<sup>(106)</sup> De Silva et al. in the same year,<sup>(111)</sup> that the C(3)-H in vincoside was actually  $\beta$ . Following further in vivo experiments using both labelled and unlabelled alkaloids, the hypothesis has been modified to meet these newly observed facts and is now represented (Shellard and Houghton. 1973) as follows :<sup>(91, 105)</sup>



- a) there are two routes of biogenesis from a common precursor, one of which is a major route and the other a minor one,
- b) the major route leads to the formation of the epiallo and pseudo indole alkaloids,
- c) the epiallo indoles are converted to epiallo and allo oxindoles, while the pseudo indoles are converted only to normal oxindoles,
- d) the minor route leads to the formation of the allo and normal indoles alkaloids and each may be converted to the corresponding oxindole, and
- e) there may be conversion between the C(3)-H $\alpha$  and C(3)-H $\beta$  oxindole alkaloids but not between the C(3)-H $\alpha$  and C(3)-H $\beta$  indole alkaloids. (91)

It is supported by the fact that the dominant indole alkaloids are the C(3)-H $\beta$  group. (39)

It might be mentioned, in passing, that the existence of mitraphylline in some species cannot be explained on the basis of the

hypothesis and it has been shown by Shellard and Houghton (1973)<sup>(39)</sup> following feeding experiments, that there is an interconversion between rhynchophylline and mitraphylline via the intermediary corynoxine [C(20) vinyl-rhynchophylline]. Using the method of Djakoure et al.<sup>(107)</sup> this conversion has now been achieved in vitro.<sup>(105)</sup>