

## CHAPTER II

## HISTORICAL

1. Alkaloids isolated from *Uncaria* species recognized by Ridsdale (10)*Uncaria acida* (Hunt.) Roxb. var. *acida*

Plant Part	Alkaloid	Reference
Leaf	Harmane	10
	Isorhynchophylline	10
	Rhynchophylline and its N-oxide	10

*Uncaria acida* (Hunt.) Roxb. var. *papuana* Val.

Plant Part	Alkaloid	Reference
Leaf	3-Isoajmalicine	10
	Isorhynchophylline and its N-oxide	10
	Rhynchophylline and its N-oxide	10
	Corynoxetine	10
Stem	Isorhynchophylline	10
	Rhynchophylline	10

Uncaria africana G. Don. ssp. africana

Plant Part	Alkaloid	Reference
Leaf, Stem	Africanine	13
Leaf	Ajmalicine	10
	3-Isoajmalicine	10
	Tetrahydroalstonine	10
	19-Epi-ajmalicine	10
	19-Epi-3-isoajmalicine	10
	Dihydrocorynantheine	10
	Dihydrocorynantheine pseudoindoxyl	10
	Isomitraphylline	10
	Mitraphylline and its N-oxide	10
	Isorhynchophylline	10
	Rhynchophylline	10

Uncaria africana G. Don. ssp. angolensis (Havil.) Ridsd.

Plant Part	Alkaloid	Reference
Leaf	Isorhynchophylline and its N-oxide	10
	Rhynchophylline and its N-oxide	10



Uncaria attenuata Korth.

Plant Part	Alkaloid	Reference
Leaf	3-Isoajmalicine	10, 14
	Akuammigine	10, 14
	Dihydrocorynantheine	10, 14
	Dihydrocorynantheine pseudoindoxyl	10, 14
	<u>Epiallo</u> corynantheine	10, 14
	Harmame	10, 14
	Hirsutine	10, 14
	Hirsuteine	10, 14
	Isomitraphylline and its N-oxide	10, 13, 14
	Mitraphylline and its N-oxide	10, 14
	Speciophylline	10, 14
	Uncarine A	10, 14
	Uncarine B	10, 14
	Isorhynchophylline and its N-oxide	10, 14
	Rhynchophylline and its N-oxide	10, 14
	Corynoxine B	13
	Isocorynoxine	10, 14
	Corynoxine	10, 14
Rotundifoline	10, 14	
Isorotundifoline	10, 14	
Speciofoline	10, 14	

Uncaria attenuata Korth. (continued)

Plant Part	Alkaloid	Reference
Stem	Dihydrocorynantheine	10
Stem, Bark, Wood	Isorhynchophylline	10
	Rhynchophylline	10
	Isocorynoxine	10
	Corynoxine	10

Uncaria barbata Merr.

Plant Part	Alkaloid	Reference
Leaf	Harmene	10

Uncaria bernaysii F.v.Muell.

Plant Part	Alkaloid	Reference
Leaf	Tetrahydroalstonine	10
	Akuammigine	10
	Isopteropodine and its N-oxide	10, 15
	Pteropodine and its N-oxide	10, 15
	Speciophylline and its N-oxide	10, 15
	Uncarine F and its N-oxide	10, 15

Uncaria bernaysii F.v.Muell. (continued)

Plant Part	Alkaloid	Reference
Flower	Isorhynchophylline N-oxide	10
	Rhynchophylline N-oxide	10
	Ajmalicine	10
	3-Isoajmalicine	10
	Tetrahydroalstonine	10
	Akuammigine	10
	Angustine	10, 12
	Isomitraphylline	10
	Mitraphylline	10
	Isopteropodine and its N-oxide	10
	Pteropodine and its N-oxide	10
	Speciophylline and its N-oxide	10
Uncarine F and its N-oxide	10	
Leaf and Stem	Tetrahydroalstonine	16
	Akuammigine	16
	Isopteropodine and its N-oxide	16
	Pteropodine and its N-oxide	16
	Speciophylline and its N-oxide	16
	Uncarine F and its N-oxide	16



Uncaria borneensis Havil.

Plant Part	Alkaloid	Reference
Leaf	Harmane	10

Uncaria callophylla Bl. ex Korth.

Plant Part	Alkaloid	Reference
Leaf, Fruit	Dihydrocorynantheine	10
Leaf	Gambirine	10
	Isomitraphylline	10
	Mitraphylline	10
	Isorhynchophylline	10
	Rhynchophylline	10
	Rotundifoline	10
	Isorotundifoline	10
Stem	Isorhynchophylline	10

Uncaria canescens Korth.

Plant Part	Alkaloid	Reference
Leaf	Harmane	10, 14
	Isopteropodine and its N-oxide	14
	Pteropodine and its N-oxide	14
	Speciophylline and its N-oxide	14
	Uncarine F and its N-oxide	14
Stem	Harmane	10

Uncaria cordata (Lour.) Merr. var. cordata Merr. f. cordata

Plant Part	Alkaloid	Reference
Leaf, Stem, Flower	Isorhynchophylline	10
	Rhynchophylline	10
Leaf	Corynoxine	10
	Corynoxine B	10

Uncaria cordata (Lour.) Merr. var. ferruginea (Bl.) Ridsd. f. ferruginea  
Ridsd.

Plant Part	Alkaloid	Reference
Leaf, Stem, Flower	Dihydrocorynantheine	10

Uncaria cordata (Lour.) Merr. var. ferruginea (Bl.) Ridsd. f. insignis  
(Bart. in DC.) Ridsd.

Plant Part	Alkaloid	Reference
Leaf	Isorhynchophylline	10
	Rhynchophylline	10

Uncaria cordata (Lour.) Merr. var. ferruginea (Bl.) Ridsd. f. leantha  
Ridsd.

Plant Part	Alkaloid	Reference
Leaf	Isorhynchophylline	10
	Rhynchophylline	10



Uncaria donisii Petit.

Plant Part	Alkaloid	Reference
Leaf	Isopteropodine and its N-oxide	10
	Pteropodine and its N-oxide	10
	Speciophylline and its N-oxide	10
	Uncarine F and its N-oxide	10

Uncaria elliptica R. Br. ex G. Don.

Plant Part	Alkaloid	Reference
Leaf	3-Isoajmalicine	10
	Akuammigine	10
	Dihydrocorynantheine	10
	Gambirine	10, 43
	Roxburghines C, D and E	10
	Roxburghines	43
	Harmane	005808 10
	Isorhynchophylline	10
	Rhynchophylline	10
	Rotundifoline	10
Isorotundifoline	10	
Stem	Dihydrocorynantheine	10

Uncaria gambir (Hunt.) Roxb.

Plant Part	Alkaloid	Reference
Leaf	Dihydrocorynantheine	19
	Gambirine	19, 20, 43
	Mitraphylline	10
	Uncarine A	10
	Uncarine B	10
	Isorhynchophylline	10, 19
	Rhynchophylline	10, 19
	Rotundifoline	19
Young leaf	Roxburghines A, B, C and E	18
Stem	Tetrahydroalstonine	18, 21
	4 R-tetrahydroalstonine N-oxide	21
	Akuammigine	21
	4 R-akuammigine N-oxide	21
	4 S-akuammigine N-oxide	21
	Dihydrocorynantheine	18, 21
	Roxburghines B and D	21
	Roxburghines D and E	18
	Mitraphylline	22
	Gambirdine	22
Isogambirdine	22	

Uncaria gambir (Hunt.) Roxb. (continued)

Plant Part	Alkaloid	Reference
Catechu (Gambir)	Gambirine	17
	Gambirtannine	17, 27
	Dihydrogambirtannine	17, 27
	Oxogambirtannine	17, 27
Plant material	Ouroparine	23

Uncaria guianensis (Auble.) Gmel.

Plant Part	Alkaloid	Reference
Leaf	Isomitraphylline and its N-oxide	10
	Mitraphylline N-oxide	10
Leaf, Stem	Dihydrocorynantheine	10, 45
	Hirsutine	10, 45
	Hirsuteine	10, 45
	Mitraphylline	10, 45
	Isorhynchophylline and its N-oxide	10, 45
	Rhynchophylline and its N-oxide	10, 45
Flower	Same as in the leaf and stem	10
Stem, Flower	Rotundifoline	10
	Isorotundifoline	10



Uncaria guianensis (Aubl.) Gmel. (continued)

Plant Part	Alkaloid	Reference
Leaf, Stem, Flower	Angustine	10, 12
	Angustoline	10
-	Rhynchophylline	44

Uncaria hirsuta Havil.

Plant Part	Alkaloid	Reference
Leaf, Flower	Isomitraphylline	10
	Mitraphylline	10
	Uncarine A	10
	Uncarine B	10
Leaf	Isomitraphylline N-oxide	10
	Mitraphylline N-oxide	10
Flower	3-Isoajmalicine	10
-	Uncarine B	24

Uncaria homomalla Miq.  
( Uncaria quadrangularis Geddes. )

Plant Part	Alkaloid	Reference
Leaf, Stem	Angustine	10
	Angustoline	10
	Angustidine	10
	Isomitraphylline	10
	Mitraphylline	10
	Isopteropodine and its N-oxide	10
	Pteropodine and its N-oxide	10
	Speciophylline and its N-oxide	10
	Uncarine F and its N-oxide	10
Leaf	3-Isoajmalicine	10
	Angustine	12
	Angustoline	12
	Angustidine	12
	Isomitraphylline	25
	Mitraphylline	25
	Isopteropodine	26
	Pteropodine	26
	Speciophylline	26
	Uncarine F	2
Stem	Isopteropodine	25
	Pteropodine	25

Uncaria kunstleri King.

Plant Part	Alkaloid	Reference
Leaf	Hirsutine	10
	Isorhynchophylline and its N-oxide	10
	Rhynchophylline and its N-oxide	10
	Corynoxine	10
	Corynoxine B	10
Twig	Isorhynchophylline	10
	Rhynchophylline	10

Uncaria laevigata Wall. ex G. Don.

Plant Part	Alkaloid	Reference
Leaf	Isomitraphylline and its N-oxide	10
	Mitraphylline and its N-oxide	10
	Isopteropodine	10
	Speciophylline	10
	Uncarine A	10
	Uncarine B	10



Uncaria lancifolia Hutch.

Plant Part	Alkaloid	Reference
Leaf	Isomitraphylline	10
	Mitraphylline and its N-oxide	10

Uncaria lanosa Wall. var. appendiculata (Benth.) Ridsd. f. appendiculata  
(Benth.) Ridsd.

(Uncaria ferrea (Bl.) DC. var. appendiculata)

Plant Part	Alkaloid	Reference
Leaf	Isomitraphylline and its N-oxide	10
	Mitraphylline	10
Leaf, Stem	Isopteropodine and its N-oxide	10
	Pteropodine and its N-oxide	10
	Speciophylline and its N-oxide	10
	Uncarine F and its N-oxide	10
Whole plant	Isopteropodine(Uncarine E)	15
	Pteropodine(Uncarine C)	15
	Speciophylline(Uncarine D)	15
	Uncarine F	15

Uncaria lanosa Wall. var. appendiculata (Benth.) Ridsd. f. grabrescens  
(Merr. et Perr.) Ridsd.

Plant Part	Alkaloid	Reference
Leaf	Akuammigine	10
	Isopteropodine and its N-oxide	10
	Pteropodine and its N-oxide	10
	Speciophylline and its N-oxide	10
	Uncarine F and its N-oxide	10

Uncaria lanosa Wall. var. appendiculata (Benth.) Ridsd. f. philippinensis  
(Uncaria kawakamii Hayata) (Elm.) Ridsd.

Plant Part	Alkaloid	Reference
-	Mitraphylline	28
Leaf, Stem, Flower	Isopteropodine and its N-oxide	10
	Pteropodine and its N-oxide	10
	Speciophylline and its N-oxide	10
Leaf, Fruit	Uncarine F and its N-oxide	10
-	Uncarine A and B	29, 30
-	Uncarines	28

Uncaria lanosa Wall. var. appendiculata (Benth.) Ridsd. f. philippinensis  
(Uncaria kawakamii Hayata) (continued) (Elm.) Ridsd.

Plant Part	Alkaloid	Reference
Stem, Root	Uncarine A and B	31
	Hanadamine	31
Root, Bark, Stem	Mitraphylline	29
	Uncarine A	29
	Uncarine B	29

Uncaria lanosa Wall. var. appendiculata (Benth.) Ridsd. f. setiloba  
(Uncaria florida Vidal.) (Benth.) Ridsd.

Plant Part	Alkaloid	Reference
Leaf	Isomitraphylline and its N-oxide	10
	Mitraphylline and its N-oxide	10
Leaf, Stem	Isopteropodine and its N-oxide	10
	Pteropodine and its N-oxide	10
	Speciophylline and its N-oxide	10
	Uncarine F and its N-oxide	10
—	Isopteropodine (Uncarine E)	36
	Pteropodine (Uncarine C)	36
	Speciophylline (Uncarine D)	36



Uncaria lanosa Wall. var. ferrea (Bl.) Ridsd. f. ferrea (Bl.) Ridsd.  
 (Uncaria ferrea (Bl.) DC.)

Plant Part	Alkaloid	Reference
Leaf, Flower	Isomitraphylline and its N-oxide	10
	Mitraphylline and its N-oxide	10
Leaf, Stem, Flower, Fruit	Isopteropodine and its N-oxide	10
	Pteropodine and its N-oxide	10
	Speciophylline and its N-oxide	10
	Uncarine F and its N-oxide	10
Leaf, Stem	Harmame	10
Leaf	Gambirine	43
Whole plant	Isopteropodine (Uncarine E)	15
	Pteropodine (Uncarine C)	15
	Speciophylline (Uncarine D)	15
	Uncarine F	15

Uncaria lanosa Wall. var. glabrata (Bl.) Ridsd.

Plant Part	Alkaloid	Reference
Leaf	Isopteropodine and its N-oxide	10
	Pteropodine and its N-oxide	10
	Speciophylline and its N-oxide	10
	Uncarine F and its N-oxide	10
Stem	Speciophylline	10

Uncaria lanosa Wall. var. korrensis (Kanehira.) Ridsd.

Plant Part	Alkaloid	Reference
Leaf	Isomitraphylline and its N-oxide	10
	Mitraphylline and its N-oxide	10
	Isopteropodine and its N-oxide	10
	Pteropodine and its N-oxide	10
	Speciophylline and its N-oxide	10
	Uncarine F and its N-oxide	10

Uncaria lanosa Wall. var. lanosa

Plant Part	Alkaloid	Reference
Leaf	Isopteropodine and its N-oxide	10
	Pteropodine and its N-oxide	10
	Speciophylline and its N-oxide	10
	Uncarine F and its N-oxide	10

Uncaria lanosa Wall. var. toppingii (Merr.) Ridsd. f. toppingii (Merr.) Ridsd.

Plant Part	Alkaloid	Reference
Leaf, Stem, Flower	Isomitraphylline	10
	Mitraphylline	10
	Isopteropodine	10
	Pteropodine	10
	Speciophylline	10
Leaf, Flower	Uncarine F	10
Leaf	Isomitraphylline N-oxide	10
	Mitraphylline N-oxide	10
	Isopteropodine N-oxide	10



Uncaria longiflora (Poir.) Merr. var. longiflora

Plant Part	Alkaloid	Reference
Leaf	Isomitraphylline and its N-oxide	10
	Mitraphylline and its N-oxide	10
	Isopteropodine and its N-oxide	10
	Pteropodine and its N-oxide	10
	Speciophylline and its N-oxide	10
	Uncarine F and its N-oxide	10
	Isorhynchophylline and its N-oxide	10
	Rhynchophylline and its N-oxide	10
	Corynoxine	10
	Corynoxine B	10
	Isocorynoxine	10
Stem	Isorhynchophylline and its N-oxide	10
	Rhynchophylline and its N-oxide	10

Uncaria longiflora (Poir.) Merr. var. pteropoda (Miq.) Ridsd.  
(Uncaria pteropoda Miq.)

Plant Part	Alkaloid	Reference
Leaf	Isomitraphylline and its N-oxide	10, 34
	Mitraphylline and its N-oxide	10, 34
	Isopteropodine and its N-oxide	10, 34
	Pteropodine and its N-oxide	10, 34
	Speciophylline and its N-oxide	10, 34
	Uncarine F	10, 34
	Isorhynchophylline	10
	Rhynchophylline	10
	Isocorynoxine	10
	Corynoxine	10
Root, Bark, Stem	Isopteropodine	32a,b
	Pteropodine	32a,b
Stem	Isopteropodine	33
	Pteropodine	33

Uncaria macrophylla Wall.

Plant Part	Alkaloid	Reference
Leaf	Isorhynchophylline and its N-oxide	10, 35
	Rhynchophylline and its N-oxide	10, 35
	Corynoxine	10, 35
	Corynoxine B	10, 35
Stem	Same as in the leaf	10

Uncaria nervosa Elm.

Plant Part	Alkaloid	Reference
Leaf	Dihydrocorynantheine	10
	Hirsutine	10
	Hirsuteine	10
	Harmame	10



Uncaria orientalis Guill.

Plant Part	Alkaloid	Reference
Leaf	Ajmalicine	10
	3-Isoajmalicine	14
	Akuammigine	10
	3-Iso-19-epiajmalicine	10
	Harmane	10, 14
	Isomitraphylline and its N-oxide	10, 14
	Mitraphylline and its N-oxide	10, 14
	Isopteropodine and its N-oxide	10, 14
	Pteropodine and its N-oxide	10, 14
	Speciophylline and its N-oxide	10, 14
	Uncarine F and its N-oxide	10, 14
	Uncarine A	10
	Uncarine B	10
Stem bark, Stem wood	Isopteropodine and its N-oxide	10
	Pteropodine and its N-oxide	10
	Speciophylline and its N-oxide	10
	Uncarine F and its N-oxide	10
Leaf	Harmane	10

Uncaria perrottetii (A. Rich.) Merr.

Plant Part	Alkaloid	Reference
Leaf	Isomitraphylline and its N-oxide	10
	Mitraphylline and its N-oxide	10
	Isopteropodine	10
	Pteropodine	10
	Speciophylline	10
	Uncarine F	10

Uncaria rhynchophylla (Miq.) Miq. ex Havil.

Plant Part	Alkaloid	Reference
Leaf	Angustine	10, 12
	Angustoline	10, 12
	Angustidine	10, 12
	Isorhynchophylline and its N-oxide	10, 40
	Rhynchophylline and its N-oxide	10
	Isocorynoxine	10
	Corynoxine	10
Hook	Rhynchophylline	39
Stem	Angustine	10
	Angustoline	10

Uncaria rhynchophylla (Miq.) Miq. ex Havil. (continued)

Plant Part	Alkaloid	Reference
Stem	Angustidine	10
	Isorhynchophylline N-oxide	10
Stem, Root	Dihydrocorynantheine	36,37,38
	Hirsutine	36,37,38
	Corynantheine	36,37,38
	Hirsuteine	36,37,38
	Isorhynchophylline	36,37,38
	Rhynchophylline	36,37,38
	Isocorynoxine	36,37,38
	Corynoxine	36,37,38
Bark, Root	Akuammigine	41, 42
	Geissoschizine methyl ether	41, 42



Uncaria roxburghiana Korth.

Plant Part	Alkaloid	Reference
Leaf, Stem, Fruit	Speciophylline	10
Leaf, Stem	Isopteropodine and its N-oxide	10
	Pteropodine	10
	Speciophylline N-oxide	10
	Uncarine F	10
Leaf	Pteropodine N-oxide	10
	Uncarine F N-oxide	10

Uncaria scandens (Smith.) Hutch.

Plant Part	Alkaloid	reference
Leaf	Isonitraphylline and its N-oxide	10
	Mitraphylline and its N-oxide	10
	Isopteropodine and its N-oxide	10
	Pteropodine and its N-oxide	10
	Speciophylline and its N-oxide	10
	Uncarine F	10

Uncaria schlenkeriae S. Moore

Plant Part	Alkaloid	Reference
Leaf	Harmaline	10

Uncaria sessilifructus Roxb.

Plant Part	Alkaloid	Reference
Leaf	3-Isoajmalicine	10
	19-Epi-3-isoajmalicine	10
	Akuanmagine	10
	Hirsutine	10
	Isomitraphylline and its N-oxide	10
	Mitraphylline and its N-oxide	10
	Uncarine A	10
	Uncarine B	10
	Isorhynchophylline	10
	Rhynchophylline	10
	Corynoxine	10
Corynoxine B	10	

Uncaria sinensis Havil.

Plant Part	Alkaloid	Reference
Leaf, Fruit	Akuanmagine	10
	Isopteropodine and its N-oxide	10
	Pteropodine and its N-oxide	10
	Speciophylline and its N-oxide	10
	Uncarine F and its N-oxide	10

Uncaria Sterrophylla Merr. et Perr.

Plant Part	Alkaloid	Reference
Leaf	3-Isoajmalicine	10
	Isopteropodine	10
	Pteropodine	10
	Speciophylline and its N-oxide	10
	Uncarine F	10
	Isorhynchophylline	10
	Rhynchophylline	10
Stem	Isopteropodine	10
	Pteropodine	10
	Speciophylline	10
Stem, Bark, Root	Isorhynchophylline	10
	Rhynchophylline	10

Uncaria talbotii Wernh.

Plant Part	Alkaloid	Reference
Leaf, Flower	Isorhynchophylline	10
	Rhynchophylline	10

Uncaria tomentosa (Willd.) DC.

Plant Part	Alkaloid	Reference
Leaf, Stem	Dihydrocorynantheine and its N-oxide	45
	Hirsutine and its N-oxide	45
	Hirsuteine	45
	Isomitraphylline and its N-oxide	45
	Mitraphylline	45
	Isorhynchophylline and its N-oxide	45
	Rhynchophylline and its N-oxide	45
	Rotundifoline	45
	Isorotundifoline	45
Leaf, Stem Flower	Isorhynchophylline	10
	Rhynchophylline	10
	Rotundifoline	10
	Isorotundifoline	10
Stem, Flower	Dihydrocorynantheine	10
	Hirsutine	10



Uncaria tomentosa (Willd.) DC. (continued)

Plant Part	Alkaloid	Reference
Stem, Flower	Hirsuteine	10
	Isomitraphylline	10
	Mitraphylline	10
	Isorhynchophylline and its N-oxide	10
	Rhynchophylline and its N-oxide	10

Uncaria velutina Havil.

Plant Part	Alkaloid	Reference
Leaf	Isomitraphylline	10
	Mitraphylline	10
	Isopteropodine and its N-oxide	10
	Pteropodine and its N-oxide	10
	Speciophylline and its N-oxide	10
	Uncarine F and its N-oxide	10



2. Uncaria indole and oxindole alkaloids isolated from other botanical sources.

2.1. Indole alkaloids

2.1.1 Pentacyclic heteroyohimbines

Alkaloid	Botanical source	Reference
Ajmalicine	<u>Catharanthus lanceus</u> Bojer (ex A.D.C.) Pichon	46
	<u>C. pusillus</u> (Murray) G. Don.	46
	<u>C. roseus</u> (L.) G. Don.	46
	<u>C. trichophyllus</u> (Baker) Pichon	46
	<u>Mitragyna javanica</u> Koord. et Valetton	47
	var. <u>microphylla</u> Koord. et Valetton	
	<u>M. parvifolia</u> (Roxb.) Korth.	66
	<u>M. speciosa</u> Korth.	73
	<u>Rauvolfia canescens</u> Linne.	50
	<u>R. heterophylla</u> Roem. et Schult.	51, 52
	<u>R. micrantha</u> Hook. f.	51
	<u>R. sellowii</u> Muell-Arg.	51, 53
	<u>R. serpentina</u> (L.) Benth. ex Kurz.	51
	<u>R. tetraphylla</u> Linne.	54
<u>R. verticillata</u> H.R. Arthur	55	
<u>R. vomitoria</u> Afz.	56	
<u>R. yunnanensis</u> Tsaing	57	

Alkaloid	Botanical source	Reference
3-Isoajmalicine	<u>Mitragyna parvifolia</u> (Roxb.) Korth.	58, 61
	<u>M. rotundifolia</u> (Roxb.) O. Kuntze	86
	<u>M. speciosa</u> Korth.	78
Tetrahydroalstonine	<u>Alstonia constricta</u> F. v. Muell.	71
	<u>Catharanthus lanceus</u> Bojer (ex A.D.C.) Pichon	46
	<u>C. roseus</u> (L.) G. Don.	46
	<u>C. trichophyllus</u> (Baker) Pichon	46
	<u>Mitragyna parvifolia</u> (Roxb.) Korth.	62, 63
	<u>Rauvolfia ligustrina</u> Roem. et Schult- Muell.	73
	<u>R. sellowii</u> Muell-Arg.	51
Akuammigine	<u>Mitragyna parvifolia</u> (Roxb.) Korth.	58, 59, 60.
	<u>M. speciosa</u> Korth.	78
	<u>Picalina nitida</u> Stapf. Th. et H. Durand	79, 80
4,R-akuammigine N-oxide	<u>Mitragyna parvifolia</u> (Roxb.) Korth.	69

### 2.1.2 Tetracyclic heteroyohimbines

Alkaloid	Botanical source	Reference
Dihydrocorhynantheine	<u>Corynanthe yohimbe</u> K. Schum.	81
	<u>Mitragyna parvifolia</u> (Roxb.) Korth.	60-68
	<u>Pseudocinchona africana</u> Aug. Chev.	49

Alkaloid	Botanical source	Reference
Hirsutine	<u>Mitragyna hirsuta</u> Havil.	83, 84
	<u>M. parvifolia</u> (Roxb.) Korth.	60-65
	<u>M. stipulosa</u> (DC.) O. Kuntze	88b
Gambirine	<u>Neonuclea schlechteri</u> (Val.) Merr. et Perr.	48
Corynantheine	<u>Corynanthe yohinbe</u> K. Schum.	81
	<u>Mitragyna parvifolia</u> (Roxb.) Korth.	85
	<u>Pseudocinchona africana</u> Aug. Chev.	49
Hirsuteine	<u>Mitragyna hirsuta</u> Havil.	83, 84
	<u>M. parvifolia</u> (Roxb.) Korth.	64, 65

### 2.1.3 Other indole alkaloids

Alkaloid	Botanical source	Reference
Angustine	<u>Mitragyna javanica</u> Koord. et Valetton	47
	var. <u>microphylla</u> Koord. et Valetton	
	<u>M. parvifolia</u> (Roxb.) Korth.	60
	<u>Nauclea coadunata</u> Roxb. ex J.E. Smith	12
	<u>Strychnos angolensis</u> Gilg.	12
	<u>S. angustiflora</u> Benth.	12, 96, 97
	<u>S. borneensis</u> Leenh.	97
	<u>S. camptoneura</u> Gilg.	12, 96
<u>S. floribunda</u> Gilg.	12	



Alkaloid	Botanical source	Reference
	<u>Strychnos ledermanii</u> Gilg. et Bened	97
	<u>S. minor</u> Dennst.	97
	<u>S. odorata</u> A. Vhev.	12
	<u>S. ovata</u> A.W. Hill.	97
	<u>S. pototarum</u> L.f.	12
	<u>S. rubicola</u> Pierre. ex Dop.	97
	<u>S. scheffleri</u> Gilg.	12
	<u>S. soubrensis</u> Gilg.	12, 97
	<u>S. trichoneura</u> Leeuwenberg	12
	<u>S. umbellata</u> Cobbr. (q.v.)	97
	<u>S. usanarensis</u> Gilg.	12
	<u>S. wallichiana</u> Steud. ex DC.	97
	<u>S. xantha</u> Leeuwenberg	12
Angustoline	<u>Strychnos angustiflora</u> Benth.	97
	<u>S. borneensis</u> Leenh.	97
	<u>S. minor</u> Dennst.	97
	<u>S. odorata</u> A. Chev.	12
	<u>S. ovata</u> A.W. Hill.	97
	<u>S. rubicola</u> Pierre. ex Dop.	97
	<u>S. samba</u> Duvign.	12
	<u>S. scheffleri</u> Gilg.	12
	<u>S. trichoneura</u> Leeuwenberg	12
	<u>S. wallichiana</u> Steud. ex DC.	97

Alkaloid	Botanical source	Reference
Angustidine	<u>Strychnos xantha</u> Leeuwenberg	12
	<u>Strychnos angolensis</u> Gilg.	12
	<u>S. angustiflora</u> Benth.	97
	<u>S. borneensis</u> Leenh.	97
	<u>S. minor</u> Dennst.	97
	<u>S. odorata</u> A. Chev.	12
	<u>S. rubicola</u> Pierre ex Dop.	97
	<u>S. scheffleri</u> Gilg.	12
	<u>S. trichoneura</u> Leeuwenberg	12
	<u>S. wallichiana</u> Steud. ex DC.	97
<u>S. xantha</u> Leeuwenberg	12	

2.2 Oxindole alkaloids2.2.1 Pentacyclic oxindoles

Alkaloid	Botanical source	Reference
Isomitraphylline	<u>Mitragyna hirsuta</u> Havil.	83,84
	<u>M. javanica</u> Koord. et Valetton var. <u>macrophylla</u> Koord. et Valetton	47
	<u>M. parvifolia</u> (Roxb.) Korth.	58-68
	<u>M. speciosa</u> Korth.	73,74,75
	<u>M. tubulosa</u> Havil.	70
Mitraphylline	<u>Catharanthus roseus</u> (L.) G. Don.	46
	<u>Mitragyna hirsuta</u> Havil,	83-84
	<u>M. javanica</u> Koord. et Valetton var. <u>macrophylla</u> Koord. et valetton	47
	<u>M. parvifolia</u> (Roxb.) Korth.	58-68
	<u>M. rotundifolia</u> (Roxb.) O. Kuntze	86
	<u>M. rubrostipulacea</u> (Roxb.) O. Kuntze	82,87
	<u>M. speciosa</u> Korth.	73-78
	<u>M. stipulosa</u> (DC.) O. Kuntze	88a
<u>M. tubulosa</u> Havil.	70	
Isopteropodine	<u>Mitragyna parvifolia</u> (Roxb.) Korth.	58-68
Pteropodine	<u>Mitragyna parvifolia</u> (Roxb.) Korth.	58-68
Speciophylline	<u>Mitragyna inermis</u> (Willd.) O. Kuntze	89
	<u>M. parvifolia</u> (Roxb.) Korth.	58-68

Alkaloid	Botanical source	Reference
Speciophylline	<u>Mitragyna speciosa</u> Korth.	77,78
Speciophylline N-oxide	<u>Mitragyna parvifolia</u> (Roxb.) Korth.	69
Uncarine F	<u>Mitragyna inermis</u> (Willd.) O. Kuntze	89
	<u>M. parvifolia</u> (Roxb.) Korth.	58-68
Uncarine F N-oxide	<u>Mitragyna parvifolia</u> (Roxb.) Korth.	69

### 2.2.2 Tetracyclic oxindoles

Alkaloid	Botanical source	Reference
Isorhynchophyl line	<u>Adina rubrostipulata</u> K. Schuman.	119
	<u>Mitragyna cilliata</u> Aubrev. et Pellgr.	90,91,92
	<u>M. hirsuta</u> Havil.	83,84
	<u>M. inermis</u> (Willd.) O. Kuntze	89,92
	<u>M. parvifolia</u> (Roxb.) Korth.	58-68,94
	<u>M. rotundifolia</u> (Roxb.) O. Kuntze	85,86
	<u>M. rubrostipulacea</u> (Roxb.) O. Kuntze	82
	<u>M. stipulosa</u> Korth.	88a,92
	<u>M. speciosa</u> Korth.	77,78
	<u>M. tubulosa</u> Havil.	70



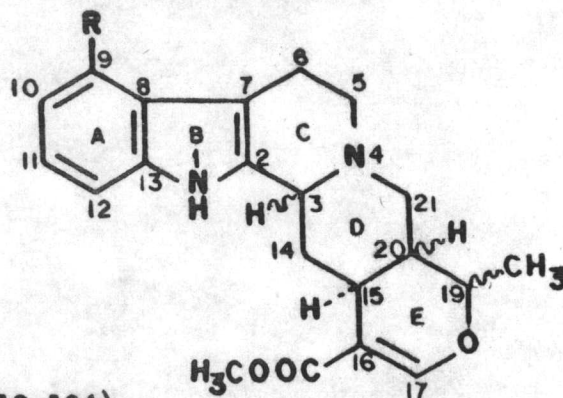
Alkaloid	Botanical source	Reference
Isorhynchophylline N-oxide	<u>Mitragyna inermis</u> (Willd.) O. Kuntze	93
	<u>M. rotundifolia</u> (Roxb.) O. Kuntze	86,93
Rhynchophylline	<u>Mitragyna ciliata</u> Aubrev. et Pellgr.	90,92
	<u>M. hirsuta</u> Havill.	83,84
	<u>M. inermis</u> (Willd.) O. Kuntze	89,92
	<u>M. parvifolia</u> (Roxb.) Korth.	58-68,94
	<u>M. rotundifolia</u> (Roxb.) O. Kuntze	85,86,91
	<u>M. rubrostipulacea</u> (Roxb.) O. Kuntze	82
	<u>M. speciosa</u> Korth.	74,76,77,78
	<u>M. stipulosa</u> (DC.) O. Kuntze	88a
	<u>M. tubulosa</u> Havil.	70
Rhynchophylline N-oxide	<u>Cephalanthus occidentalis</u> L.	95
	<u>Mitragyna inermis</u> (Willd.) O. Kuntze	93
	<u>M. rotundifolia</u> (Roxb.) O. Kuntze	86,93
Corynoxine	<u>Mitragyna speciosa</u> Korth.	76,77,78
	<u>Pseudocinchona africana</u> Aug. Chev.	49
Corynoxine B	<u>Mitragyna speciosa</u> Korth.	76,77,78
Corynoxine	<u>Mitragyna hirsuta</u> Havil.	83,84
	<u>M. parvifolia</u> (Roxb.) Korth.	65-68

Alkaloid	Botanical source	Reference
Corynoxetine	<u>Mitragyna rotundifolia</u> (Roxb.) O. Kuntze	86
	<u>M. speciosa</u> Korth.	76,78
	<u>M. stipulosa</u> (DC.) O. Kuntze	88a
	<u>Pseudocinchona africana</u> Aug. Chev.	49
Isocorynoxetine	<u>Mitragyna rotundifolia</u> (Roxb.) O. Kuntze	86
Rotundifoline	<u>Mitragyna ciliata</u> Aubrev. et Pellgr.	90,92
	<u>M. inermis</u> (Willd.) O. Kuntze	89,92
	<u>M. parvifolia</u> (Roxb.) Korth.	94
	<u>M. rotundifolia</u> (Roxb.) O. Kuntze	91,86
	<u>M. rubrostipulacea</u> (Roxb.) O. Kuntze	87
	<u>M. speciosa</u> Korth.	75
	<u>M. stipulosa</u> (DC.) O. Kuntze	88a,92
	<u>M. tubulosa</u> Havil.	70
Isorotundifoline	<u>Mitragyna ciliata</u> Aubrev. et Pellgr.	90,92
	<u>M. inermis</u> (Willd.) O. Kuntze	89
	<u>M. parvifolia</u> (Roxb.) Korth.	94
	<u>M. rotundifolia</u> (Roxb.) O. Kuntze	86
	<u>M. speciosa</u> Korth.	75
	<u>M. stipulosa</u> (DC.) O. Kuntze	88a
<u>M. tubulosa</u> Havil.	70	

### 3. Basic structures of indole alkaloids from species of

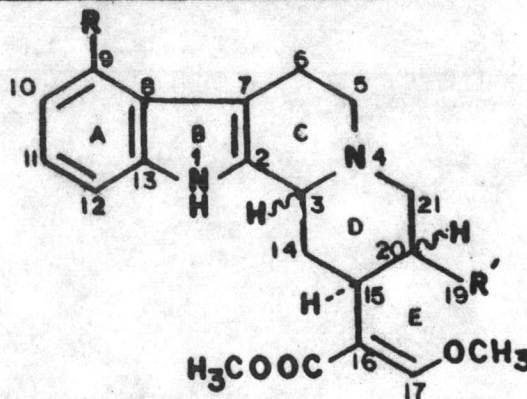
#### Uncaria

##### 3.1 Pentacyclic heteroyohimbines (Closed E ring)



R = H, OH (10,104)

##### 3.2 Tetracyclic heteroyohimbines (Open E ring or E-seco)



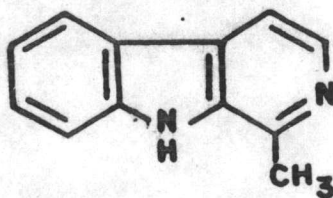
R = H, OH

(10,104)

R' = ethyl, vinyl

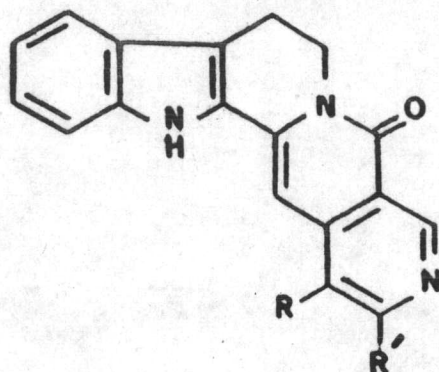
##### 3.3 Other indole alkaloids

###### 3.3.1 $\alpha$ -carboline

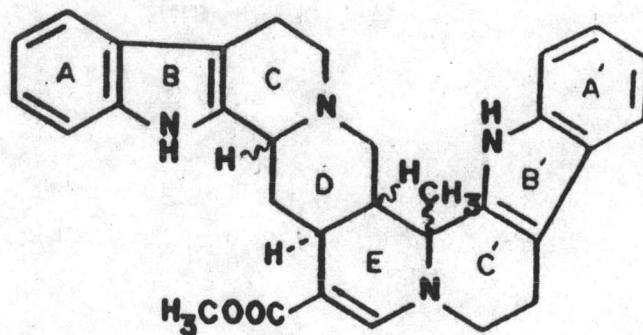


Harmone (10)



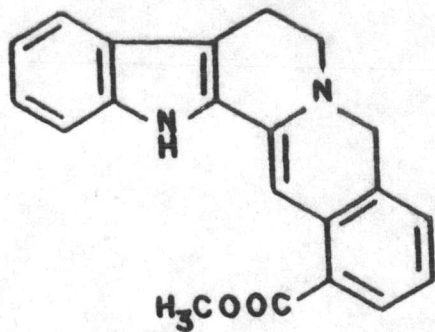
3.3.2 Pyridino-indolo-quinolizidinones

- Angustine,  $R = -CH = CH_2$  ;  $R' = H$  (12,96)  
 Angustoline,  $R = -CH(OH)CH_3$  ;  $R' = H$  (12,96)  
 Angustidine,  $R = H$  ;  $R' = -CH_3$  (12,96)

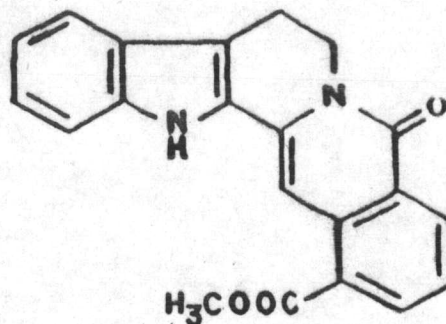
3.3.3 Roxburghines

- Roxburghine A, B, C, D and E (18,100,104)

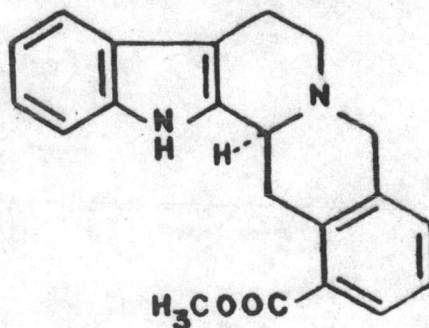
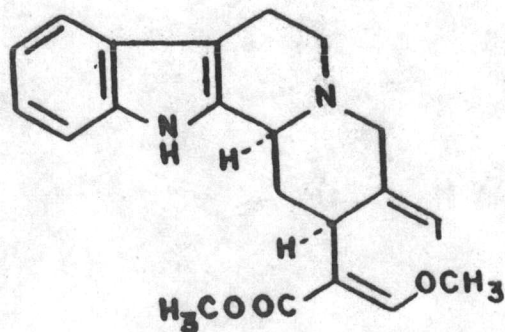


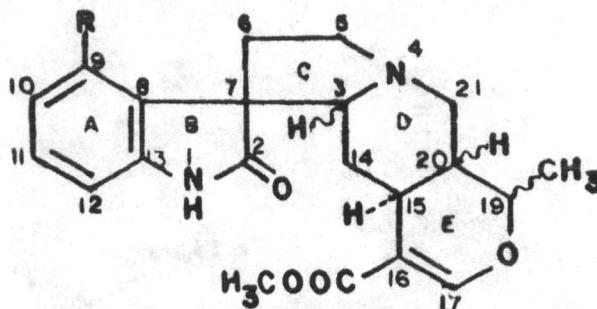
3.3.4 Gambirtannines

Gambirtannine (10)



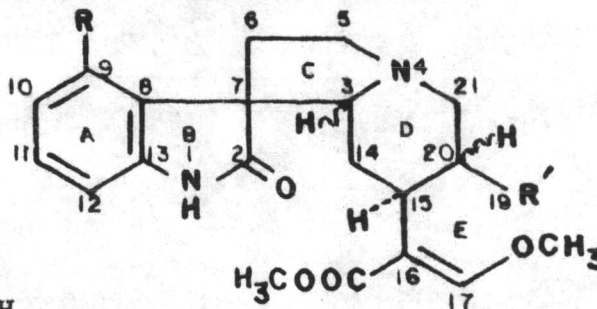
Oxogambirtannine (10)

3.3.5 Dihydrogambirtannine (10)3.3.6 Geissoschizine methyl ether (41,42)

4. Basic structures of oxindole alkaloids from species ofUncaria4.1 Pentacyclic oxindoles (Closed E ring)

(10,104)

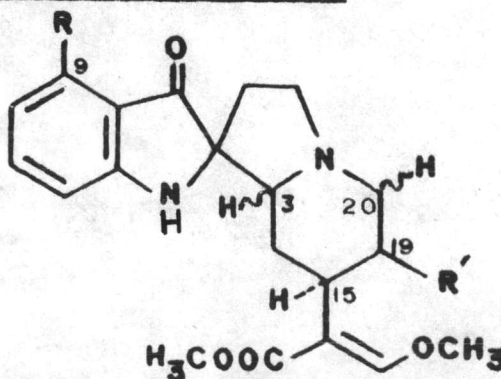
R = H

4.2 Tetracyclic oxindoles (Open E ring or E-seco)

R = H, OH

(10,104)

R' = ethyl, vinyl

4.3 Other oxindole alkaloids (10)Tetracyclic pseudoindoxyl

### 5. Configurations of indole alkaloids

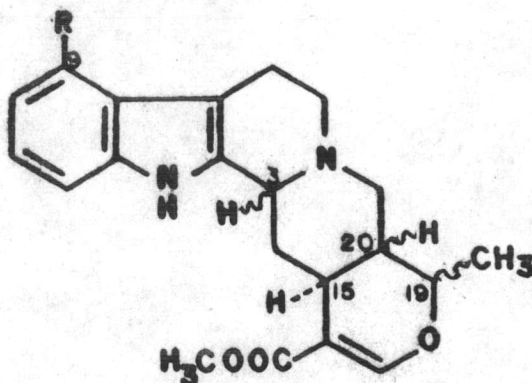
Both types of alkaloids, pentacyclic and tetracyclic heteroyohimbines, have asymmetric centres at C(3), C(15), and C(20). These alkaloids isolated so far possess a C(15)-H<sub>α</sub> configuration and have asymmetric centres at C(3) and C(20), thus there are four possible configurations as follows. (104,105,106)

Configuration	C(3)-H	C(20)-H
<u>Normal</u>	α	β
<u>Pseudo</u>	β	β
<u>Allo</u>	α	α
<u>Epiallo</u>	β	α

The pentacyclic heteroyohimbines possess another asymmetric centre at C(19), i.e. CH<sub>3</sub><sup>α</sup> or β, so that eight isomers are possible. (102,105)

The tetracyclic heteroyohimbines may show geometric isomerisation because of the double bond between C(16) and C(17). All known alkaloids possess a C(17)-H cis to the C(16) ester group. (102)

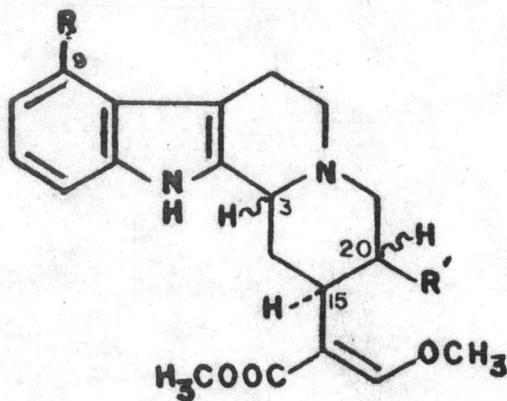
5.1 Configurations of pentacyclic heteroyohimbine alkaloids  
from species of Uncaria



R	Configuration	Alkaloid	C(19)-CH <sub>3</sub>	Reference
H	<u>Normal</u>	Ajmalicine	$\alpha$	100,101, 102,114
	<u>Pseudo</u>	3-Isoajmalicine	$\alpha$	100,101, 102,111
	<u>Allo</u>	Tetrahydroalstonine	$\alpha$	100,101, 102,116
	<u>Epiallo</u>	Akuanmagine	$\alpha$	100,101, 102,116
	<u>Normal</u>	19-Epi-ajmalicine	$\beta$	100,101, 102,114
	<u>Pseudo</u>	19-Epi-3-isoajmalicine	$\beta$	100,101, 102,111
	<u>Allo</u>	Rauniticine	$\beta$	100,101, 102
OH	Has not yet been found	-		
OCH <sub>3</sub>	Has not yet been found	-		



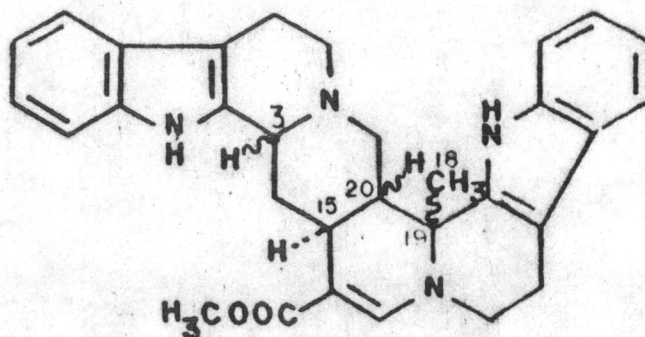
5.2 Configurations of tetracyclic heteroyohimbine alkaloids  
from species of Uncaria



R	C(20)-R'	Configuration	Alkaloid	Reference
H	CH <sub>2</sub> -CH <sub>3</sub>	<u>Normal</u>	Dihydrocorynantheine	100,101, 102
		<u>Pseudo</u>	Hirsutine	100,101, 102
	CH=CH <sub>2</sub>	<u>Normal</u>	Corynantheine	100,101, 102
		<u>Pseudo</u>	Hirsuteine	100,101, 102
		<u>Epiallo</u>	<u>Epiallo</u> corynantheine	100,101, 102
OH OCH <sub>3</sub>	CH <sub>2</sub> -CH <sub>3</sub>	<u>Normal</u>	Gambirine	20,100
		Has not yet been found	-	

5.3 Configurations of other indole alkaloids from species of Uncaria

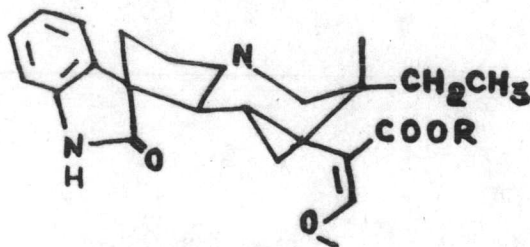
Roxburghines



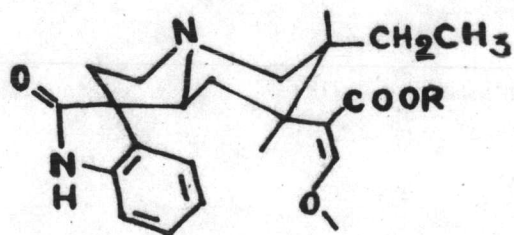
Configuration	Alkaloid	C(18)	Reference
<u>Normal</u>	Roxburghine C	$\alpha$	10,107,108
<u>Pseudo</u>	Roxburghine D	$\alpha$	10,107,108
<u>Pseudo</u>	Roxburghine E	$\beta$	10,107,108
<u>Epialle</u>	Roxburghine B	$\beta$	10,107,108

## 6. Configurations of oxindole alkaloids

Oxindole alkaloids possess the same four configurations as heteroyohimbine alkaloids, i.e. normal, pseudo, allo and epiallo. In addition the oxindole alkaloids have asymmetric centre at C(7), thus eight configurations may exist as either A or B series alkaloids. The isomerisation takes place about the spiro carbon, C(7). A and B oxindole alkaloids are classified in accordance with 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 belong to the A series and those in which the lactam carbonyl lies above the plane of the C ring belong to the B series. (106,109)



A series

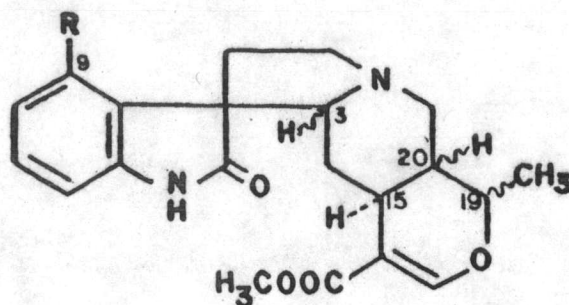


B series

Inversion of N(4) is theoretically possible for both of the A and B series so that the lone pair of electrons may be either on the same side of the C(7) as the lactam carbonyl group or on the opposite side and they are known as syn and anti alkaloids respectively. (110)



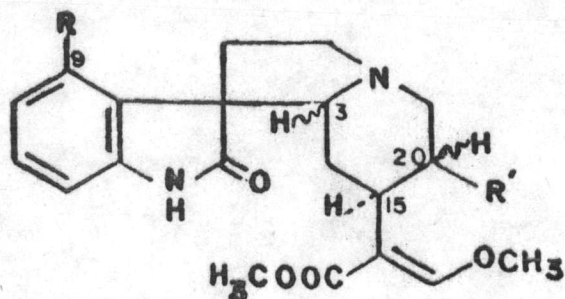
6.1 Configurations of pentacyclic oxindole alkaloids from species of Uncaria



R	Configuration	C(7)	Alkaloid	C(19)-CH <sub>3</sub>	Reference
H	<u>Normal</u>	A	Isomitraphylline	α	100,104,110
		B	Mitraphylline	α	100,104,110
	<u>Allo</u>	A	Isopteropodine	α	100,104,110
		B	Pteropodine	α	100,104,110
	<u>Epiallo</u>	A	Speciophylline	α	100,104,110
		B	Uncarine F	α	100,104
	<u>Normal</u>	A	Uncarine A (Isoformosanine)	β	100,104,110
		B	Uncarine B (Formosanine)	β	100,104,110
OH	Has not yet been found	-	-	-	-
OCH <sub>3</sub>	Has not yet been found	-	-	-	-



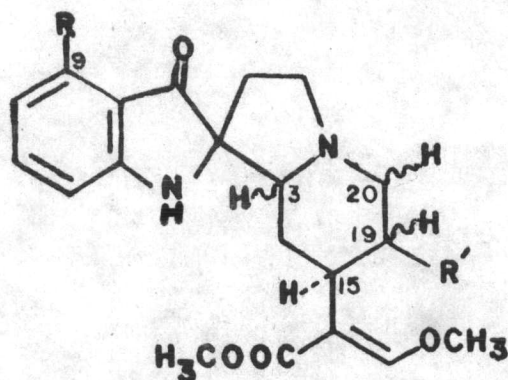
6.2 Configurations of tetracyclic oxindole alkaloids from species of Uncaria



R	C(20)-R'	Configuration	C(7)	Alkaloid	Reference
H	CH <sub>2</sub> -CH <sub>3</sub>	<u>Normal</u>	A	Isorhynchophylline	100,104
			B	Rhynchophylline	100,104
		<u>Allo</u>	A	Corynoxine	100,104
			B	Corynoxine B	100,104
OH	CH-CH <sub>2</sub>	<u>Normal</u>	A	Isocorynoxine	100,104
			B	Corynoxine	100,104
		<u>Normal</u>	A	Rotundifoline	100,104
			B	Isorotundifoline	100,104
OCH <sub>3</sub>	Has not yet been found	<u>Epiallo</u>	A	-	
			B	Speciofoline	100,104

6.3 Configurations of other oxindole alkaloids from species  
of Uncaria

Tetracyclic pseudoindoxyl

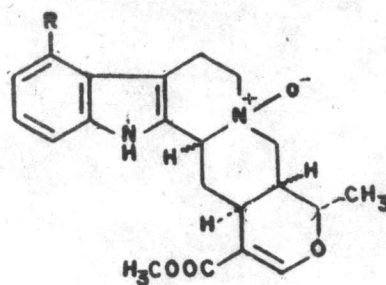


Dihydrocorynantheine pseudoindoxyl <sup>(10,14)</sup>

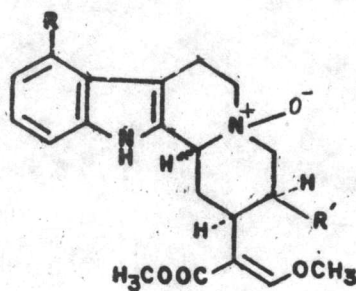
R = H, R' = -CH<sub>2</sub>-CH<sub>3</sub>, C(3) = H<sub>α</sub>, C(20) = H<sub>β</sub>, C(19) = H<sub>β</sub>.

7. Basic structures and configurations of alkaloid N-oxides  
from species of Uncaria

7.1 Indole N-oxides

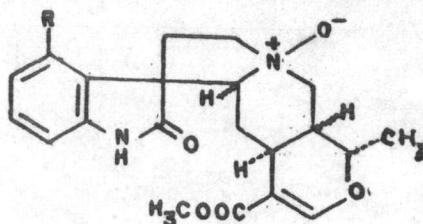
7.1.1 Pentacyclic heteroyohimbine N-oxides

Configuration	Alkaloid	Reference
<u>Allo</u>	(4R)-Tetrahydroalstonine N-oxide	21
<u>Epiallo</u>	(4R)-Akuammigine N-oxide	21
<u>Epiallo</u>	(4S)-Akuammigine N-oxide	21

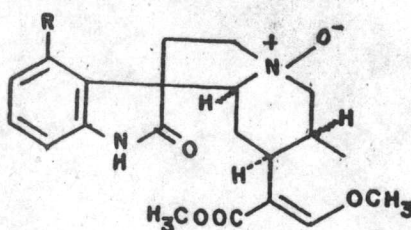
7.1.2 Tetracyclic heteroyohimbine N-oxides

Configuration	Alkaloid	Reference
<u>Normal</u>	Dihydrocorynantheine N-oxide	45
<u>Pseudo</u>	Hirsutine N-oxide	45



7.2. Oxindole N-oxides7.2.1 Pentacyclic oxindole N-oxides

Configuration	Alkaloid	Reference
<u>Normal</u> A	Isomitraphylline N-oxide	10,16,34,69
B	Mitraphylline N-oxide	10,16,34,69
<u>Allo</u> A	Isopteropodine N-oxide	10
B	Pteropodine N-oxide	10
<u>Epiallo</u> A	Speciophylline N-oxide	10
B	Uncarine F N-oxide	10

7.2.2 Tetracyclic oxindole N-oxides

Configuration	Alkaloid	Reference
<u>Normal</u> A	Isorhynchophylline N-oxide	10
B	Rhynchophylline N-oxide	10



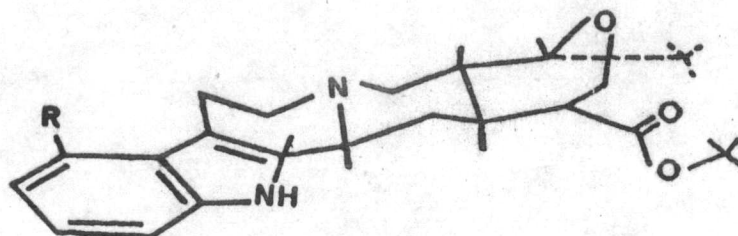
## 8. Preferred conformations

### 8.1 Indole alkaloids

The preferred conformations of indole alkaloids were illustrated as follows (15, 106, 125):-

#### 8.1.1 Pentacyclic heteroyohimbines

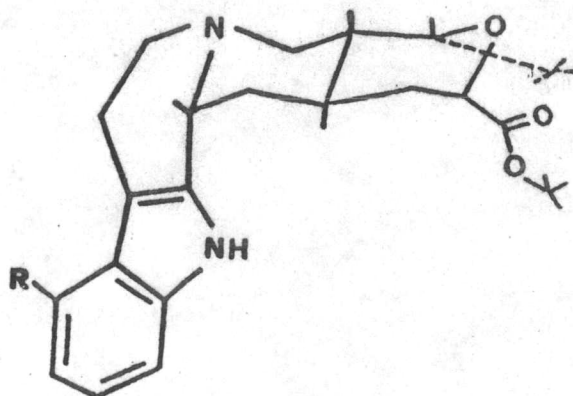
##### Normal



R = H, Ajmalicine

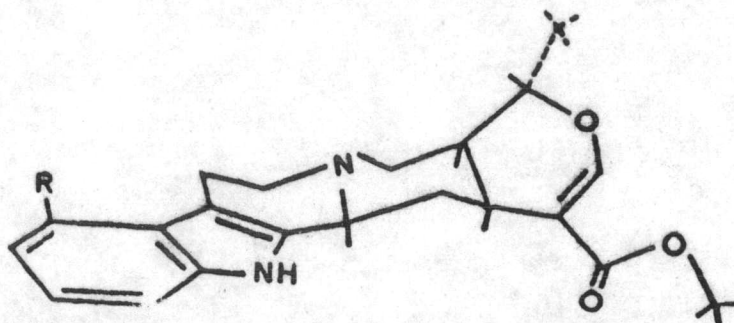
R = H and C(19)-CH<sub>3</sub>, 19-Epiajmalicine

##### Pseudo



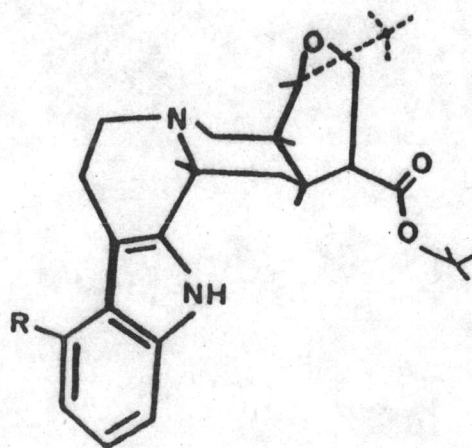
R = H, 3-Isoajmalicine

R = H and C(19)-CH<sub>3</sub>, 19-Epi-3-isoajmalicine

Allo

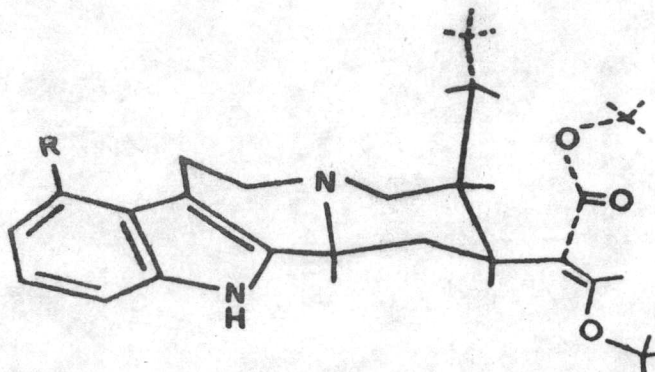
R = H, Tetrahydroalstonine

R = H and C(19)-CH<sub>3</sub> β, Rauniticine

Epiallo

R = H, Akuammigine

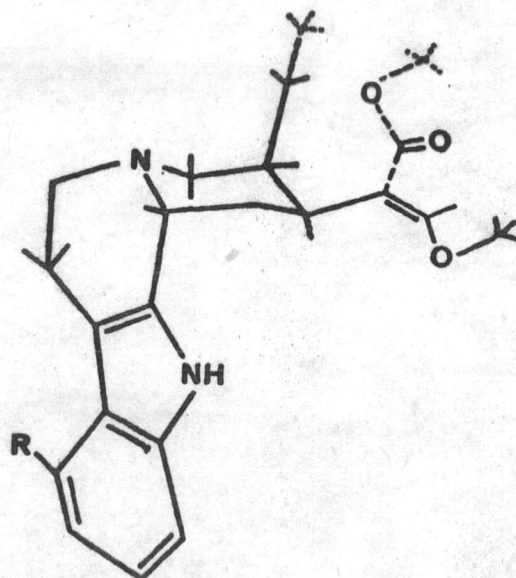
R = H and C(19)-CH<sub>3</sub> β, 3-Isorauniticine

8.1.2 Tetracyclic heterochimbinNormal

R = H, Dihydrocorynantheine

R = H and C(20)Et = vinyl, Corynantheine

R = OH, Gambirine

Pseudo

R = H, Hirsutine

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

R = OH, Isogambirine

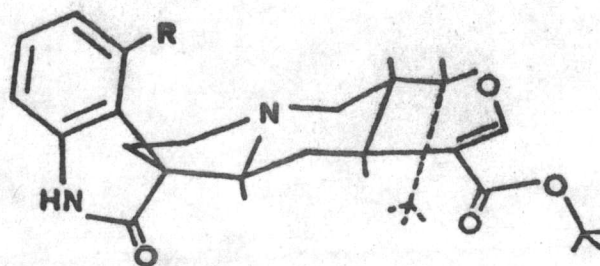
## 8.2 Oxindole alkaloids

The preferred conformations of oxindole alkaloids were illustrated as follows (100, 101, 106);-

### 8.2.1 Pentacyclic oxindoles

#### Normal

A.

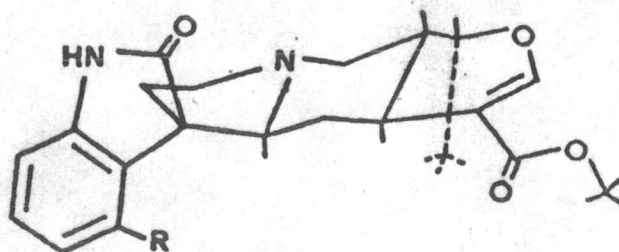


R = H, Isomitraphylline

R = H and C(19)-CH<sub>3</sub> β, Uncarine A (Isoformosanine)

#### Normal

B.



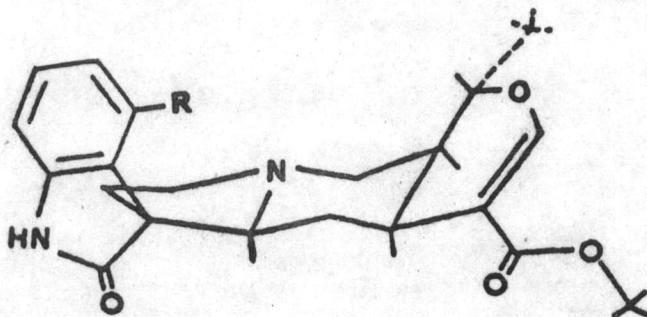
R = H, Mitraphylline

R = H and C(19)-CH<sub>3</sub> β, Uncarine B (Formosanine)



Allo

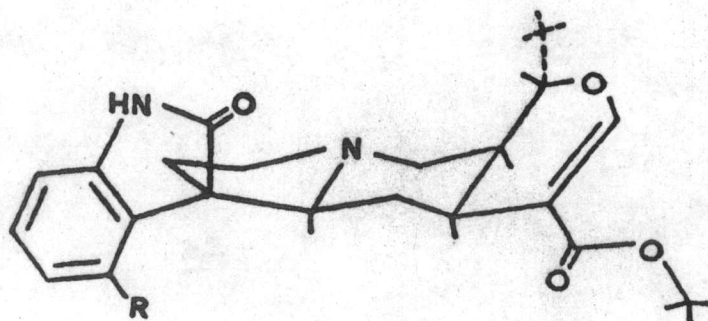
A.



R = H, Isopteropodine

Allo

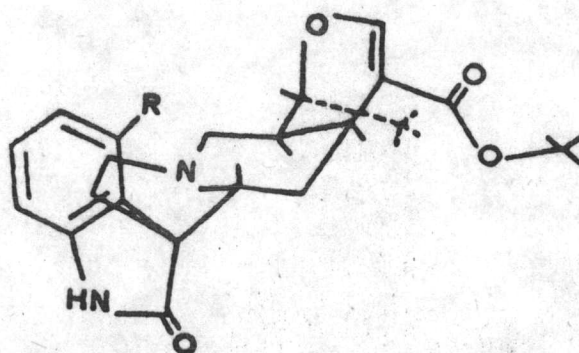
B.



R = H, Pteropodine

Epiallo

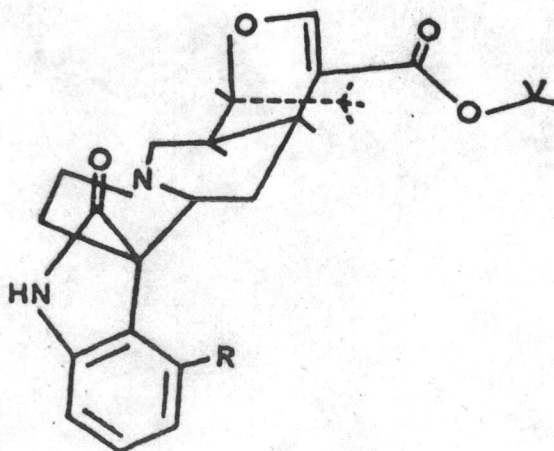
A.



R = H, Speciophylline

Epiallo

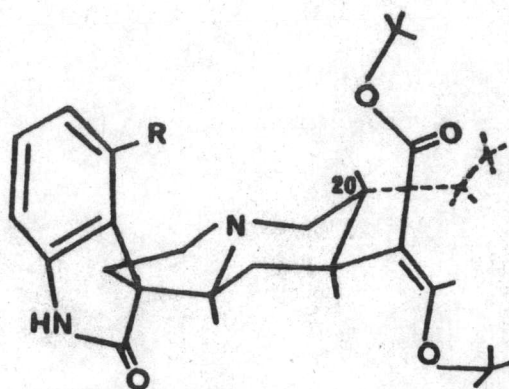
B.



R = H, Uncarine F

8.2.2 Tetracyclic oxindolesNormal

A.



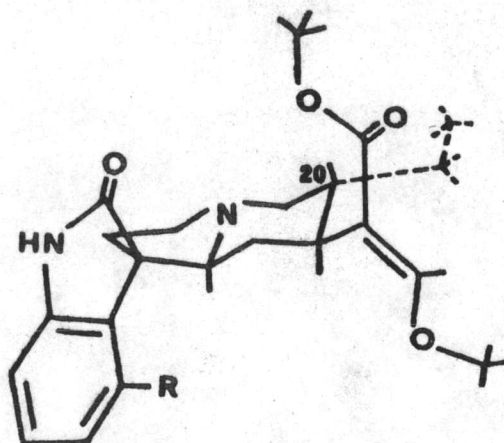
R = H, Isorhynchophylline

R = H and C(20)Et = vinyl, Isocorynoxine

R = OH, Rotundifoline

Normal

B.



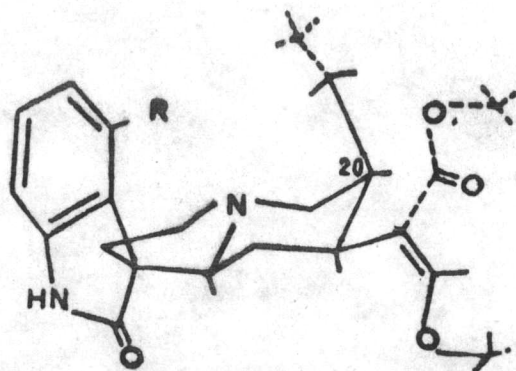
R = H, Rhynchophylline

R = H and C(20)Et = vinyl, Corynoxine

R = OH, Isorotundifoline

Allo

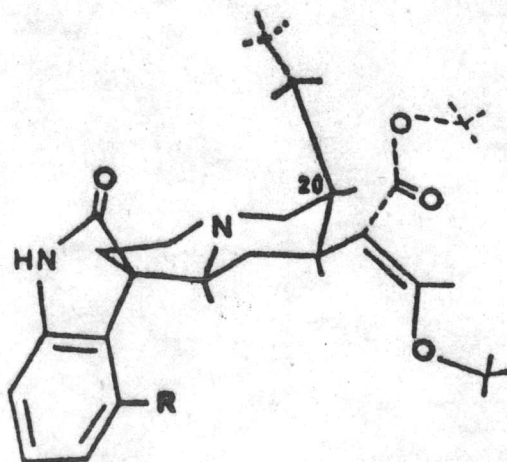
A.



R = H, Corynoxine

Allo

B.

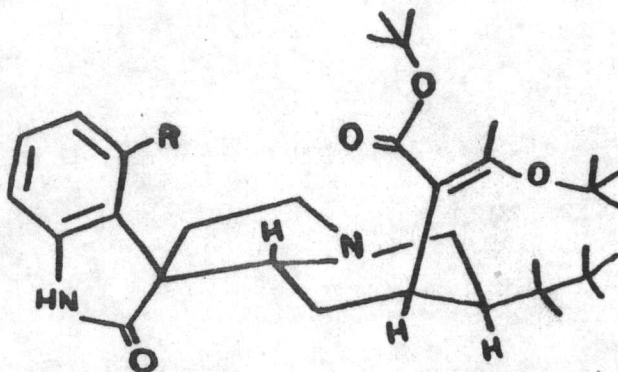


R = H, Corynoxine B



Epiallo

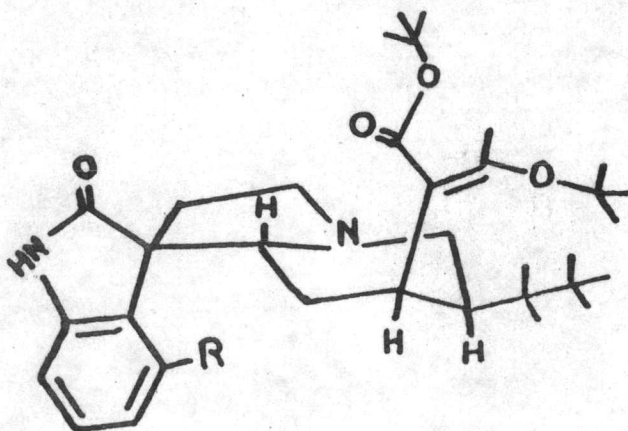
A.



R = OH, Isospeciofoline

Epiallo

B.



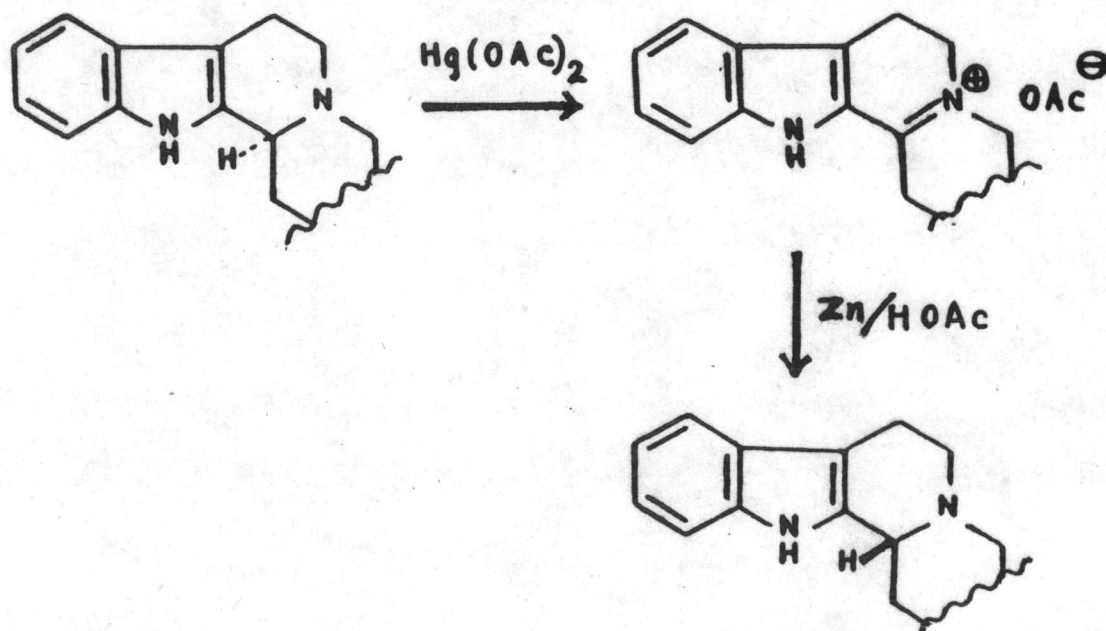
R = OH, Speciofoline

## 9. Transformation

### 9.1. Isomerisation

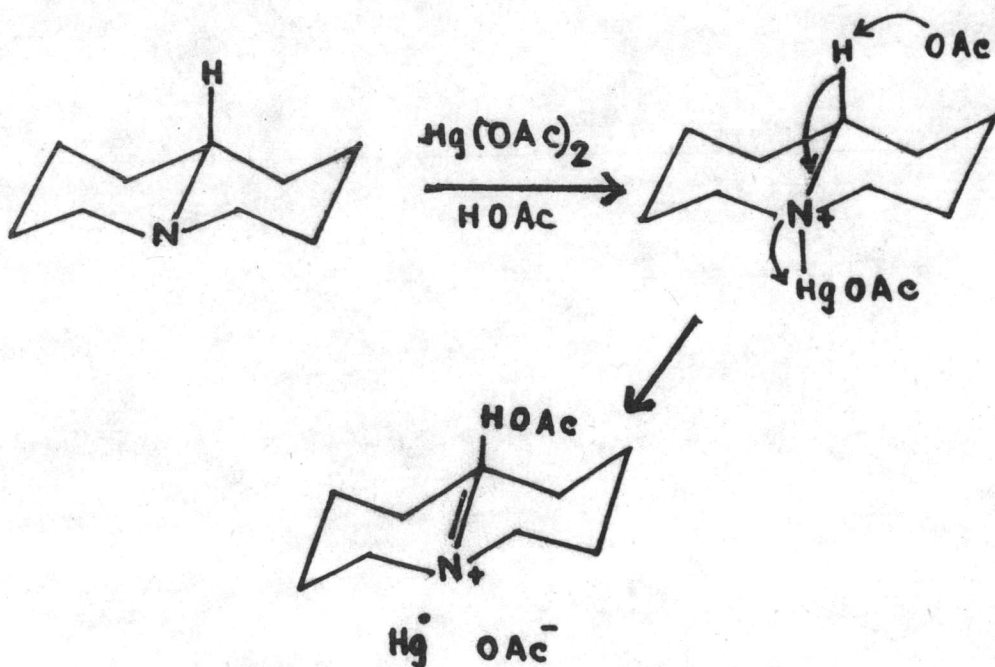
#### 9.1.1 Isomerisation of indole alkaloids

The epimerisation is an equilibrium reaction with the position of the equilibrium depending upon the solvent and temperature. Experiments in the field of indole alkaloids reveal many procedures for ascertaining the C(3) configuration. For example, the acid-catalysed or acetic anhydride-induced C(3) equilibration of D/E ois systems has been of diagnostic value.<sup>(51,111)</sup> By mercuric acetate oxidation, yohimbine and ajmalicine were transformed into 3-dehydro compounds, and subsequent reduction of the 3-dehydro salts by zinc-acetate yielded their C(3) epimers<sup>(111,112,113)</sup> as shown below :-



Isomerisation of indole alkaloids

All compounds possessing C(3)-H $\alpha$  i.e. normal and allo such as yohimbine, d-1 allo yohimbine and ajmalicine undergo the oxidation, while the compounds containing a C(3)-H $\beta$  i.e. pseudo or epiallo such as pseudo yohimbine, d-1 epiallo yohimbine and 3-isoajmalicine do not. (111,114) Since, in compounds of the normal and allo series, the preferred configuration of the N-mercured complex is that in which the axial hydrogen at C(3) is trans to the N-Hg bond, and thus the stereochemistry is favourable for a four-centre elimination. The mechanism is illustrated below :- (115)



In compounds of the pseudo and epiallo series, C(3)-H is cis to the N-Hg bond, and thus it would be unfavourable for the normal course of elimination. Some heteroyohimbine alkaloids had been converted into their corresponding isomers as summarised in the following table :-



Isomerisation		Reference
<u>Ajmalicine</u> <u>normal</u>	————→ 3-Isoajmalicine <u>pseudo</u>	112,116
<u>Tetrahydroalstonine</u> <u>allo</u>	————→ <u>Akuammigine</u> <u>epiallo</u>	112,116
<u>Rauniticine</u> <u>allo</u>	————→ <u>Isorauniticine</u> <u>epiallo</u>	105
<u>Dihydrocorynantheine</u> <u>normal</u>	————→ <u>Hirsutine</u> <u>pseudo</u>	109
<u>Speciogynine</u> <u>normal</u>	————→ <u>Mitraciliatine</u> <u>pseudo</u>	109
<u>Paynantheine</u> <u>normal</u>	————→ <u>Isopaynantheine</u> <u>pseudo</u>	78,117
<u>Corynantheidine</u> <u>allo</u>	————→ <u>Isocorynantheidine</u> <u>epiallo</u>	78,117
<u>Isomitrajavine</u> <u>normal</u>	————→ <u>Mitrajavine</u> <u>pseudo</u>	98

### 9.1.2 Isomerisation of oxindole alkaloids

In general pentacyclic and tetracyclic oxindole alkaloids may be isomerised about the C(3) and C(7) centres by treatment with either pyridine or acetic acid, or simply by heating. Because the oxindoles have a further asymmetric centre at C(7) allowing the oxindole carbonyl to be either below ( A configuration ) or above ( B configuration ) the plane of the C/D ring. Six isomeric compounds should result upon isomerisation namely two normal (A and B), two allo (A and B) and two epiallo (A and B)



configurations. The existence of the pseudo ( A and B ) configuration has been thought to be precluded on the grounds of excessive steric hindrance. (109)

Determination of the isomerisation medium for the predominant isomers in the final mixture has been conducted by many workers. In acid isomerisation, the B oxindoles predominate due to the stabilisation of the cation by means of intramolecular hydrogen bond between the protonated N(4) and the lactam carbonyl group. This stabilisation is not possible with the A oxindoles as the lactam carbonyl is below the plane of the C/D ring.

In a pyridine isomerisation, the A isomers predominate and this is thought to be due to the electrostatic repulsion between the lone pair of electrons of N(4) and the lactam carbonyl group in the free base form of the B isomer.

The isomerisation products of pentacyclic and tetracyclic oxindoles in acetic acid and pyridine medium are shown in the followings :-

a. Acetic acid isomerisation

Starting isomer	Isomerisation product	Reference
Isomitraphylline, or Mitrephylline	50% Isomitraphylline <u>normal A</u> 50% Mitrephylline <u>normal B</u>	15,99
Uncarine A, or Uncarine B	minor Uncarine A <u>normal A</u> major Uncarine B <u>normal B</u>	15,99

Starting isomer	Isomerisation product	Reference
Isopteropodine, or Pteropodine	30% Isopteropodine <u>allo A</u> 70% Pteropodine <u>allo B</u>	32b,99
Uncarine C, or Uncarine D	50% Uncarine C <u>allo B</u> 50% Uncarine D <u>epiallo A</u>	15,99
Isorhynchophylline, or Rhynchophylline	20% Isorhynchophylline <u>normal A</u> 80% Rhynchophylline <u>normal B</u>	109,118 119
Rotundifoline, or Isorotundifoline	60% Rotundifoline <u>normal A</u> 40% Isorotundifoline <u>normal B</u>	109
Rhynchociline, or Ciliaphylline	50% Rhynchophylline <u>normal A</u> 50% Ciliaphylline <u>normal B</u>	109
Rotundifoleine, or Isorotundifoleine	Rotundifoleine <u>normal A</u> Isorotundifoleine <u>normal B</u>	120
Isospecionoxeine, or Specionoxeine	50% Isospecionoxeine <u>normal A</u> 50% Specionoxeine <u>normal B</u>	109

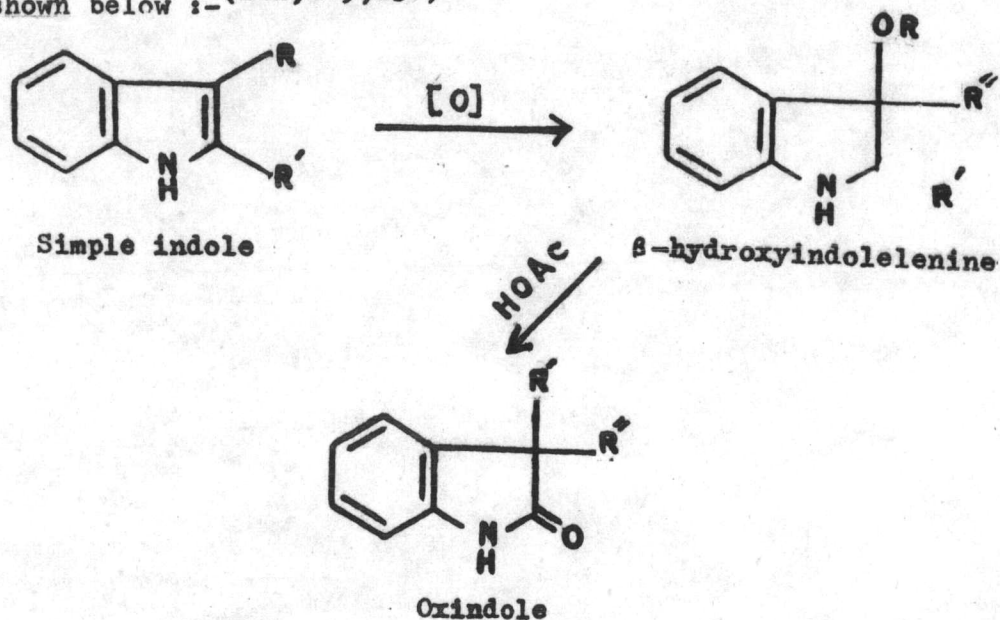
b. Pyridine isomerisation

Starting isomer	Isomerisation product	Reference
Isomitraphylline, or Mitraphylline	80% <u>Isomitraphylline normal A</u> 20% <u>Mitraphylline normal B</u>	15,99
Uncarine A, or Uncarine B	80% <u>Uncarine A normal A</u> 20% <u>Uncarine B normal B</u>	15,99
Isopteropodine, or Pteropodine	80% <u>Isopteropodine allo A</u> 20% <u>Pteropodine allo B</u>	32b,99
Uncarine C, or Uncarine D	100% <u>Uncarine C allo B</u> <u>Uncarine D epialle A</u>	15,99
Isorhynchophylline, or Rhynchophylline	80% <u>Isorhynchophylline normal A</u> 20% <u>Rhynchophylline normal B</u>	109,118 119
Rotundifoline, or Isorotundifoline	90% <u>Rotundifoline normal A</u> 10% <u>Isorotundifoline normal B</u>	109
Rhynchocilline, or Ciliaphylline	35% <u>Rhynchocilline normal A</u> 65% <u>Ciliaphylline normal B</u>	109
Isospecionoxeine, or Specionoxeine	35% <u>Isospecionoxeine normal A</u> 65% <u>Specionoxeine normal B</u>	109



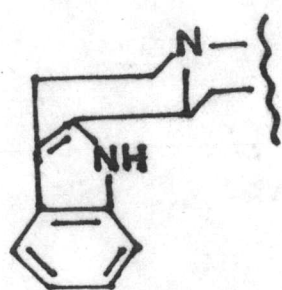
## 9.2 Transformation of indole alkaloids to oxindole alkaloids

The reactivity of the  $\beta$ -position of indoles to electrophilic reagent has long been known. This property has been utilised to effect the transformation of simple indoles into their corresponding oxindoles via the intermediate  $\beta$ -hydroxyindolenine, subsequent treatment with acetic acid in methanol yielded oxindoles as shown below :- (121,129,130)

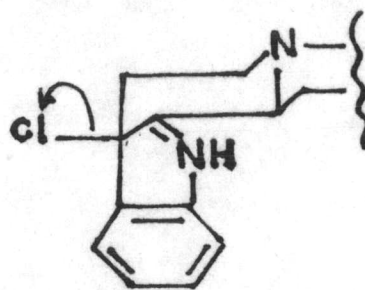
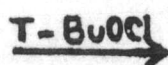


Finch and Taylor,<sup>(102)</sup> and Zinnes and Shavel<sup>(123)</sup> showed that alkaloids of yohimbine and heteroyohimbine types were transformed into a mixture of epimeric C(7) chloroindolenines by the action of tertiary butyl hypochlorite. Methanolysis of the chloroindolenines gave the imido ester which on hydrolysis in aqueous acetic acid yielded a mixture of oxindoles. The stronger base of the pair being named oxindole B and the weaker one, oxindoles A. The mechanism is as follows :- (122)

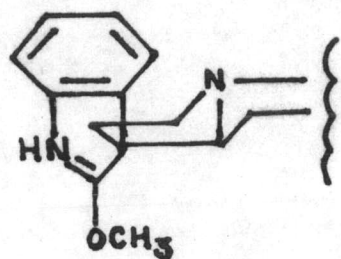
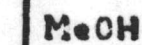




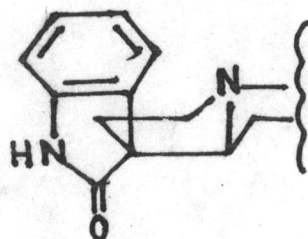
Yohimbine



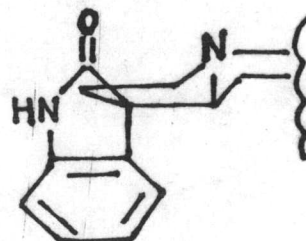
Chloroindolenine



Imido ester



Oxindole A



Oxindole B

Zinnes and Shavel also noted that the universality of the C(15)-Ha configuration of indole alkaloids also extended to the oxindole alkaloids.<sup>(123)</sup> Finch et al. and many workers have performed the conversion of heteroyohimbine alkaloids into their corresponding oxindoles and the results are summarised as follows :-

Heteroyohimbine	Oxindole	Reference
Ajmalicine (normal)	Isomitraphylline Mitraphylline (normal)	122,123 129,130
Dihydrocorynantheine (normal)	Isorhynchophylline Rhynchophylline (normal)	112
Mitrajavine (pseudo)	Javaphylline Isojavaphylline (normal)	127
Mitraciliatine (pseudo)	Rhynchociline Ciliaphylline (normal)	127
Tetrahydroalstonine (allo)	Uncarine E Uncarine C (allo)	15
Corynantheidine (allo)	Corynoxine Corynoxine B (allo)	117
Mitragynine (allo)	Mitragynine oxindole A Mitragynine oxindole B (allo)	117

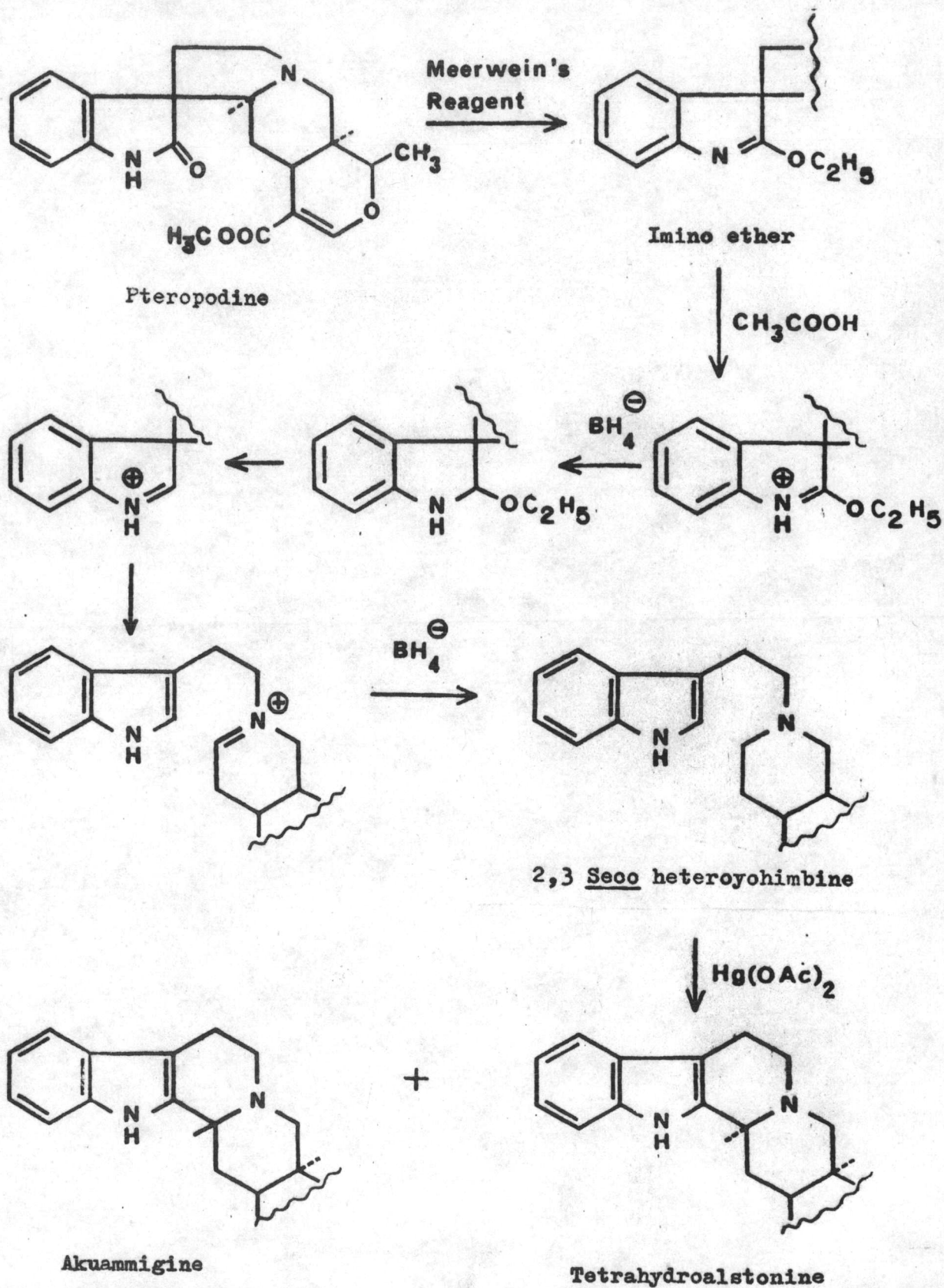
Apart from the above mentioned method Finch et al.<sup>(124)</sup> showed that the reaction of lead tetra-acetate with yohimbine and related

alkaloids afforded acetoxy indolenine. On refluxing this compound in methanol containing a few drops of acetic acid, a rearrangement occurred and an oxindole was obtained. Hart et al.<sup>(125)</sup> also succeeded in the conversion of tetrahydroalstonine into its corresponding oxindoles, isopteropodine, pteropodine, speciophylline and uncarine F.

### 9.3 Transformation of oxindole alkaloids to indole alkaloids

Aimi et al. succeeded in transforming both isopteropodine and pteropodine into 2,3-seco-heteroyohimbine by treating with Meerwein's reagent in acetic acid. The reaction first yielded ethylimino ether, which on reduction with sodium borohydride in acetic acid, 2,3 seco-heteroyohimbine alkaloid with dilute acetic acid containing excess mercuric acetate, then treated with hydrogen sulphide, afforded the mixture of tetrahydroalstonine and akuammigine.<sup>(126)</sup> The reaction is shown in page 80.







They also used the same method to convert tetracyclic oxindole, isorhynchophylline into dihydrocorynantheine and hirsutine.<sup>(126)</sup>

#### 9.4 The interconversion of tetracyclic and pentacyclic oxindole alkaloids

The natural occurrence of both tetracyclic and pentacyclic oxindole alkaloids together in various species of Mitragyna without the presence of the corresponding pentacyclic heteroyohimbine alkaloids led Houghton and Shellard<sup>(162)</sup> to suggest that the pentacyclic oxindoles might arise by the ring closure of the tetracyclic oxindoles. The presence of the C(20) vinyl tetracyclic oxindoles, corynoxine and isocorynoxine, in those plants containing mitraphylline and rhynchophylline suggested that they might be involved as intermediates.

In vivo closure of the E ring occurred when rhynchophylline labelled with <sup>14</sup>C was fed just below the leaf base of young plants of Mitragyna parvifolia (Roxb.) Korth. grown from seeds obtained from Sri Lanka.<sup>(68)</sup> In this plant the xylem contains the tetracyclic oxindoles although they could not be detected in the leaves in which pentacyclic oxindoles are present. Shellard and Houghton<sup>(67)</sup>,<sup>(68)</sup> therefore suggested that E ring closure occurred in the xylem of the leaf base at 24 hours after the plant had been fed with radioactive rhynchophylline, as radioactive corynoxine and mitraphylline were detected in the leaf. Conversely, when <sup>14</sup>C-mitraphylline was fed into the stem bark, radioactivity was detected in the corynoxine and rhynchophylline lower down the stem indicating that the reverse process, tetracyclic took place, with corynoxine as an intermediate.<sup>(68)</sup>

Following the method used by Djakoure, Jarreau and Goutard<sup>(163)</sup> for the closure of the open E ring in heteroyohimbine alkaloids, corynoxine has been converted in vitro to mitraphylline and uncarine B.<sup>(162)</sup>

## 10. Alkaloid N-oxides

### 10.1 Pentacyclic heteroyohimbine N-oxides

Merlini and Nasini believed that the N-oxides are not artifacts, because of the rather mild extractions, and of the difficulty of oxidation of the base to N-oxides. They found that conditions employed with hydrogen peroxide in acetic acid or in ethanol were unsatisfactory, but oxidation of the base with m-chloroperbenzoic acid in chloroform gave good yield (30-70%) of the N-oxides. Tetrahydroalstonine, ajmalicine, 3-iscajmalicine and akuammigine, each yielded only one N-oxide on treatment with m-chloroperbenzoic acid. However, 4-R-akuammigine, 4-S-akuammigine and 4-R-tetrahydroalstonine N-oxides were indentified as natural products in a species of Uncaria.<sup>(21)</sup>

### 10.2 Tetracyclic heteroyohimbine N-oxides

Dihydrocorynantheine and hirsutine N-oxides have been isolated from the leaves and stems of Uncaria tomentosa (Willd.) DC.<sup>(45)</sup> No other tetracyclic N-oxide have been reported, so it would seem highly probable that they exist as natural products.

### 10.3 Pentacyclic oxindole N-oxides

N-oxides of the isomitraphylline, mitraphylline, isopteropodine,

pteropodine, speciophylline and uncarine F were reported as natural products in several species of uncaria and Mitragyna.<sup>(10), (69)</sup>

#### 10.4 Tetracyclic oxindole N-oxides

It has been shown that the B series oxindoles give only one N-oxide, where as those in A series give two forms of N-oxides, an anti and a syn.

Isorhynchophylline treated with hydrogen peroxide yielded three products; anti-isorhynchophylline N-oxide, syn-isorhynchophylline N-oxide and rhynchophylline N-oxide.<sup>(166)</sup> But only the isorhynchophylline N-oxide with the anti configuration has been isolated as a natural product.<sup>(167)</sup> Rhynchophylline (normal B) yielded only one N-oxide and this also has been obtained as a natural product.<sup>(93)</sup> Similarly, rotundifoline yielded an anti and a syn N-oxides, while isorotundifoline yielded only one N-oxide.<sup>(167)</sup>

The facile conversion of N-oxide to tertiary base and vice versa under laboratory conditions might have their counterpart in plants, and N-oxide may simple be implicated in general oxidation-reduction processes. Certainly when the natural occurrence and chemical reactivity of N-oxides is taken into account, it makes them likely biosynthetic intermediates in the sequence which follow alkaloid formation.<sup>(168)</sup>



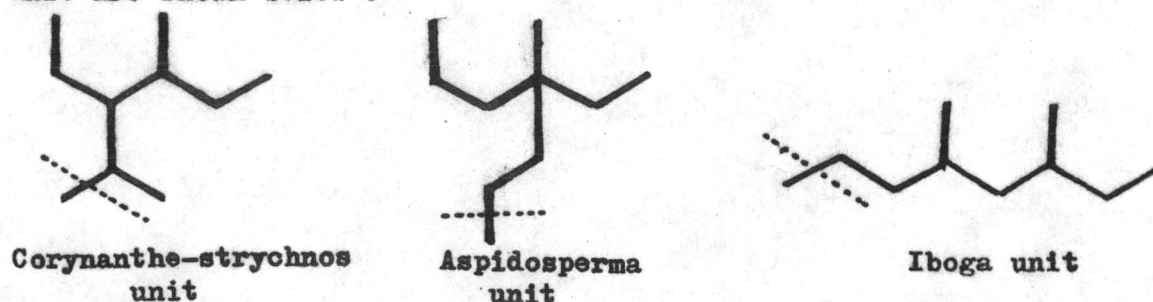
## 11. Biogenesis

### 11.1. Indole alkaloids

The indole alkaloids of Uncaria species and nearly all of the naturally occurring indole alkaloids are formally derived from the condensation of a monoterpenoid moiety ( $C_9-C_{10}$ ) unit with a tryptamine unit. (131)

#### 11.1.1 Origin of the $C_9-C_{10}$ unit

This unit appears in three skeleton forms (132) which are referred to as the corynanthe-strychnos, the aspidosperma and the iboga types. (133) Three forms of the non-tryptophan derived unit are shown below :-

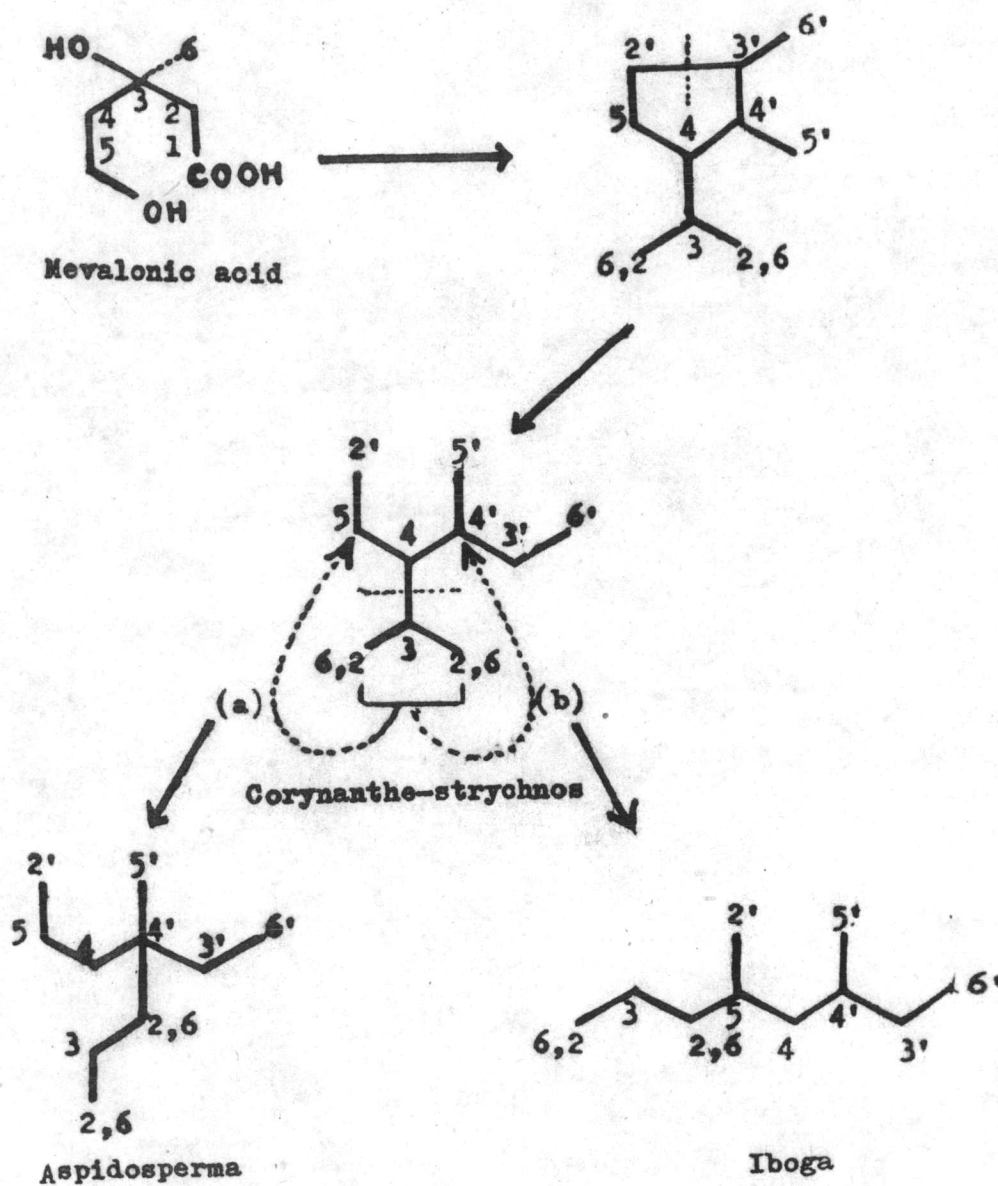


(The dotted line indicates that carbon atom which is consistently absent from those alkaloids having only nine skeleton carbons in addition to the tryptamine moiety.)

There were many hypotheses suggested the origin of monoterpenoid moiety of indole alkaloids, e.g. Woodward fission, (134) Prephenic hypothesis (136) and Acetate hypothesis (137,138) but each of them has now been disproven. (136,139,140,141,142) The accepted hypothesis was based on feeding experiment by administration of 2- $^{14}C$ -mevalonate



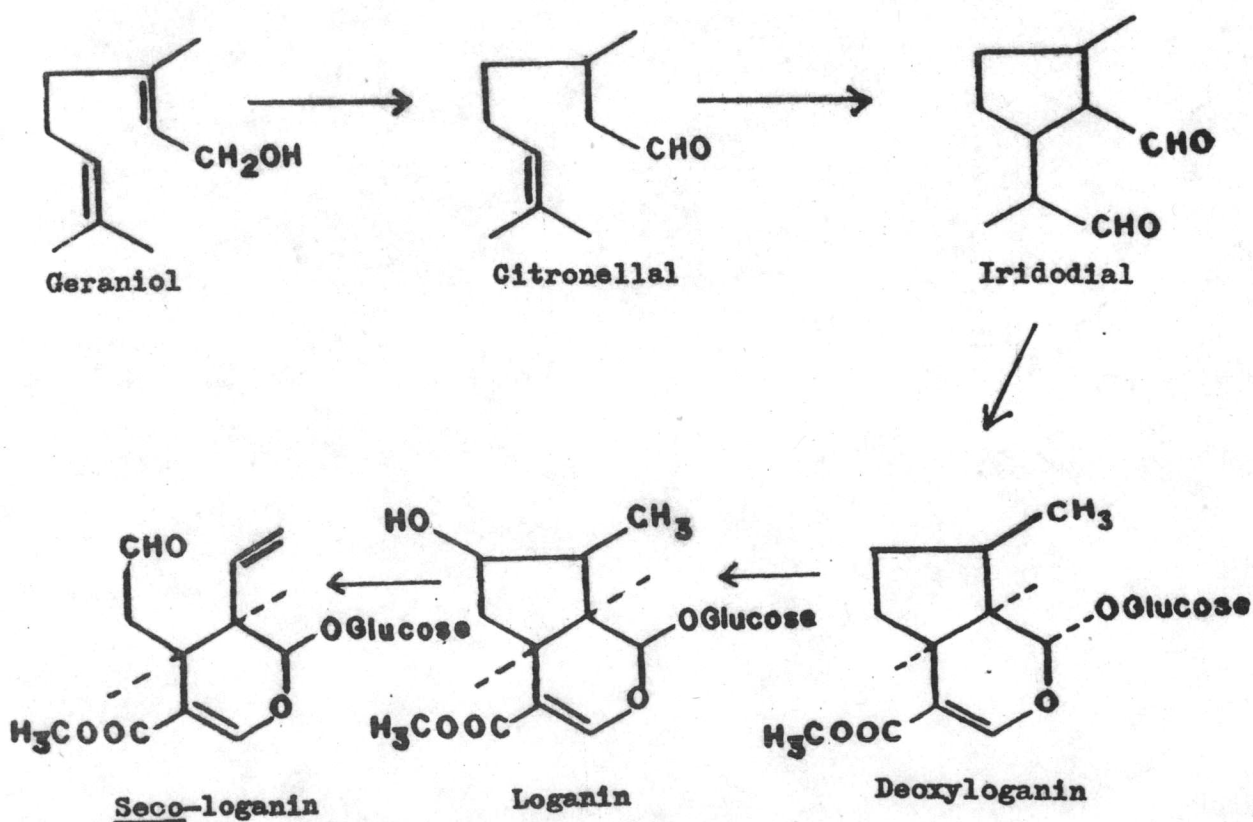
to Catharanthus roseus L. shoots, afforded radioactive ajmalicine, reserpinine (corynanthe type), vindoline (aspidosperma type) and catharanthine (iboga type). The results indicated that radioactive mevalonate was incorporated into each of the alkaloids. (143)



Geraniol serves as the alicyclic monoterpene bridge between mevalonic acid and a cyclopentanoid monoterpene. (144,145,146) This was confirmed by feeding experiment using labelled geraniol. There

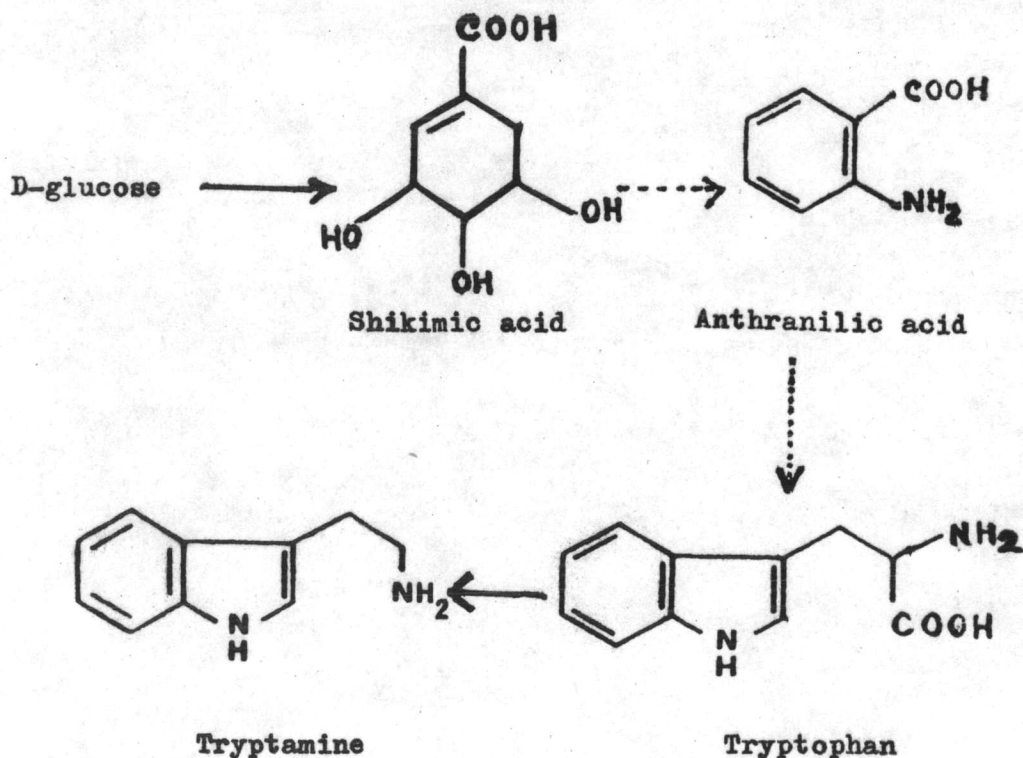
are four naturally occurring cyclopentanoid monoterpenes namely verbenalin, genepin, monoterpeine ester and loganin. Each of these compounds was tested for its ability to serve as the precursor of the indole alkaloids of Catharanthus roseus L.. Only loganin with 3-H-labelled in the methyl ester group was proved as being the precursor of the indole alkaloids. (147)

The transformation of geraniol into the C<sub>10</sub> skeleton of loganin requires oxidation of the C<sub>9</sub> and C<sub>10</sub> methyl groups, oxidation of C-1 to the aldehyde level, saturation of the  $\Delta^2$ -double bond and formation of the cyclopentane ring. The intermediates in the pathway from geraniol to loganin are citronellal, iridodial and deoxyloganin. The rupture of cyclopentane ring leads to the formation of seco-loganin. (148a,b) The pathway is shown below :-



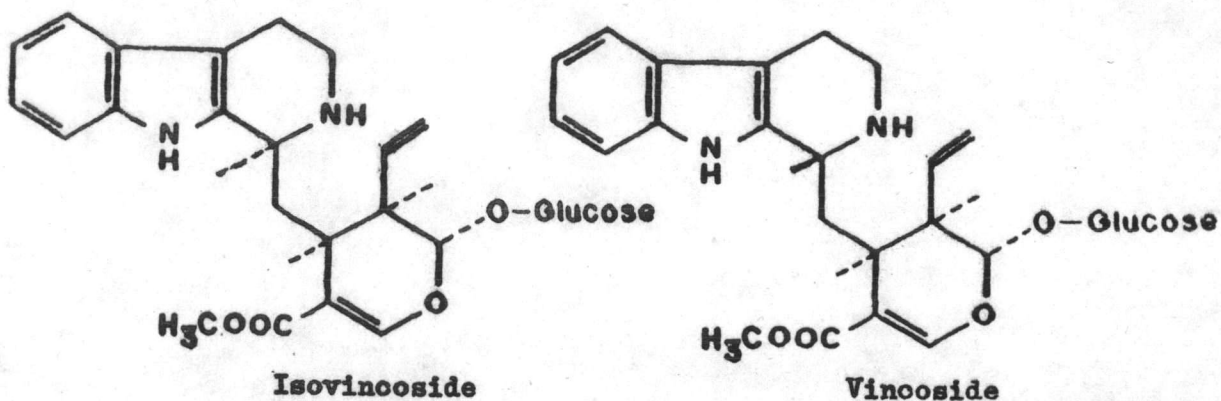
### 11.1.2 Tryptamine formation

Tryptamine widely distributes amongst plants and animals. It derives from tryptophan by decarboxylation. Early experimental work had demonstrated the ability of the amino acid tryptophan to serve as a precursor of the tryptamine moiety of the indole alkaloids. (154,155) Recent work has been done on the biosynthesis of the amino acid tryptophan. Careful studies with labelled intermediates have confirmed that tryptophan is synthesised via shikimic acid pathway, having anthranilic acid as an intermediate. (156,157) The pathway of tryptophan biosynthesis is illustrated as follows :-



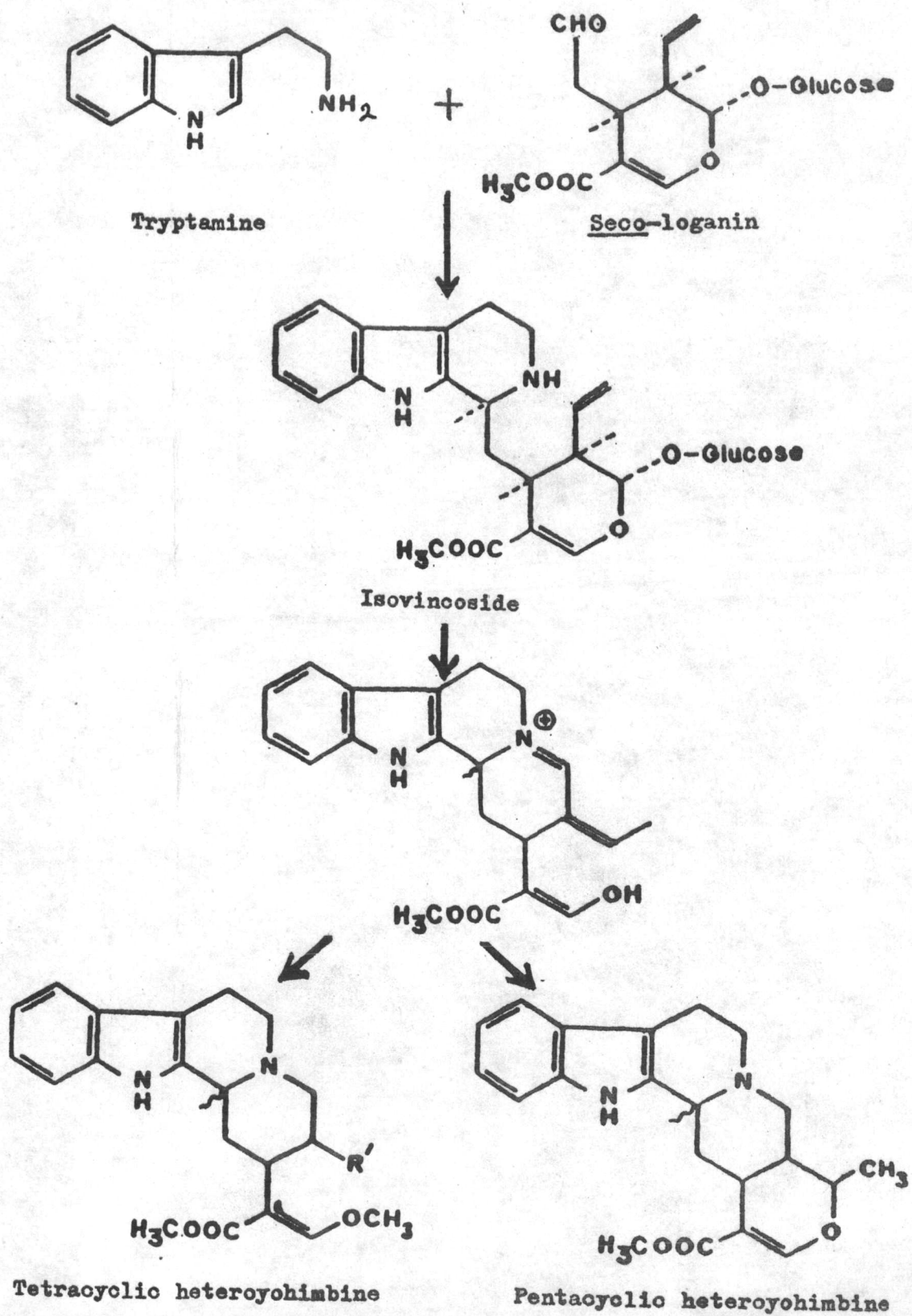


When aryl-<sup>3</sup>H-tryptamine hydrochloride was fed to Catharanthus roseus L. shoots, the hydrochlorides of the two epimeric  $\beta$ -carbolines namely isovincoside (strictosidine) and vincoside were produced. (149)



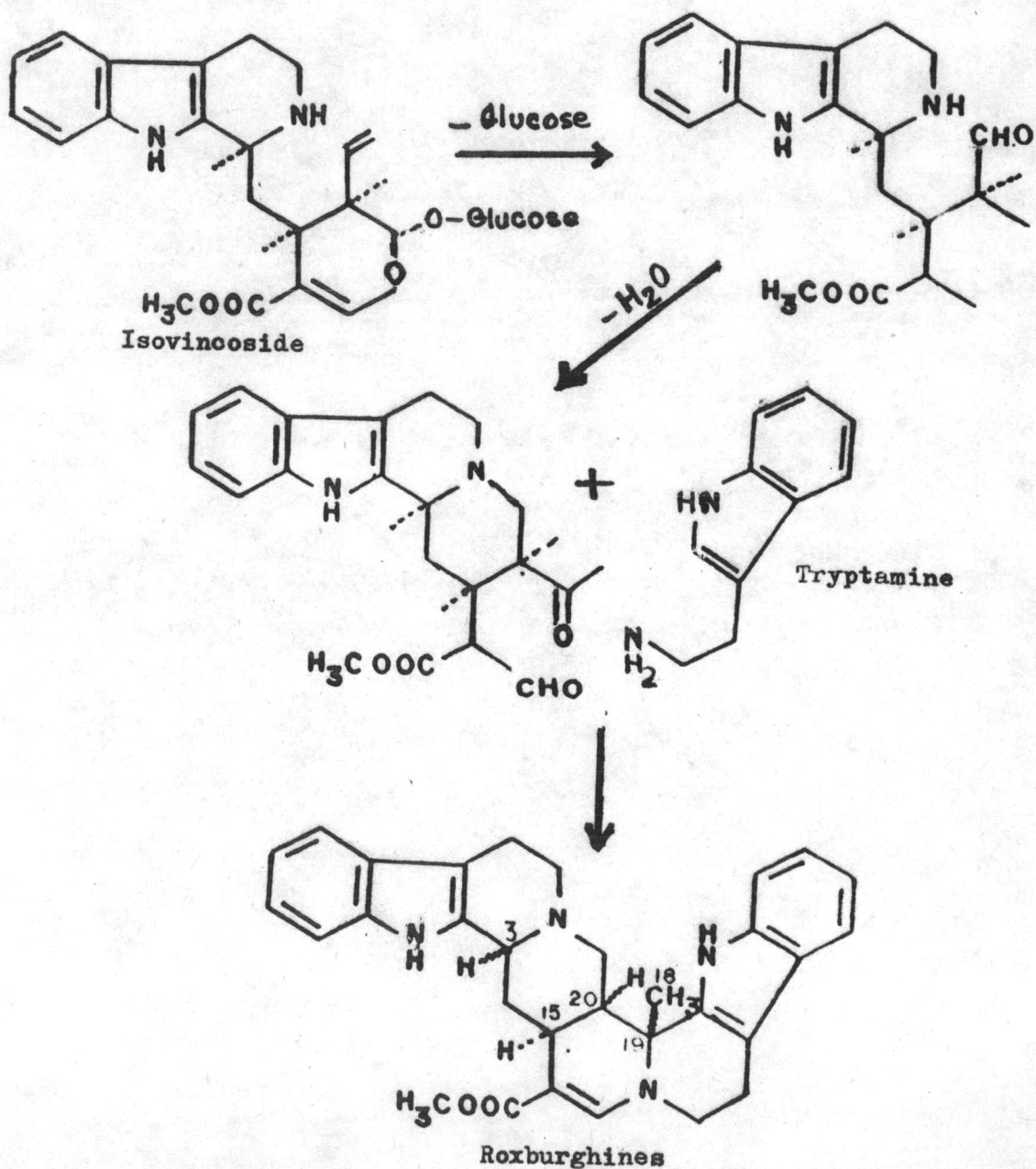
In the feeding experiment to the same plant, (149,150) only vincoside was shown to be incorporated into indole alkaloids. If as it now appears, vincoside bears a C(3)-H $\beta$  configuration, (165,166) then an inversion must occur at that carbon during the later stages of biosynthesis which lead to those indole alkaloids having the C(3)-H $\alpha$  configuration.

However, recently isovincoside (strictosidine) was shown to be the common precursor for indole alkaloids, not vincoside as originally thought. (151,152,153) The proposed biosynthetic pathways leading to the corynanthe type are shown in the following three pages.

a. Heteroyohimbine alkaloids

b. Roxburghines

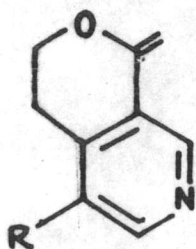
Roxburghines are indole alkaloids, being first isolated from Uncaria gambir Roxb. They are apparently derived from two tryptamines and one monoterpenoid  $C_{10}$  unit. They contain a loganin derived  $C_{10}$  unit of the corynanthe type. The following is a possible biogenetic scheme of roxburghines:- (18,150)





c. Pyridino-indolo-quinolizidinones

Pyridino-indolo-quinolizidinones is another type of alkaloids found in Uncaria species namely angustine, angustoline and angustidine. Angustine and angustoline are possibly derived from a tryptamine unit combined with a seco-loganin monoterpene unit closely related to the alkaloid gentianine. Gentianine has been shown in most but not all instances to be artifacts resulting from treatment of seco-iridoides such as gentiopicroside, swertiamarin and sweroside with ammonia. Thus there is the possibility that angustine and angustoline are artifacts. (96)



Gentianine



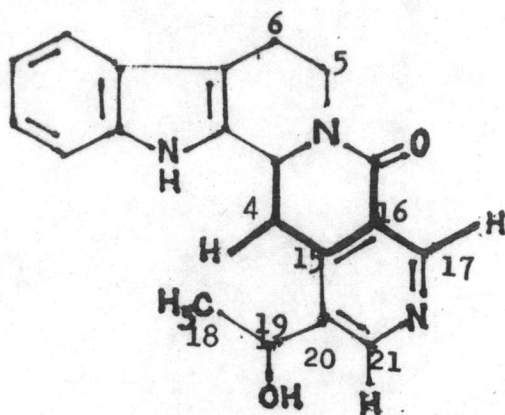
5-ene; gentiopicroside

R = OH; swertiamarin

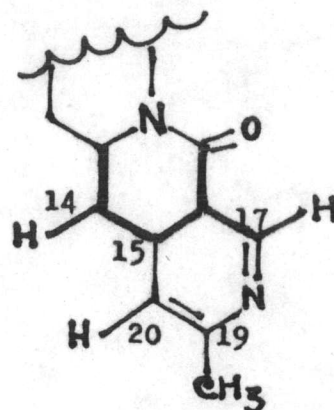
R = H; sweroside

Alternatively, angustine and angustoline might possibly be formed from glycoside mixtures related to vincoside-lactam or isovincoside-lactam (strictosamide), (149) which are in turn derived biogenetically from tryptamine and seco-loganin.

The biogenesis of angustidine might involve the loss of a carbon atom C(21) from the seco-loganin portion of a corynanthe precursor. (96) For numbering see the next page.



corynanthe alkaloid  
structure

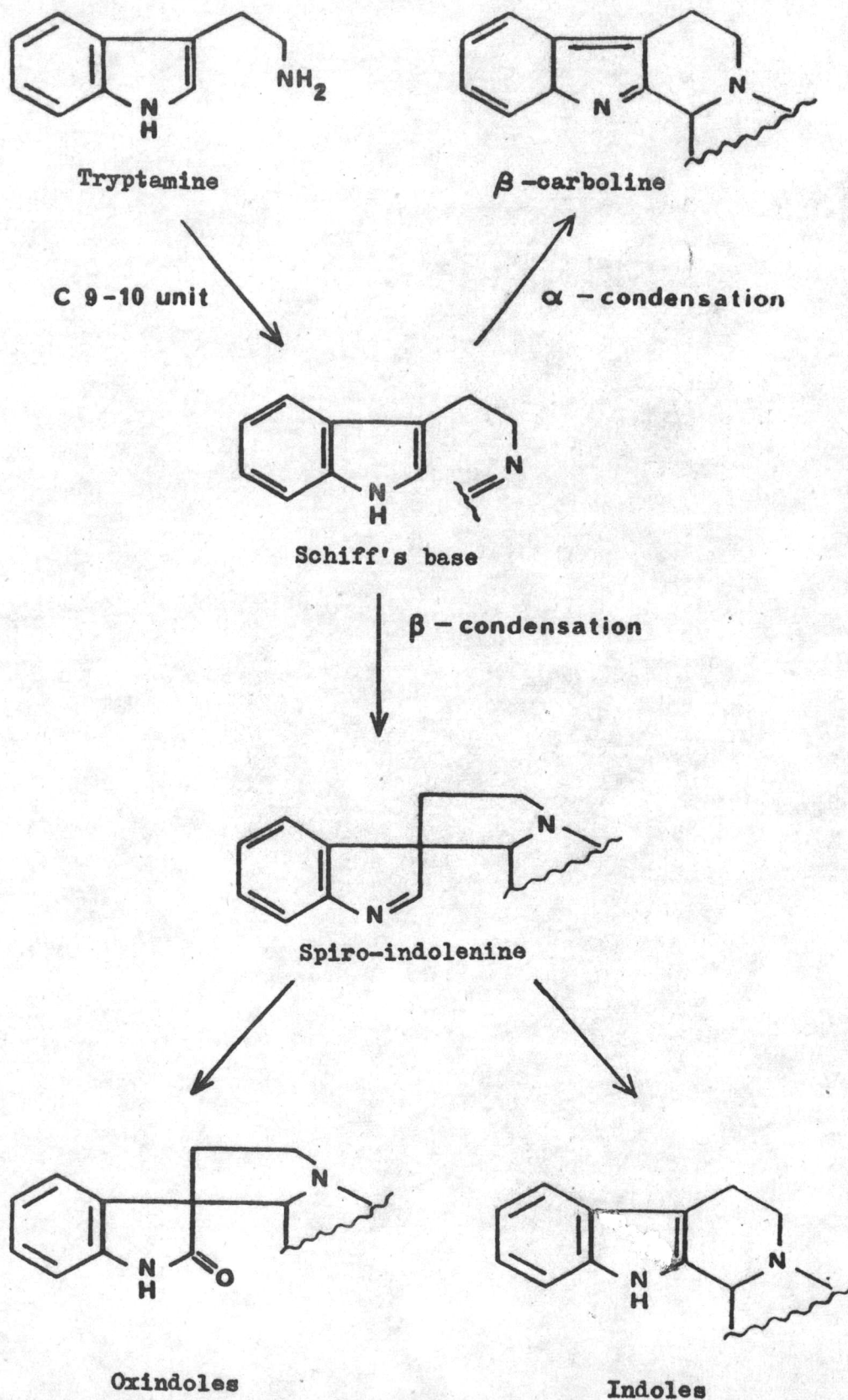


21-nor-corynanthe alkaloid  
structure

### 11.2 Oxindole alkaloids

Woodward's proposal regarding the condensation between tryptamine and seco-loganin was that an intermediary, a Schiff's base, was formed which by  $\alpha$ -condensation, gave indoles and the  $\beta$ -condensation yielded oxindoles. (131)

Jackson and Smith argued that the  $\beta$ -condensation was more likely than an  $\alpha$ -condensation as the latter being less stable. They stated that tryptamine and the  $C_{10}$  mevalonate gave a Schiff's base which could undergo either  $\alpha$  or  $\beta$ -condensation but that the  $\beta$ -condensation was more favoured because the intermediate product did not necessitate a rearrangement of the  $\pi$  electron system of the benzene ring which would be the case with an  $\alpha$ -condensation. The indolenine can either isomerise in mild acid condition to give indole alkaloids or oxidise to give oxindole alkaloids. (158) This can be illustrated as shown in the next page.





## 12. Biogenesis of the Uncaria Alkaloids

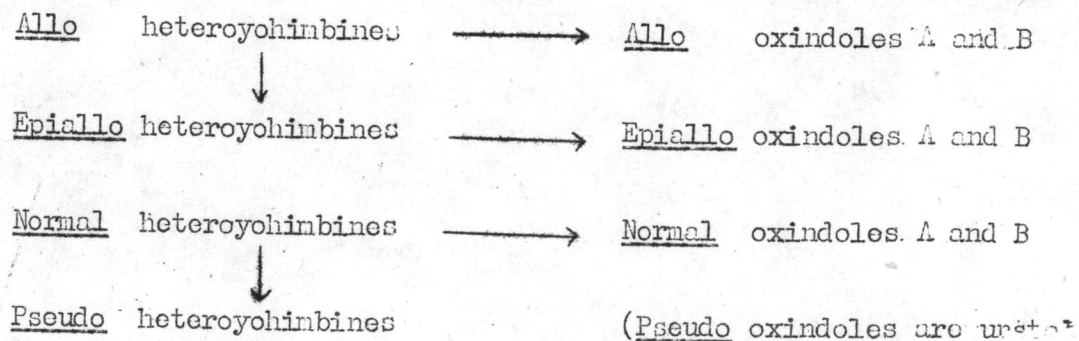
When the alkaloids present in individual species of Mitragyna are considered in terms of their configurations and D/E ring systems (61) it will be seen that :-

- a. when both heteroyohimbine and oxindole alkaloids are in the same plant, the D/E ring configurations of both are identical,
- b. heteroyohimbines are present in the major quantities as their least stable configuration, i.e. pseudo and epiallo.

These showed the possibility that there was a well defined biogenetic link between the heteroyohimbine and oxindole alkaloids in plant and Shellard, Phillipson and Gupta postulated that :- (61)

1. the plant synthesises the thermodynamically more stable heteroyohimbine alkaloids,
2. these alkaloids are then isomerised to give the less stable heteroyohimbine alkaloids, and
3. that both types of heteroyohimbines are then converted to the corresponding oxindole alkaloids (pseudo oxindoles are unstable to exist because of steric interference.) (109) (62)

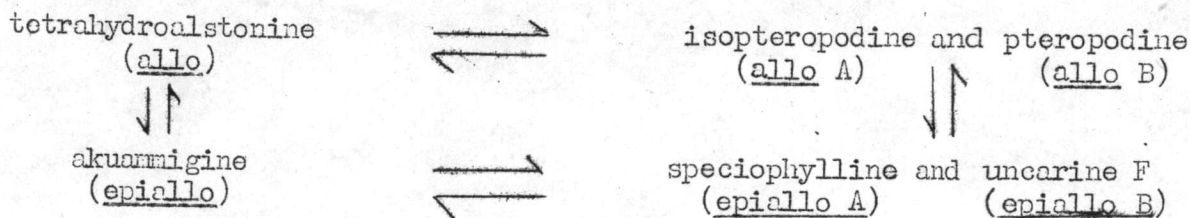
The hypothesis can be represented as follows :-



In this connection it is interesting to note that the chemical transformation of one indole alkaloid to the less stable isomer was achieved by Wenkert and Roychaudhuri. (112) In addition the chemical conversion of heteroyohimbine alkaloids to the corresponding oxindoles was carried out by Finch and Taylor, (117) Zinnes and Shavel, (123) and Beckett, Dwuma-Badu, and Haddock. (130)

The alkaloids initially isolated from the leaves of Uncaria bernaysii F.v.Miell. supported this hypothesis. Tetrahydroalstonine and akuammigine are the pentacyclic heteroyohimbine alkaloids which occur together with the corresponding oxindole alkaloids, isopteropodine, pteropodine, speciophylline and uncarine F.

Recently, isopteropodine and pteropodine have been converted into tetrahydroalstonine and akuammigine (126) and it is possible that oxindole alkaloids may be converted to heteroyohimbine alkaloids within the plant. The relationship between the alkaloids isolated from Uncaria bernaysii F.v.Miell. may be illustrated as follows: (16)



"In vitro" conversion of the allo and epiallo heteroyohimbine alkaloids into mixtures of allo and epiallo oxindoles had already been achieved and Shellard and Sarpong (127) were able to use the same method

to convert pseudo heteroyohimbine into the normal oxindole alkaloids.

"In vivo" Shellard and Houghton<sup>(128)</sup> fed ajmalicine and 3-iso-ajmalicine into young plants of Mitragyna parvifolia (Roxb.) Korth. grown from seeds obtained from Sri Lanka and in both cases obtained isomitraphylline and mitraphylline. It is significant, however, that no 3-isoajmalicine was detected in the leaves when the plant was fed with ajmalicine; neither ajmalicine was detected when 3-isoajmalicine was fed to plant.

Similarly, akuammigine was not detected when <sup>14</sup>C-tetrahydroalstonine was fed into the plant and vice versa.<sup>(67)</sup>

All of this experiments seem to confirm that in Mitragyna species, there is no interconversion between normal and pseudo, and allo and epiallo heteroyohimbine alkaloids during their biogenesis.<sup>(67)</sup>

It was considered that the C(3)-H $\alpha$  and C(3)-H $\beta$  heteroyohimbine alkaloids were separately synthesised from a precursor but that epiallo and pseudo heteroyohimbine alkaloids were the dominant alkaloids and offered the main pathway to the oxindole alkaloids. The modification of this hypothesis later becomes more rational with Blackstock et al.<sup>(164)</sup> and De Silva et al.<sup>(165)</sup> revelation that the C(3)-H in vincoside was actually  $\beta$ . The hypothesis has been modified to meet this observed facts and was represented as follows:-<sup>(68)</sup>



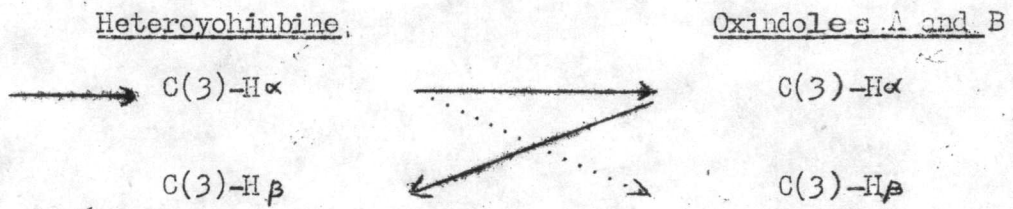


Heteroyohimbine alkaloids corresponding to eight biosynthetic routes

Series	Closed E ring	Open E ring
<u>Normal-pseudo</u>	1. C(9)-H 2. C(9)-OCH <sub>3</sub>	5. C(9)-H 6. C(9)-OCH <sub>3</sub>
<u>Allo-epiallo</u>	3. C(9)-H 4. C(9)-OCH <sub>3</sub>	7. C(9)-H 8. C(9)-OCH <sub>3</sub>

Only unsubstituted heteroyohimbine alkaloids are reported from Uncaria species, series 1, 3, 5 and 7 may be found.

However Stockigt and Zenk (153) have shown that in cell-free enzyme systems from Catharanthus roseus L. cell suspension cultures, the precursor is isovincoside C(3)-H $\alpha$ . This led Shellard, Houghton (78) and Resha to modify their hypothesis and they suggested that the major route is via the C(3)-H $\alpha$  heteroyohimbine alkaloids which are then converted primarily to the C(3)-H $\alpha$  oxindole alkaloids and these alkaloids are then converted to the C(3)-H $\beta$  heteroyohimbine alkaloids. There is probably, in addition, a minor route via the C(3)-H $\beta$  heteroyohimbine alkaloids which are converted to the oxindoles since this has been shown (78) to occur in vivo. The scheme may be shown diagrammatically as follows :-

Major routeMinor route