CHAPTER 1

INTRODUCTION

1.1 THE GENUS *UNCARIA* - BOTANY AND DISTRIBUTION

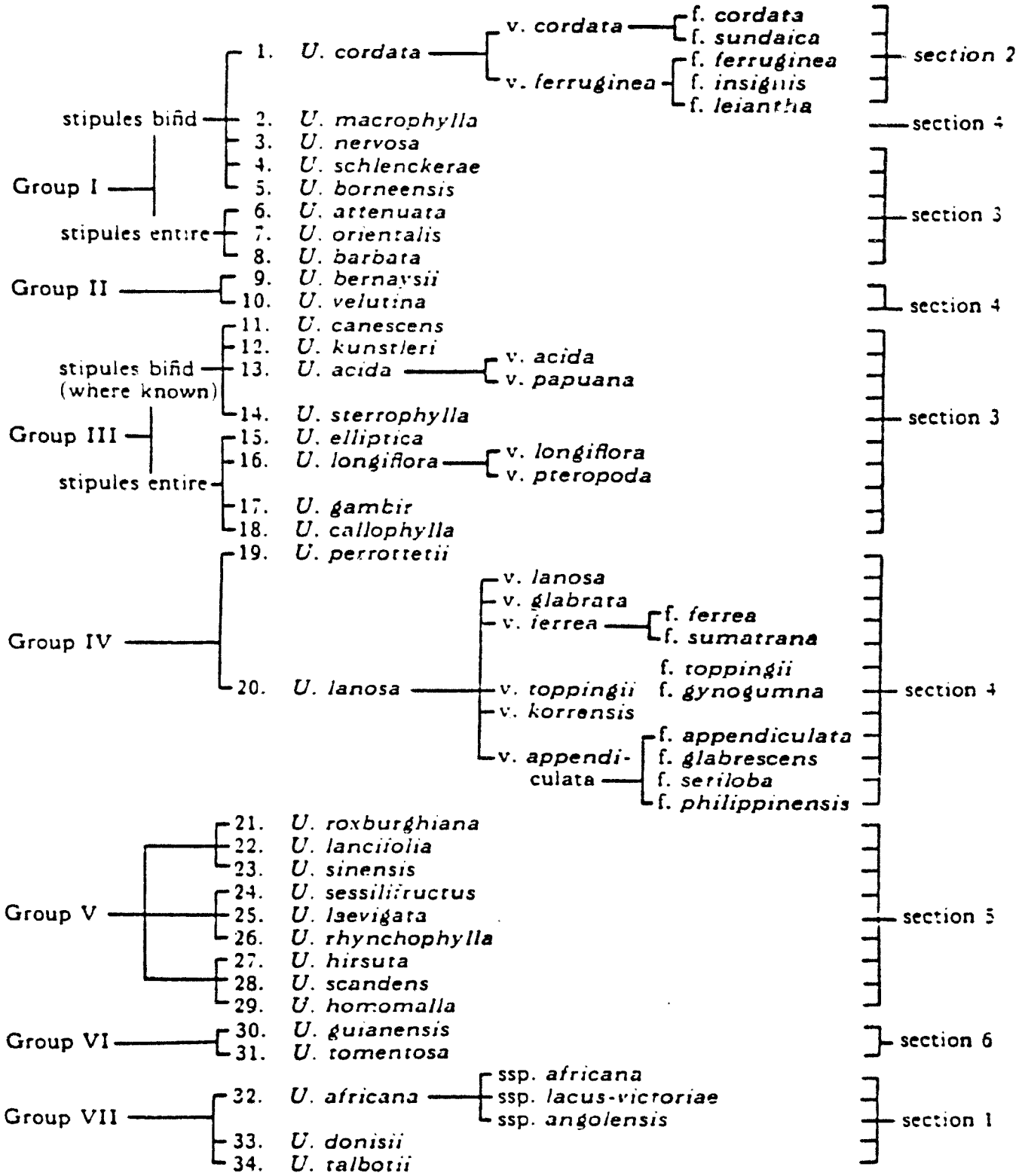
Uncaria belongs to the sub-tribe Mitragynineae, tribe Cinchoneae, sub-family Cinchonoideae of the family *Rubiaceae.* The genus is widely distributed in tropical regions, its stronghold being South East Asia, from Malaysia to the Solomon Islands. It is nevertheless also found in other parts of Asia, Africa, South America and Australia.[1] Haviland noted that *Uncaria* formed an easily recognizable genus, all species having a climbing habit with peduncles converted into recurved hooks as outstanding characters.[1] These plants climb by means of their grapples which are called 'kait-kait' or 'kekait' in Malay, thus leading to their common Malay name. However, difficulties are encountered in delineating the species. This is reflected in the 120 names in the Index Kewensis which has now been reduced to 34 in Risdale's recent revision.[1] The main characters presently used in the classification of *Uncaria* species are the absence or presence of interfloral bracts and whether the flowers are pedicellate or sessile. Additional important characters are the stipules-whether entire, shallowly or deeply bifid.

Unfortunately all of these characters may occur in parallel series in unrelated groups of species; therefore it is possible that uniting species with, for example, entire stipules is artificial.[1,2]

Generally, there are groups of species which seem to be more closely related to each other than other groups of species. Haviland, in 1897, divided the species of the genus known to him into six informal sections as indicated in Figure 1.1.

Risdale, in 1978, reinvestigated the genus and his conclusions on the inter-relationships of the species are summarized in Figure 1.1. Seven groups emerged which correspond well to the sections recognized by Haviland, with the exception of group II which now contains *U. bernaysii* and *U. velutina* (from section 4). Otherwise the main difference is that the species with the entire stipules in Risdale's group I were placed in section 3 by Haviland, together with species of the revised group III. About 14 species were reported to be found in Peninsular Malaysia, as listed below:[2]

1. *U. gambir*
2. *U. cordata*
3. *U. borneensis*
4. *U. attenuata*
5. *U. barbata*
6. *U. canescens*
7. *U. kunstleri*
8. *U. acida*
9. *U. elliptica*
10. *U. longiflora*
11. *U. callophylla*
12. *U. roxburghiana*
13. *U. lanosa*
14. *U. homomalla*



*Interfloral bracteoles: absent in Groups I, II, III
either absent or present in Group IV
present in Groups V, VI, VII.

Figure 1.1: Relationships within *Uncaria* arranged as a Dendrogram[1]

1.2 ETHNOBOTANY OF MALAYSIAN *UNCARIA*

Traditional medicine is an integral part of Asian culture and has been practised by various ethnic groups long before the introduction of modern medicine. Even in the modern society of today, traditional medicine is still being practised either as an alternative or as a supplement to modern medicine.

In Malaysia, there are about 1300 species of higher plants reported to have medicinal properties and used either singly or in concert with modern medicine to treat various diseases and ailments.[3] Various species of *Uncaria* are known to have diverse medicinal uses. The reported uses include treatment of fevers, common cold, sore throats, diarrhoea, dysentery, cholera, pains, wounds, burns, scatia and lumbago, asthma, rheumatism, skin diseases, skin and mouth ulcers, syphilitic sores, children's diseases including infantile fevers (Japan, China) and hypertension (China, Taiwan, Japan).[2,3,4] Some of these uses are summarized in Table 1.1. However, their real therapeutic value, side effects and toxicological implications are not well known. In recent years however, in vitro and in vivo screening programmes for antimicrobial, central nervous system depressant activity, and antihypertensive action have led to the isolation and identification of the active constituents. These studies have received added impetus in the face of rapid deforestation accompanying development.

Table 1.1 : Ethnobotany of the Genus *Uncaria*

Name	Part Used	Notes / Comments[ref.]
U. acida v. *acida*	leaves	to relieve pain by rubbing onto the body[3], for thrush, skin diseases, and in betel chewing, as an astringent, source of gambier[2]
U. africana v. *africana*	-	treatment of stomach pains and syphilis[2]
	bark	common cold[2]
	leaves	chest complains[2]
U. bernaysii	-	source of gambier[2]
U. callophylla		reported to have same uses as *U. gambir*[2]
U. cordata v. *cordata* f. *cordata*	young stem	black dye[2]
	stem wood	used in the preparation of axe handles[2]
	bark	dyeing threads[2]
	roots	skin ulcers[2]
U. gambir	-	source of gambier[2]
	leaves & stem	used for skin dyeing and tanning,[2] used as an astringent, lotion for burns,[2] paste for skin diseases.[2]
	-	relief of scatia and lumbago[3]
	leaves & shoots	remedy for diarrheoa and dysentery,[2] gargles for sore throats and mouth ulcers[3]
	gambier	relief of asthma, external application for syphilitic sores, treatment of cholera, dysentery, intermitent fever, bleeding, stomatitis and sore throats.[2]
U. guianensis	leaves	healing of wounds, treatment of dysentery.[2]
U. hirsuta	hooks	hypertension[4]
U. homomalla	-	as a depurative[2]

Table 1.1 continued.....

Name	Part Used	Notes / Comments[ref.]
U. lanosa *v. appendiculata* *f. setiloba*	old stems	provide drinkable water[2]
U. lanosa *v. ferrea* *f. ferrea*	young shoots leaves roots	source of dye[2] cleaning wounds, ulcers[2] relief for the inflammation of the intestine[2]
U. lanosa *v. lanosa*	-	source of gambier[2]
U. longiflora *v. longiflora*	leaves	treatment of thrush, frambesioma and rheumatism,[2] rubbed into the body for relief of pain[3]
U. perrotletii	-	alkaloid extract shown to have anti-tumour activity[2]
U. rhynchophylla	- hooks stems & twigs	treatment of infantile, fever and nervous diseases, dizziness, vision and bilious disorders[2] antispasmodic activity and sedative action[2] treatment of 'liver fire' fever, headache, dizziness, flushed face and eyes, pediatric fever, colds and convulsions[2]
U. sessilfructus	bark	betel substitute[2]
U. sinensis	hooks	treatment of fevers and various nervous disorders[2]

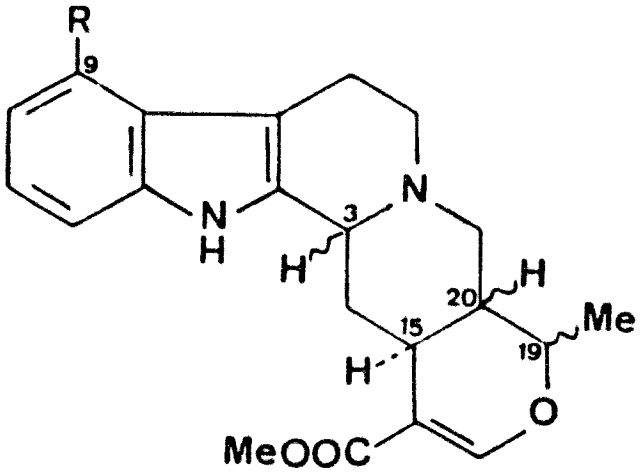
1.3 ALKALOIDS OF THE GENUS *UNCARIA*

A number of alkaloids have been obtained from *Uncaria* species. Whereas in some instances characterization and identification of the isolated alkaloids have been carried out, in others only results of phytochemical screening have been reported. It is to be noted that some of the *Uncaria* alkaloids listed in the chemical literature are of dubious origin, either being obtained from plant material of doubtful identity or from the extraction of mixed collections.[2] To a large extent these difficulties may be attributed to the problems encountered in the identification of the individual species in this taxonomically difficult genus. Risdale's recent revision of the genus,[1] which has resulted in a considerable reduction of the number of species (from 120 to 34) has helped resolve many of the problems posed in the identification of individual species. The work of Phillipson *et al*[2] in particular as well as of others on the alkaloidal content and chemotaxonomic aspects of the genus has also helped substantially to clarify matters. Phillipson *et al* examined some 400 small samples, (mainly leaf fragments obtained from herbarium specimens) representing all the known species collected over a wide geographical range. Using primarily t.l.c. and gc comparison with reference alkaloids and in some cases by their mass spectra, some 40 different alkaloids were identified from 34 species. Some species were found to show variation between samples in respect of the alkaloids present but in others the alkaloidal composition appeared quite constant.

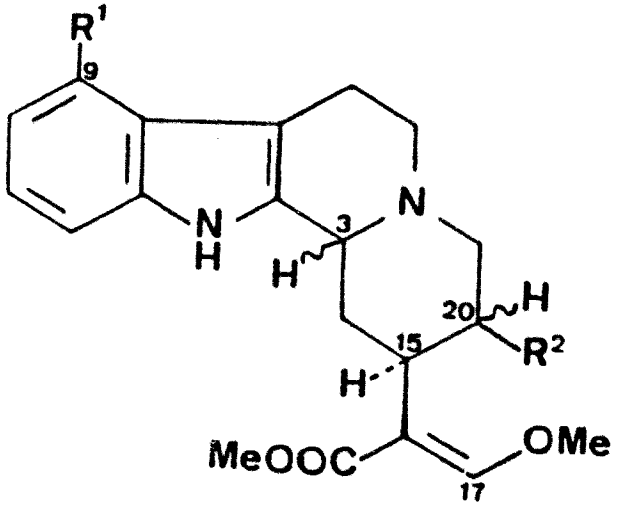
The alkaloids found in *Uncaria* are reported to be mainly the pentacyclic and tetracyclic heteroyohimbine types [1 & 2] and the corresponding oxindoles [3 & 4].[2] The alkaloids isolated were usually variants of these strutures [1 -4] differing only in their stereochemistry and/or aromatic substitution. These alkaloids are also frequently accompanied by their respective N-oxides which are polar (base line) alkaloids. Less common alkaloids encountered in *Uncaria* include the roxburghines [5], β-carbolines [6], the pyridino-indolo quinolizidinones [7], yohimbines [8] and their oxindoles [9], tetracyclic pseudoindoxyl [10] and the benzenoid E ring pentacyclic alkaloids (gambirtannines [11] and dihydrogambirtannine [12]).

1.3.1 The Heteroyohimbine Alkaloids [1 & 2]

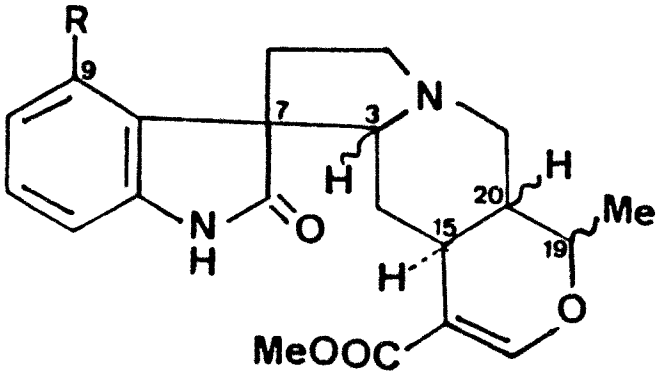
The pentacyclic and tetracyclic heteroyohimbines have asymmetric centres at C3, C5 and C20. However, all those isolated so far have C15-Hα configuration since these alkaloids are derived from the monoterpene secologanin. There are 4 possible diastereomers designated as normal, pseudo, allo and epiallo. The pentacyclic heteroyohimbines [1] have an additional asymmetric centre at C19 (C19 methyl group α or β) so that a total of eight stereoisomers are possible. Although in principle the tetracyclic heteroyohimbines may show geometric isomerism because of the double bond between C16 and C17, the geometry of the enol - ether double bond has always been found to be *E*.



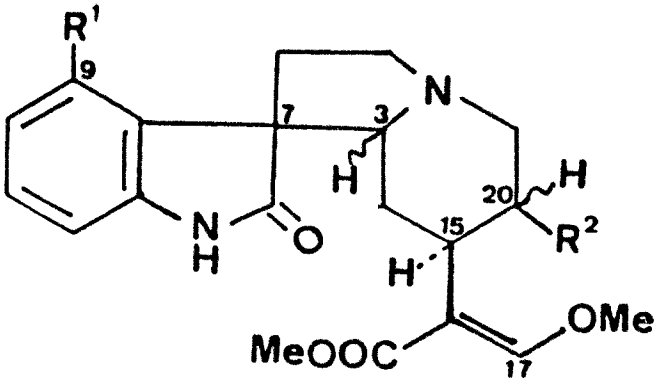
[1] PENTACYCLIC HETEROYOHIMBINES
(R = H or OH)



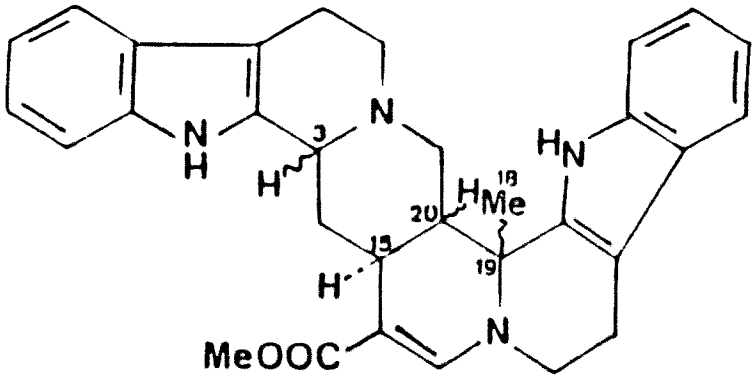
[2] TETRACYCLIC HETEROYOHIMBINES
(R^1_2 = H or OH
R^2 = ethyl or vinyl)



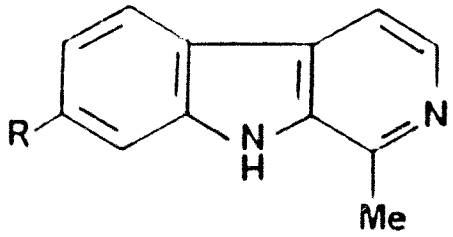
[3] PENTACYCLIC OXINDOLES
(R = H or OH)



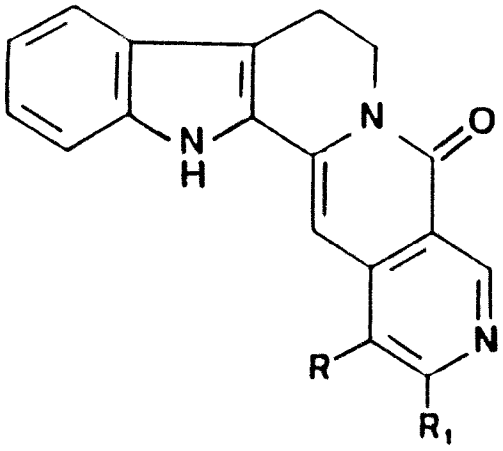
[4] TETRACYCLIC OXINDOLES
(R^1_2 = H or OH
R^2 = ethyl or vinyl)



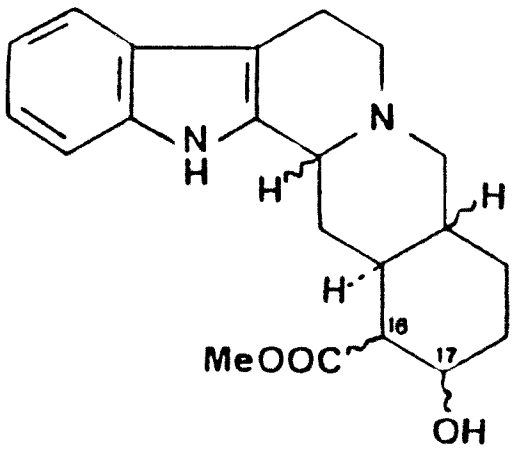
[5] ROXBURGHINES



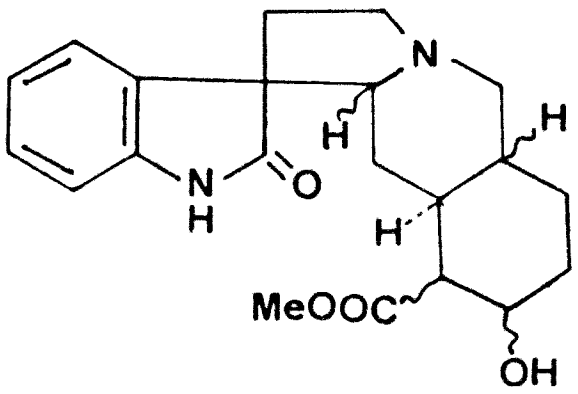
[6] β-CARBOLINES



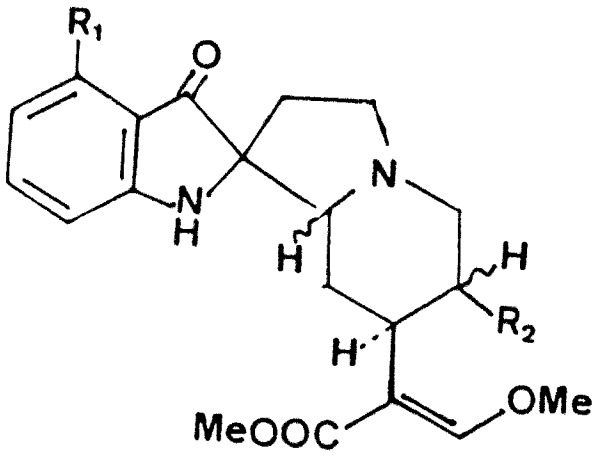
[7] PYRIDINO-INDOLO QUINOLIZIDINONES



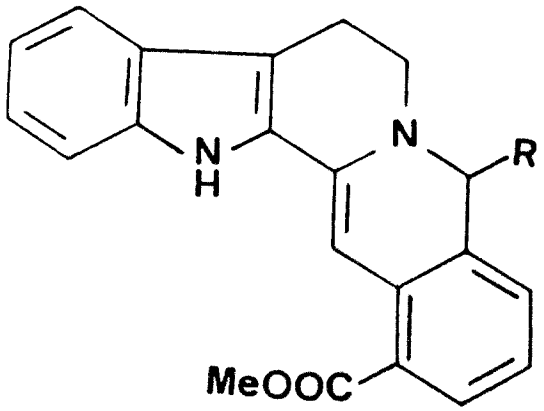
[8] YOHIMBINES



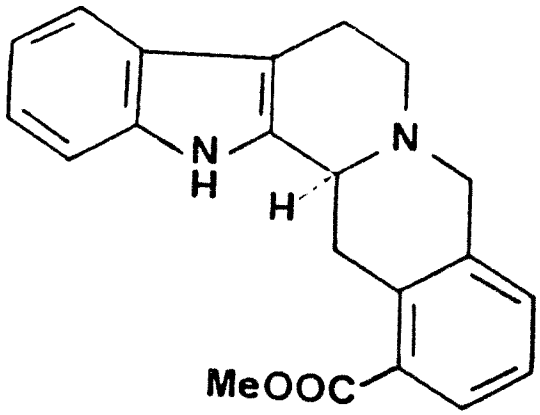
[9] YOHIMBINE OXINDOLES



[10] TETRACYCLIC PSEUDOINDOXYL



[11] GAMBIRTANNINES



[12] DIHYDROGAMBIRTANNINE

Table 1.2 shows the configuration terminology used for the heteroyohimbine alkaloids [1 & 2].

Table 1.2 : Configuration Terminology For Heteroyohimbine Alkaloids [1 & 2]

Configuration	H-3	H-15	H-20
Normal	α	α	β
Pseudo	β	α	β
Allo	α	α	α
Epiallo	β	α	α

Hitherto, all previously known heteroyohimbine alkaloids reported from *Uncaria* have aromatic substitution only at C-9.[2] In the tetracyclic heteroyohimbines [2], the R^2 group may be either an ethyl or a vinyl group. The heteroyohimbine alkaloids found in *Uncaria* species are listed in Table 1.3 and 1.4.

Table 1.3 : Pentacyclic Heteroyohimbine Alkaloids [1]

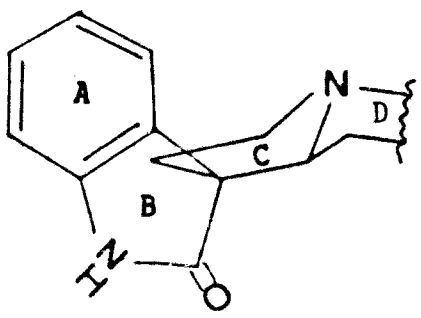
Alkaloid	Configuration	C9-R	C19-CH_3
Ajmalicine [13]	normal	H	α
19-Epi-ajmalicine [14]	normal	H	β
3-Isoajmalicine [15]	pseudo	H	α
3-iso-19-epiajmalicine [16]	pseudo	H	β
Tetrahydroalstonine [17]	allo	H	α
Rauniticine [18]	allo	H	β
Akuammigine [19]	epiallo	H	α

Table 1.4 : Tetracyclic Heteroyohimbine Alkaloids [2]

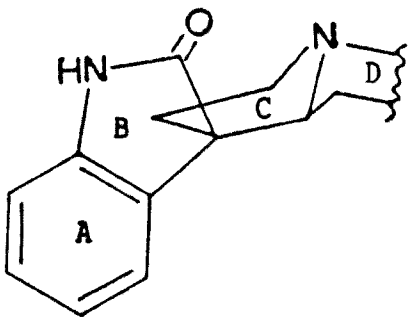
Alkaloid	Configuration	R^1	R^2
Dihydrocorynantheine [20]	normal	H	CH_2CH_3
Corynantheine [21]	normal	H	$CH{=}CH_2$
Gambirine [22]	normal	OH	CH_2CH_3
Hirsutine [23]	pseudo	H	CH_2CH_3
Hirsutheine [24]	pseudo	H	$CH{=}CH_2$
Epiallo-corynantheine [25]	epiallo	H	CH_2CH_3

1.3.2 The Oxindole Alkaloids [3 & 4]

The oxindole alkaloids (pentacyclic and tetracyclic oxindoles) have the same asymmetric centres as the heteroyohimbine alkaloids. In addition, they have a further asymmetric centre at C7, so that the lactam carbonyl may be either below (A series) or above (B series) the plane of the C and D rings.

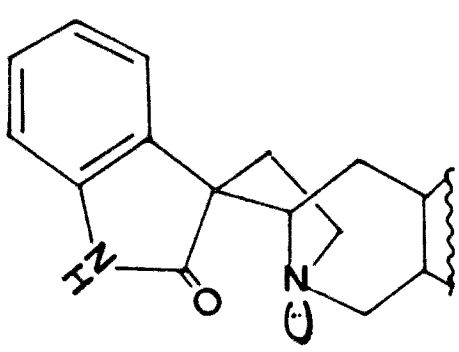


[26] A SERIES

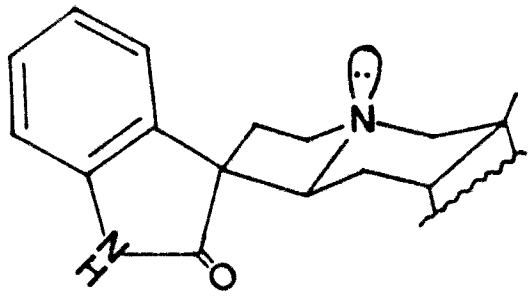


[27] B SERIES

In addittion, in both the A and B series, the lone pair electrons in N(4) may be either on the same side of the molecule as the lactam carbonyl (syn conformation) or on the opposite side (anti conformation).



[28] SYN CONFORMATION



[29] ANTI CONFORMATION

Table 1.5 shows the configuration terminology used for the oxindole alkaloids [3 and 4].

Table 1.5: Configuration Terminology For Oxindole Alkaloids

Configuration	H-3	H-15	H-20	Series
Normal	α	α	β	A or B
Pseudo	β	α	β	A or B
Allo	α	α	α	A or B
Epiallo	β	α	α	A or B

Although all 4 configurations are possible, the pseudo oxindole alkaloids cannot exist due to the steric interference between the oxindole unit and the underside of ring D .

The oxindole alkaloids found in *Uncaria* species are summarized in Table 1.6 and 1.7.

Table 1.6: Pentacyclic Oxindole Alkaloids [3]

Alkaloid	Configuration	Series	C9-R	C19-CH_3
Isomitraphylline [30]	normal	A	H	α
Mitraphylline [31]	normal	B	H	α
Isoformosanine [32]	normal	A	H	β
Formosanine [33]	normal	B	H	β
Isopteropodine [34]	allo	A	H	α
Pteropodine [35]	allo	B	H	α
Speciophylline [36]	epiallo	A	H	α
Uncarine F [37]	epiallo	B	H	α

Table 1.7: Tetracyclic Oxindole Alkaloids [4]

Alkaloid	Configuration	Series	R^1	R^2
Isorhynchophylline [38]	normal	A	H	CH_2CH_3
Rhynchophylline [39]	normal	B	H	CH_2CH_3
Isocorynoxeine [40]	normal	A	H	$CH{=}CH_2$
Corynoxeine [41]	normal	B	H	$CH{=}CH_2$
Rotundifoline [42]	normal	A	OH	CH_2CH_3
Isorotundifoline [43]	normal	B	OH	CH_2CH_3
Corynoxine A [44]	allo	A	H	CH_2CH_3
Corynoxine B [45]	allo	B	H	CH_2CH_3
Speciofoline [46]	epiallo	B	OH	CH_2CH_3

1.3.3 Yohimbine Alkaloids

Yohimbine [47] was first found in *Corynanthe yohimbe* (*Rubiaceae*). Yohimbine and its isomers were also reported to occur in various genera of plants such as *Uncaria* (*Rubiaceae*), *Rauwolfia* (*Apocynaceae*), *Gelsemium* (*Loganiaceae*), and *Alchornea* (*Euphorbiaceae*) among others.[5]

The structure of the alkaloid has been confirmed by several syntheses of its derivatives and of yohimbine itself.[6-11] There are 5 asymmetric centres in the yohimbine skeleton; *viz.* C3, C15, C16, C17 and C20. All natural isomers of yohimbine possess the α-configuration at C15 (Table 1.8). As in the heteroyohimbine alkaloids, yohimbines can also be divided into four groups according to the relative configurations of the stereocentres C3, C15 and C20, *viz.*, normal, pseudo, allo and epiallo as shown in Table 1.2.

Only one known alkaloid of the pseudo configuration, i.e. pseudoyohimbine [50], has been previously reported from *Uncaria*, namely from *U. callophylla*[12] and *U. attenuata*[13]. Other isomers were reportedly detected but not firmly identified in some other *Uncaria* species.[2,13] Substituted yohimbine alkaloids although present in other families have not been reported from *Uncaria*.

Table 1.8 : Yohimbine Alkaloids[42]

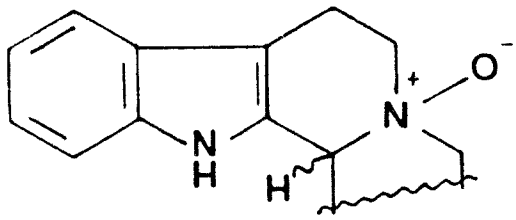
Alkaloid*	Configuration					Type
	H-3	H-15	H-20	H-16	H-17	
Yohimbine [47]	α	α	β	β	β	Normal
Corynanthine [48]	α	α	β	α	β	Normal
17-Epi-corynanthine [48a]	α	α	β	α	α	Normal
β-Yohimbine [49]	α	α	β	β	α	Normal
Pseudoyohimbine [50]	β	α	β	β	β	Pseudo
3-Epi-corynanthine [51]#	β	α	β	α	β	Pseudo
3-Epi-β-yohimbine [52]#	β	α	β	β	α	Pseudo
Alloyohimbine [53]	α	α	α	β	β	Allo
17-Epi-alloyohimbine [53a]	α	α	α	β	α	Allo
α-yohimbine [54]	α	α	α	α	β	Allo
17-Epi-α-yohimbine [54a]	α	α	α	α	α	Allo
3-Epi-alloyohimbine [55]	β	α	α	β	β	Epiallo
3,17-Epi-allo-yohimbine [55a]	β	α	α	β	α	Epiallo
3-Epi-α-yohimbine [56]	β	α	α	α	β	Epiallo
3,17-Epi-α-yohimbine [56a]	β	α	α	α	α	Epiallo

*known yohimbine isomers - natural/synthetic
#revision of reference no. 5

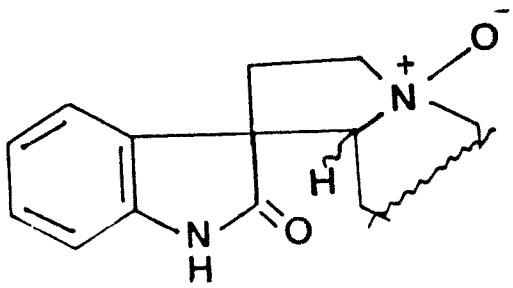
1.3.4 Alkaloid N-Oxides

The N-oxide alkaloids reported from *Uncaria* species were mostly of the oxindole type [57].[2] Only two species of *Uncaria* were reported as having the N-oxides of the heteroyohimbine type [58], i.e. *U. gambir*[14] and *U. tomentosa*[15].

Table 1.9 shows the heteroyohimbine and oxindole N-oxides reported in *Uncaria* species.



[58] HETEROYOHIMBINE N-OXIDES



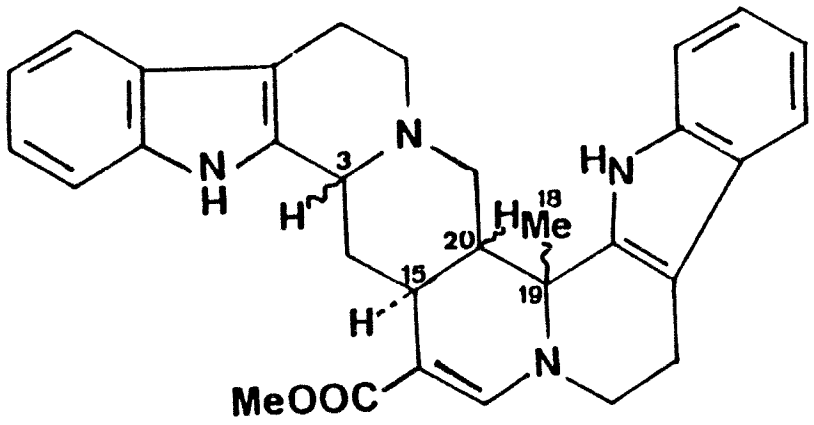
[57] OXINDOLE N-OXIDES

Table 1.9 : N-Oxides of *Uncaria* Alkaloids

Alkaloids	Configuration
Tetracyclic Heteroyohimbine	
Dihyrocorynantheine N-oxide	Normal
Hirsutine N-oxide	Pseudo
Pentacyclic Heteroyohimbine	
4,R-Tetrahydroalstonine N-oxide	Allo
4,R-Akuammigine N-oxide	Epiallo
4,S-Akuammigine N-oxide	Epiallo
Tetracyclic Oxindole	
Isorhynchophylline N-oxide	Normal (A)
Rhynchophylline N-oxide	Normal (B)
Pentacyclic Oxindole	
Isomitraphylline N-oxide	Normal (A)
Mitraphylline N-oxide	Normal (B)
Isopteropodine N-oxide	Allo (A)
Pteropodine N-oxide	Allo (B)
Speciophylline N-oxide	Epiallo (A)
Uncarine F N-oxide	Epiallo (B)

1.3.5 Other Miscellaneous Alkaloids

In addition to the alkaloids discussed above, there are other less common alkaloids which occur in some *Uncaria* species. These include the roxburghines B [59], C [60], D [61] and E [62] (derived from two tryptamine moieties and a C_{10} monoterpene unit) purportedly isolated from *U. elliptica*,[2,16,25,30] the simple β-carboline alkaloid, e.g. harmane [63],[2] pyridino-indolo quinolizidinones [64-66],[2,22] the tetracyclic pseudoindoxyl, dihydrocorynantheine pseudoindoxyl [67],[2,18] yohimbine oxindoles [9], gambirtannines [68-69][29] and dihydrogambirtannines [12].[29]

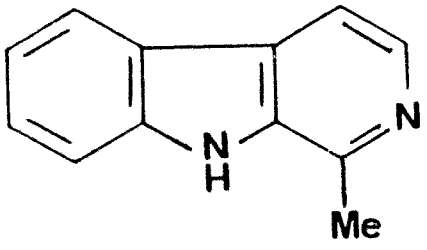


[59] ROXBURGHINE B (epiallo, C-18β)

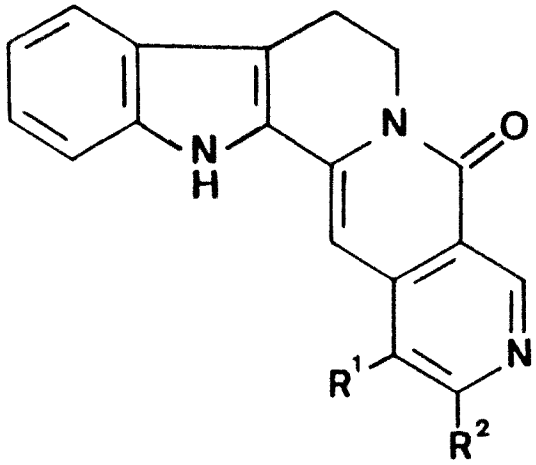
[60] ROXBURGHINE C (normal, C-18α)

[61] ROXBURGHINE D (pseudo, C-18α)

[62] ROXBURGHINE E (pseudo, C-18β)



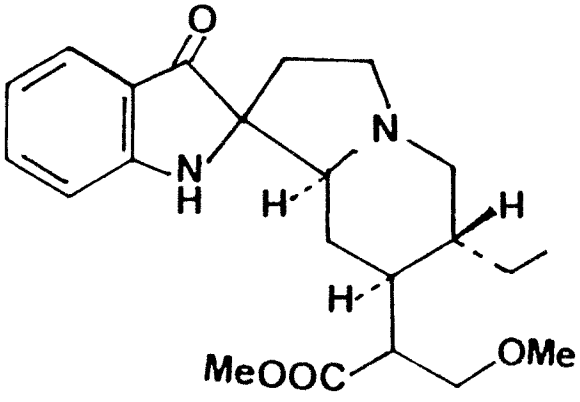
[63] HARMANE



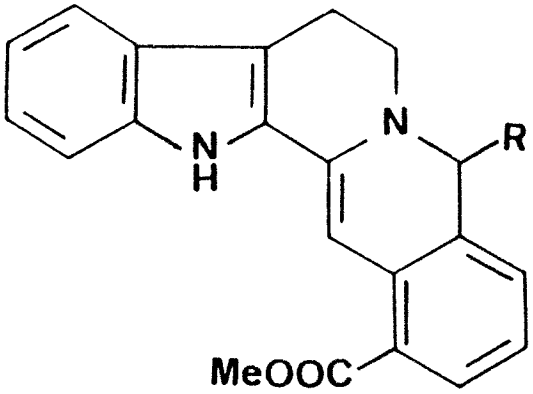
[64] ANGUSTINE (R^1=CH=CH_2, R^2=H)

[65] ANGUSTOLINE (R^1=CH(OH)Me, R^2=H)

[66] ANGUSTIDINE (R^1=H, R^2=Me)



[67] DIHYDROCORYNANTHEINE PSEUDOINDOXYL



[68] GAMBIRTANNINE (R=H_2)

[69] OXOGAMBIRTANNINE (R=O)

1.4 ALKALOIDS REPORTED FROM *UNCARIA*

The alkaloids isolated from *Uncaria* by previous investigators are summarized in Table 1.10. The species are arranged according to the same order as in Figure 1.1

Table 1.10 : Alkaloids Reported From *Uncaria* Species

Species	Plant part	Alkaloids	Ref.
1. *U. cordata* *var. cordata* *f. cordata*	st, l, fl	isorhnchophylline rhynchophylline	2
	l	corynoxine corynoxine B	2
var. cordata *f. sundaica*	l	unn.	2
var. ferruginea *f. ferruginea*	st, l, fl	dihydrocorynantheine	2
var. ferruginea *f. insignis*	l	isorhynchophylline rhynchophylline dihydrocorynantheine	2
var. ferruginea *f. leiantha*	l	isorhynchophylline rhynchophylline dihydrocorynantheine	2
2. *U. macrophylla*	l	isorhynchophylline rhynchophylline	2,17
	l, st	corynoxine corynoxine B	2
		isorhynchophylline N-O rhychophylline N-O	2
3. *U. nervosa*	l	dihydrocorynantheine hirsuteine hirsutine harmane	2
4. *U. schlenckerae*	l	unn.	2

Table 1.10 continued .....

Species	Plant part	Alkaloids	Ref.
5. *U. borneensis*	l	harmane	2
6. *U. attenuata*	l	tetrahydroalstonine	18
		rauniticine	
		14-β-hydroxy-3 -isorauniticine	
		3-isoajmalicine	2, 13
		19-epi-3-isoajmalicine	
		dihydrocorynantheine	
		akuammigine	
		harmane	
		hirsuteine	
		hirsutine	
		dihydrocorynantheine -pseudoindoxyl	
		epiallo corynantheine	
		speciophylline	
		formosanine	
		isoformosanine	
		isomitraphylline & N-O	
		mitraphylline & N-O	
		isorhynchophylline & N-O	
		rhynchophylline & N-O	
		corynoxine B	
		isocorynoxeine	
		corynoxeine	
		rotundifoline	
		isorotundifoline	
		speciofoline	
		pseudoyohimbine	
		yohimbine isomer	
		yohimbine oxindole	
	st, sb	isocorynoxeine	2
		corynoxeine	
		dihydrocorynantheine	
		hirsuteine	
		hirsutine	
		isorhynchophylline & N-O	
		rhynchophylline & N-O	
		pseudoyohimbine	
		yohimbine isomer	
		yohimbine oxindole	
	fl	isorhynchophylline	
		rhynchophylline	

Table 1.10 continued .....

Species	Plant part	Alkaloids	Ref.
7. *U. orientalis*	l	3-isoajmalicine	2,13
		harmane	
		isomitraphylline & N-O	
		mitraphylline & N-O	
		pteropodine & N-O	
		isopteropodine & N-O	
		uncarine F & N-O	
		speciophylline & N-O	
	st, sb, sw	ajmalicine	2
		akuammigine	
		19-epi-3-isoajmalicine	
		formosanine	
		isoformosanine	
		isopteropodine & N-O	
		pteropodine & N-O	
		speciophylline & N-O	
		uncarine F & N-O	
		harmane	
	fl	isopteropodine	
		pteropodine	
		speciophylline	
8. *U. barbata*	l, fr	harmane	2
9. *U. bernaysii*	l	pteropodine	19,20
		speciophylline	
		isopteropodine	20
		uncarine	
	l, st, fl	tetrahydroalstonine	21, 2
		akuammigine	
		isopteropodine & N-O	
		pteropodine & N-O	
		speciophylline & N-O	
		uncarine F & N-O	
	fr	angustine	2
		ajmalicine	
		3-isoajmalicine	
		isomitraphyline	
		mitraphylline	
	l	isorhynchophylline & N-O	
		rhynchophylline & N-O	
10. *U. velutina*	l	isomitraphylline	2,13
		mitraphylline	
		isopteropodine & N-O	
		pteropodine & N-O	
		speciophylline & N-O	
		uncarine F & N-O	

Table 1.10 continued .....

Species	Plant part	Alkaloids	Ref.
11. *U. canescens*	l, st	harmane	2
12. *U. kunstleri*	l	hirsutine rhynchophylline & N-O isorhynchophylline & N-O corynoxine	2
	l, twg	corynoxine B isorhynchophylline rhynchophylline	
13. *U. acida* *var. acida*	l	harmane isorhynchophylline rhynchophylline & N-O	2
var.papuana	l	3-isoajmalicine isorhynchophylline & N-O rhynchophylline & N-O corynoxeine	2
	l, st	isomitraphylline mitraphylline speciophylline	
14. *U. sterrophylla*	l	3-isoajmalicine speciophylline & N-O isomitraphylline mitraphylline	
	l, st	isopteropodine pteropodine speciophylline isorhynchophylline rhynchophylline uncarine F	2
15. *U. elliptica*	l	roxburghines B,C,D,E	23,24
	l	3-isoajmalicine akuammigine roxburghines C, D, E isorhynchophylline rhynchophylline dihydrocorynantheine	2
	bk	roxburghines X,D formosanine mitraphylline	25

Table 1.10 continued .....

Species	Plant part	Alkaloids	Ref.
15. *U. elliptica*	l	tetrahydroalstonine & N-O rauniticine 3-isoraunticine ajmalicine 19-epiajmalicine 3-isoajmalicine 19-epi-3-isoajmalicine 14-β-hydroxy-3 -isoraunticine raunticine pseudoindoxyl akuammigine -pseudoindoxyl isoraunticine -pseudoindoxyl raunticine oxindole A mitraphylline isomitraphylline formosanine isoformosanine	26
16. *U. longiflora* *var. longiflora*	l	isomitraphylline & N-O mitraphylline & N-O isopteropodine & N-O pteropodine & N-O speciophylline & N-O uncarine F & N-O corynoxeine isocorynoxeine	2
	l, st	isorhynchophylline & N-O rhynchophylline & N-O	
var. pteropoda	l	isopteropodine & N-O pteropodine & N-O isomitraphylline & N-O mitraphylline & N-O speciophylline & N-O	2,28
	st, sb, rt	uncarine F formosanine isoformosanine isorhynchophylline rhynchophylline isocorynoxeine corynoxeine isopteropodine pteropodine	2

Table 1.10 continued .....

Species	Plant part	Alkaloids	Ref.
17. *U. gambir*	l	dihydrocorynantheine isomitraphylline mitraphylline isorhynchophylline rhynchophylline harmane	2
	gambier	gambirtannine dihydrogambirtannine oxogambirtannine neogambirtannine	29
U. gambir' (mixed collection comprising several *Uncaria sp.*)[2]	l	roxburghines A-E tetrahydroalstonine dihydrocorynantheine	30
		4,R-akuammigine N-O 4,S-akuammigine N-O 4,R-tetrahydro-alstonine N-O	14
		dihydrocorynantheine gambirine dimeric alkaloid	57
18. *U. callophylla*	l	dihydrocorynantheine gambirine isomitraphylline mitraphylline isorhynchophylline rhynchophylline rotundifoline isorotundifoline	2
	l	dihydrocorynantheine gambirine callophylline isomitraphylline mitraphylline isorhynchophylline rhynchophylline	12,31
	st	dihydrocorynantheine pseudoyohimbine	12

Table 1.10 continued .....

Species	Plant part	Alkaloids	Ref.
19. *U. perrottetii*	l	isomitraphylline mitraphylline & N-O isopteropodine pteropodine speciophylline uncarine F	2
20. *U. lanosa* *var. lanosa*	l	isopteropodine & N-O pteropodine & N-O speciophylline & N-O uncarine F & N-O	2
var. glabrata	l	isopteropodine & N-O pteropodine & N-O speciophylline & N-O uncarine F & N-O	2
var. ferrea *f. ferrea*	l, fl	isomitraphylline & N-O mitraphylline & N-O isopteropodine & N-O pteropodine & N-O speciophylline & N-O uncarine F & N-O harmane	2
var. toppingii *f. toppingii*	l	isomitraphylline & N-O mitraphylline & N-O isopteropodine & N-O speciophylline & N-O	2
	st, fl, l	isomitraphylline mitraphylline isopteropodine speciophylline	
	fl, l	pteropodine uncarine F	
var. korrensis	l	isomitraphylline & N-O mitraphylline & N-O isopteropodine & N-O pteropodine & N-O speciophylline & N-O uncarine F & N-O	2
var. appendiculata *f. appendiculata*	l	isomitraphylline & N-O mitraphylline	
	l, st	isopteropodine & N-O pteropodine & N-O speciophylline & N-O uncarine F & N-O	2

Table 1.10 continued .....

Species	Plant part	Alkaloids	Ref.
var. appendiculata f. grabrescens	l	akuammignine isopteropodine & N-O pteropodine & N-O speciophylline & N-O uncarine F & N-O	2
var. appendiculata f. setiloba	l l. st	isomitraphylline & N-O mitraphylline & N-O isopteropodine & N-O pteropodine & N-O speciophylline & N-O uncarine F & N-O	2
var. appendiculata f. philippinensis	l	isopteropodine & N-O pteropodine & N-O uncarines F & N-O speciophylline & N-O formosanine isoformosanine mitraphylline	2 -32 33
21. *U. roxburghiana*	l, st fr	isopteropodine & N-O pteropodine & N-O speciophylline & N-O uncarine F & N-O speciophylline	2
22. *U. lancifolia*	l	isomitraphylline mitraphylline & N-O	-2
23. *U. sinensis*	l, fr	akuammigine isopteropodine & N-O pteropodine & N-O speciophylline & N-O uncarine F & N-O	2
24. *U. sessilifructus*	l	3-isoajmalicine 19-epi-3-isoajmalicine akuammignine hirsutine isomitraphylline & N-O mitraphylline & N-O formosanine isoformosanine isorhynchophylline rhynchophylline corynoxine corynoxine B	2

Table 1.10 continued .....

Species	Plant part	Alkaloids	Ref.
25. *U. laevigata*	l	isomitraphylline & N-O	2
		mitraphylline & N-O	
		isopteropodine	
		speciophylline	
		formosanine	
		isoformosanine	
26. *U. rhynchophylla*	l, st	angustine	22,2
		angustoline	
		angustidine	
		isorhynchophylline & N-O	2
		rhynchophylline & N-O	
		isocorynoxeine	
		corynoxeine	
	st, rt	geissochizine methyl ether	32
		dihydrocorynanthine	
		hirsuteine	
		corynantheine	
		hirsutine	
		isorhynchophylline	
		rhynchophylline	
		isocorynoxeine	
		corynoxeine	
	bk, rt	akuammignine	34
	l	rhynchophine	
27. *U. hirsuta*	l, fl	isomitraphylline	2
		mitraphylline	
		formosanine	
		isoformosanine	
	l	isomitraphylline N-O	
		mitraphylline N-O	
	fl	3-isoajmalicine	
28. *U. scandes*	l	isomitraphylline & N-O	2
		mitraphylline & N-O	
		isopteropodine & N-O	
		pteropodine & N-O	
		speciophylline & N-O	
		uncarine F	

Table 1.10 continued .....

Species	Plant part	Alkaloids	Ref.
29. *U. homomalla*	l, st	angustine	2,22
		angustoline	
		angustidine	
		isomitraphylline	2
		mitraphylline	
		isopteropodine & N-O	
		pteropodine & N-O	
		speciophylline & N-O	
		uncarine F & N-O	
	l	3-isoajmalicine	
30. *U. guianensis*	l, st, fl	angustine	2, 22
		angustoline	
		rhynchophylline & N-O	2
	l, st	dihydrocorynantheine	
		hirsutine	
		hirsuteine	
		isomitraphylline & N-O	
		mitraphylline & N-O	
		isorhynchophylline & N-O	
31. *U. tomentosa*	l	dihydrocorynanthine & N-O	2,15
		hirsutine & N-O	
		isomitraphylline & N-O	
		isorhynchophylline & N-O	
		rhynchophylline & N-O	
	l, st, flw	mitraphylline	2
		dihydrocorynantheine	
		hirsutine	
		hirsuteine	
		rotundifoline	
		isorotundifoline	
		isomitraphylline	
		mitraphylline	
32. *U. africana ssp. africana*	l	ajmalicine	2
		3-isoajmalicine	
		tetrahydroalstonine	
		19-epi-ajmalicine	
		dihydrocorynantheine -pseudoindoxyl	
		isomitraphylline	
		mitraphylline & N-O	
		isorhynchophylline	
		rhynchophylline	
		dihydrocorynantheine	
		19-epi-3-isoajmalicine	

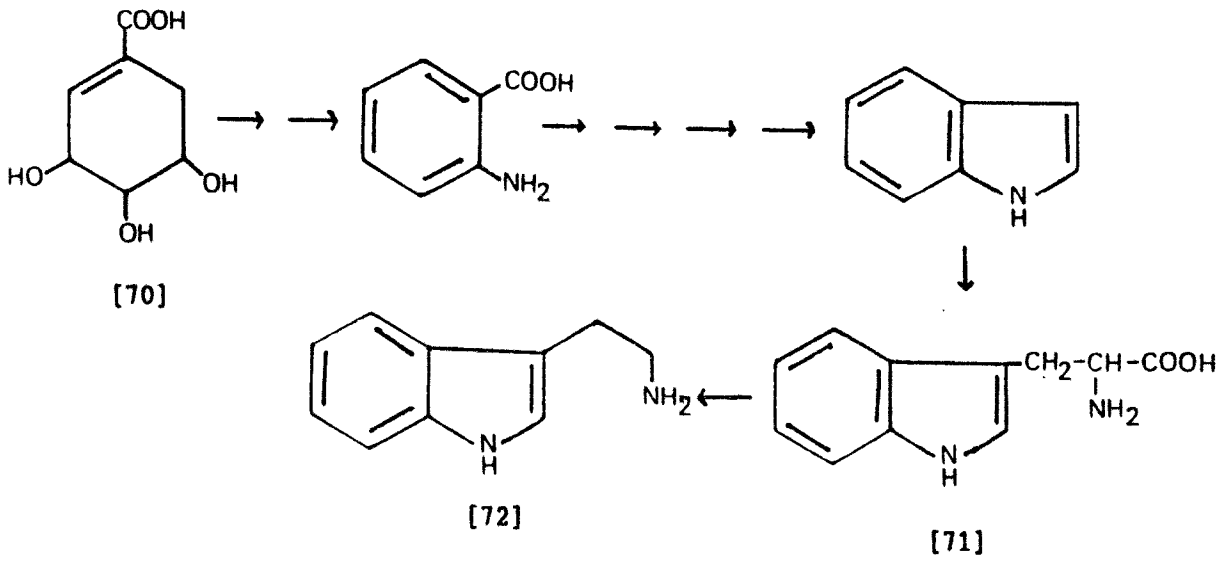
Table 1.10 continued .....

Species	Plant part	Alkaloids	Ref.
ssp. angolensis	l	isorhynchophylline & N-O rhynchophylline & N-O	2
33. *U. donisii*	l	isopteropodine & N-O pteropodine & N-O speciophylline & N-O uncarine F & N-O	2
34. *U. talbotii*	fl, l	isorhynchophylline rhynchophylline	2

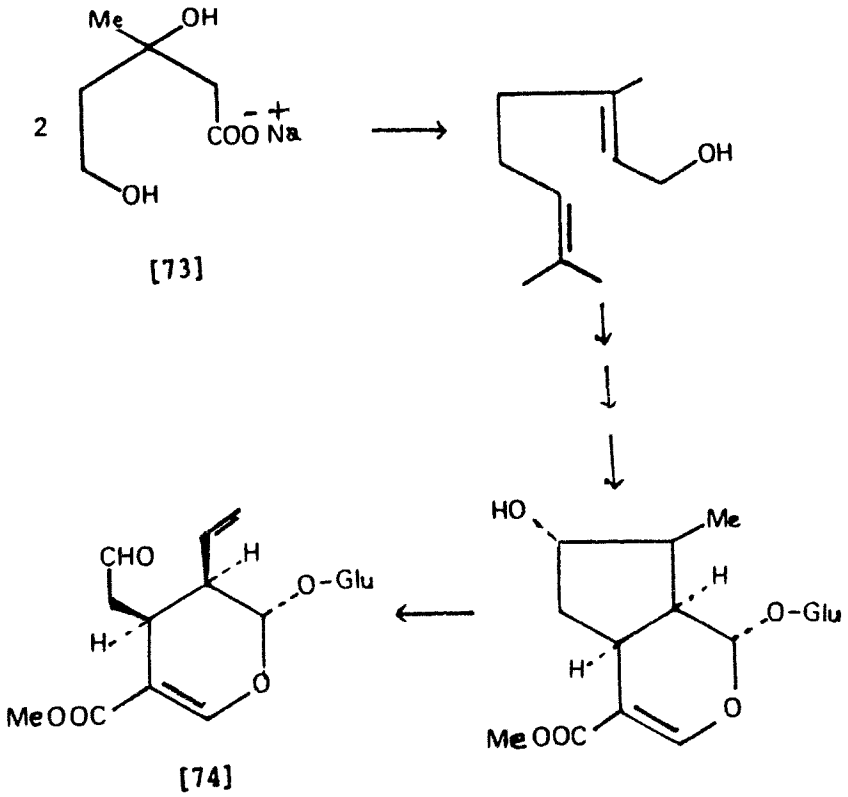
* fl = flowers, l = leaves, twg = twigs, st = stems, rt = roots
  fr = fruits, sb = stem bark, fl = flowers, sw = stem wood
  bk = bark
# N-O = N-oxide, unn. = unidentified alkaloids

1.5 BIOGENESIS OF *UNCARIA* ALKALOIDS

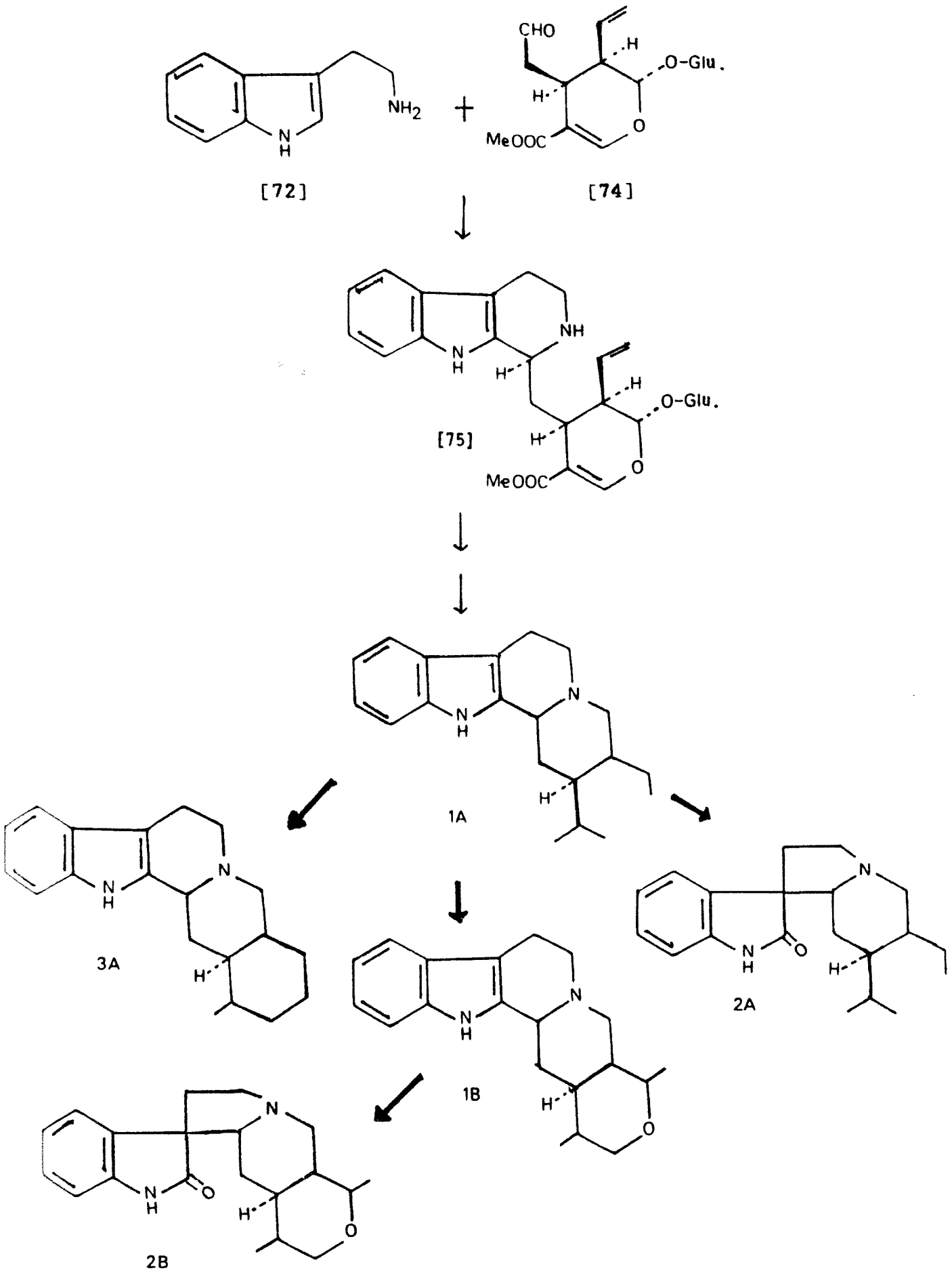
The main alkaloids found in *Uncaria* are mainly those of the corynanthean skeletal type which are biogenetically derived from tryptophan (or tryptamine) and secologanin, constituting the indole and C_9 or C_{10} monoterpene portions respectively.[35a] The origin of tryptophan [71] (tryptamine [72]) and secologanin [74] are well established as being derived fron shikimic acid [70] and sodium mevalonate [73] respectively.[35b] These well established routes are shown in Schemes 1 and 2. Condensation of tryptamine and secologanin provides the key intermediate strictosidine [75] from which the various alkaloids (heteroyohimbines 1A, 1B; oxindoles 2A, 2B; and yohimbines 3A) are elaborated as summarized in Scheme 3.[35c]



Scheme 1 : Biosynthesis of tryptamine [35b]



Scheme 2 : Biosynthesis of secologanin [35b]



Scheme 3 : Biogenesis of *Uncaria* alkaloids

1.6 PHARMACOLOGICAL ACTIVITY OF INDOLE ALKALOIDS

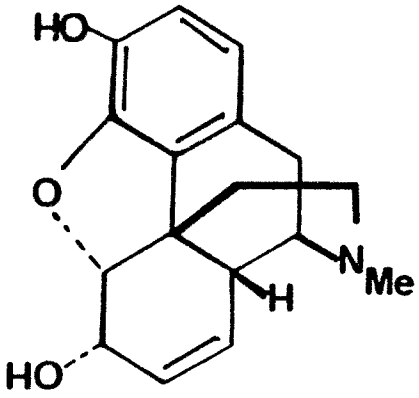
Prior to their recognition as useful therapeutic agents, alkaloids were known for their poisonous properties. It was Sertuner's discovery of morphine [76] from opium (1817)[36] that spearheaded the subsequent rapid research of alkaloids. Many classes of drugs have been discovered of which a plant alkaloid was the initial lead. A good example is the discovery of morphine from *Papaver* species which led to the many narcotic analgesics and quinine [77] from *Cinchona* species which led to a large group of anti-malaria drugs.[3] An important class of biologically active alkaloids are the indole alkaloids, derived biogenetically from tryptophan. These alkaloids include more than 1000 well defined compounds isolated from higher plants from families such as *Apocynaceae, Leguminoseae, Loganiaceae, Rubiaceae* and others.[37] Inspite of the large number of indole alkaloids found to be biologically active, only a few are considered of value as therapeutic agents in human medicine. This is because many of these alkaloids are known to have adverse side effects and a high degree of toxicity. Some representatives of biologically active indole alkaloids including some which are in clinical use are listed in Table 1.11

Table 1.11 : Pharmacological Activity of some Indole Alkaloids

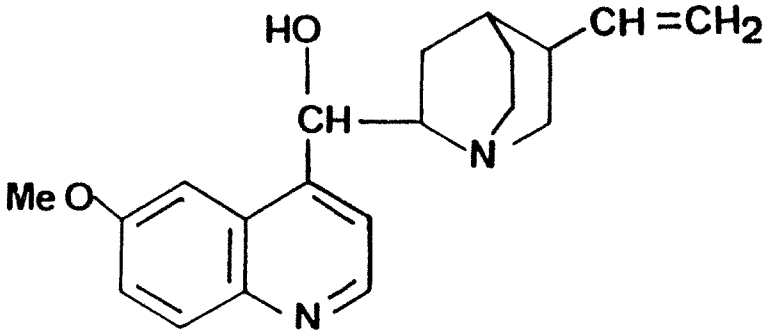
Alkaloids	Source	Pharmacological Activity[ref.]
ajmalicine [13]	*Catharanthus sp.*	hypotensive[37]
ajmaline [78]	*Rauvolfia sp.*	cardiac antiarhythmia[37]
catharanthine [79]	*Catharanthus roseus*	hypoglycemic activity[37]
dihydrocory-nantheine [20]	*U. callophylla* *U. rhynchophylla*	hypotensive activity[31,30,39] mild central depressant[39]
ellipticine [80]	*Ochrosia sp.*	antitumour[37]
gambirine [22]	*U. callophylla*	hypotensive[31,40,41]
hirsuteine [23]	*U. rhychophylla*	mild central depressant[39] hypotensive[39]
hirsutine [24]	*U. rhychophylla*	mild central depressant[39] hypotensive[39] antiarrhythmic[39]
isorhyncophy-lline [38]	*U. rhychophylla* & other *Uncaria* sp.	mild central depressant[39] hypotensive[39,41]
reserpine [81]	*Rauvolfia sp.*	hypotensive[37] tranquilizer[37] bradycadia[37]
rhyncophy-lline [39]	*U. rhychophylla* & other *Uncaria* sp.	mild central depressant[39] hypotensive[39,41]
vincamine [82]	*Tabernaemontana sp.* *Vinca minor* other *Apocynaceae sp.*	vasodilator[37] hypotensive[37]
vinblastine [83]	*Catharanthus roseus*	antineoplastic[37] (leukemia)
vincristine [84]	*Catharanthus roseus*	antineoplastic[37]

Table 1 continued...

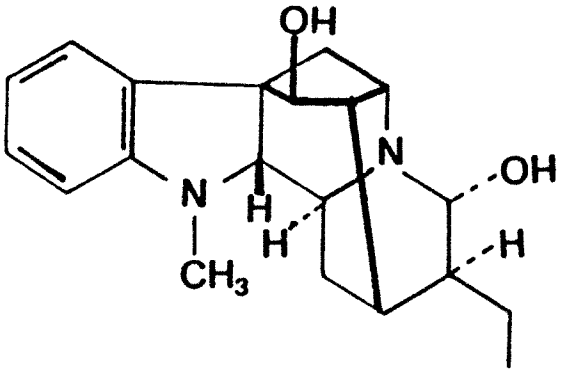
Alkaloids	Source	Pharmacological Activity[ref.]
vindoline [85]	*Catharanthus roseus* & other *Apocynaceae sp.*	hypoglycemic activity[37]
β-yohimbine [49]	*Amsonia elliptica*	mild anti depressive[39] hypotensive[39]
yohimbine [47]	*Corynanthe yohimbe* & *Uncaria* & other *Apocynaceae sp.*	hypertensive[42] vertenary aphrodisiac[37, 43]



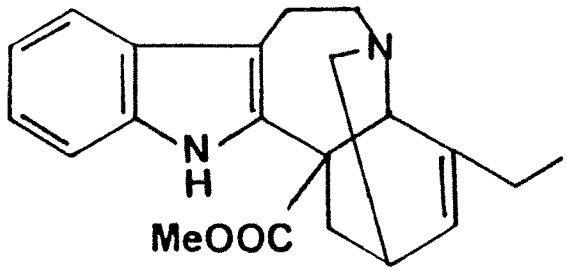
[76] MORPHINE



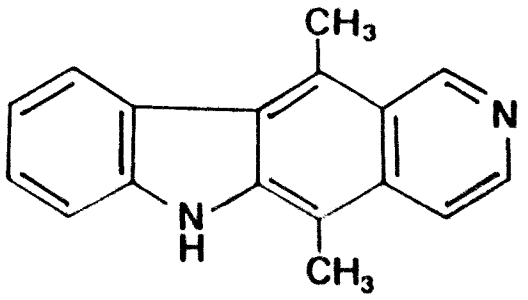
[77] QUININE



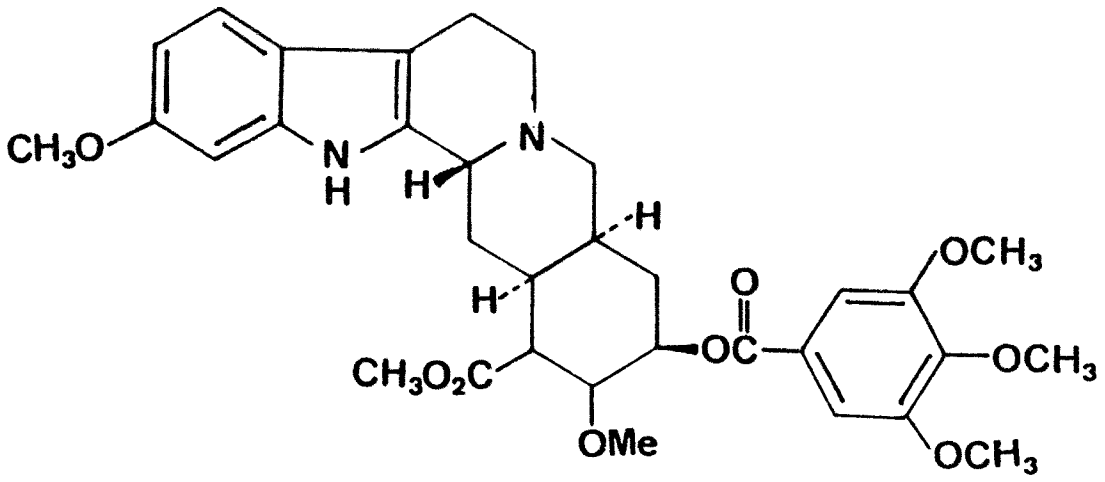
[78] AJMALINE



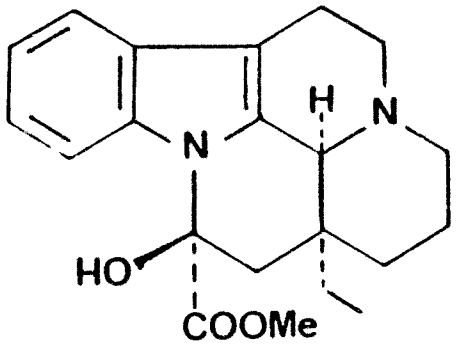
[79] CATHARANTHINE



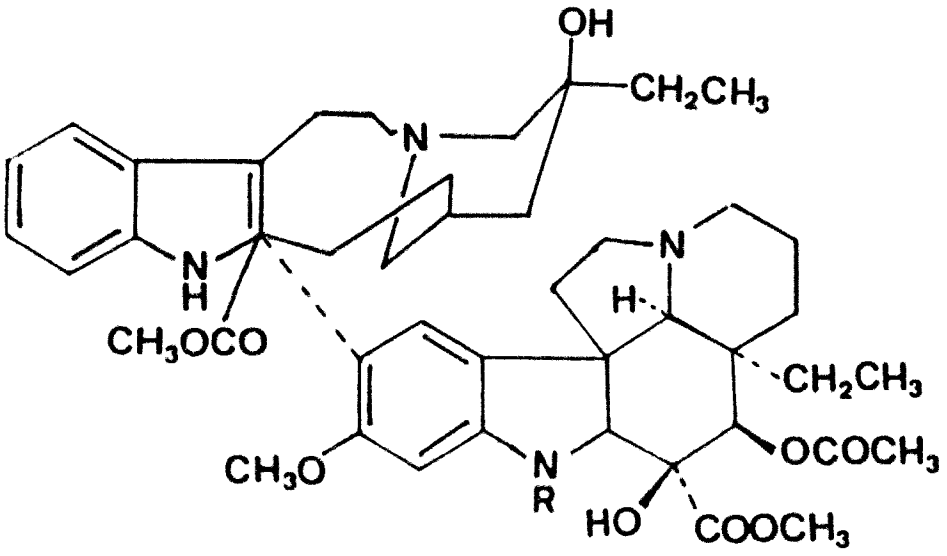
[80] ELLIPTICINE



[81] RESERPINE

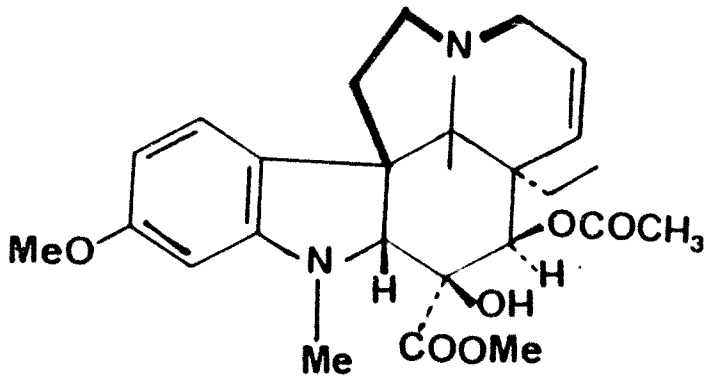


[82] VINCAMINE



[83] VINCRISTINE R = CHO

[84] VINBLASTINE R = CH_3



[85] VINDOLINE