CHAPTER I

GENERAL INTRODUCTION

Introduction

The genus *Strychnos* in the Loganiaceae, tribe Strychneae, is organized into 12 sections (Table 1) base on more or less natural system (1-3). This genus comprises about 200 species range from forest lianes to shrubs and trees, all of which are pantropical in distribution and may be subdivided into three geographically seperated groups. There are at least 73 species which are native of south and central America (4),75 species of Africa (3,5) and 44 species of Asia and Australia (2,6-8). All of the species, except *Strychnos potatorum* Linn. which is found in both Africa and Asia (7), are clearly separated among these three continents.

In Asia, the geographical distribution of the 44 Asian *Strychnos* species currently recognized (Table 2), most species are large forest lianes, scrambling or erect shrubs, or small trees in more open vegetation. Some species, like *Strychnos lucida*, *Strychnos nux-blanda*, *Strychnos nux-vomica*, and *Strychnos potatorum*, are known only as tree; *Strychnos ignatii* is found both as a tree and as a liane; some species, like *Strychnos angustiflora*, *Strychnos ovata*, and *Strychnos rupicola*, grow as scrambling shrubs as well as

lianes; and *Strychnos cathayensis* is primarily a climbling shrub (8).

The taxonomic position of the genus *Strychnos* together with the geographical distribution of *Strychnos* species in Asian continent are summerized in table 1 and table 2 (page) respectively.

Table 1 (3)

Taxonomic Position of the Genus Strychnos within the Family Loganiaceae

Family	Tribe	Genus	Section
Loganiaceae	Spigelieae		
	Loganieae		
	Strychneae	Gardneria	
		Neuburgia	
		Strychnos	Strychnos
			Rouhamon
			Breviflorae
			Penicillatae
			Aculeatae
			Spinosae
			Brevitubae
			Lanigerae
			Phaeotrichae
			Densiflorae
			Dolichanthae
			Scyphostrychnos
	Gelsemieae		
	Plocospermeae		
	Antonieae		
	Buddlejeae		
	Retzieae		
	Potalieae		
	Desfontainieae		

Table 2 (8)

The Known Geographical Distribution of the Asian Species of *Strychnos*

Geographical Area	Species
Sri Lanka.....	*S. axillaris* Colebr
	S. benthamii C.B. Clarke
	S. coriacea Thwaites
	S. minor Dennst.
	(S. lenticellata A.W. Hill
	S. micrantha Thwaites*)*
	S. nux-vomica Linn.
	S. potatorum L.f.
	S. tetragona A.W. Hill
	S. trichocalyx A.W. Hill
	S. wallichiana Steud. ex DC.
	(S. cinnamomifolia Thwaites*)*
Indian sub-continent.....	*S. axillaris* Colebr
	S. bicirrhosa Lesch et Wall
	S. dalzellii C.B. Clarke
	S. minor Dennst.
	(S. colubrina Benth.
	S. lenticellata A.W. Hill*)*
	S. nitida G.Don *(S. kerrii* A.W. Hill
	S. wallichiana Benth.)
	S. nux-blanda A.W. Hill
	S. nux-vomica Linn.

Geographical Area	Species
Indian sub-continent.....	*S. potatorum* L.f.
	S. vanprukii Craib
	(S. aenea A.W. Hill*)*
	S. wallichiana Steud. ex DC.
	(S. cinnamomifolia Thwaites
	S. colubrina L.*)*
Andaman and Nicobar Islands....	*S. andamanensis* A.W. Hill
	S. narcondamensis A.W. Hill
	S. wallichiana Steud. ex DC.
	(S. tubiflora A.W. Hill*)*
Myanmar.....	*S. axillaris* Colebr.
	S. hypogyna C.B.Clarke
	S. minor Dennst.
	(S. laurina Wall. ex DC.*)*
	S. nitida G. Don
	(S. kerrii A.W. Hill
	S. wallichiana Benth.*)*
	S. nux-blanda A.W. Hill
	S. nux-vomica Linn.
	S. potatorum L.f.
	S. rufa var. *candollei* C.B. Clarke
	S. thorelii Pierre ex Dop.
Thailand.....	*S. axillaris* Colebr.
	(S. chloropetala A.W. Hill
	S. kawbet A.W. Hill

Geographical Area	Species
Thailand.....	*S. mucronata* A.W. Hill
	S. plumosa A.W. Hill
	S. schmidtii Gilg)
	S. curtisii King et Gamble
	S. ignatii Berg.
	(S. krabiensis A.W. Hill*)*
	S. lucida R.Br.
	(S. roborans)
	S. minor Dennst.
	(S. silvicola A.W. Hill*)*
	S. myrioneura Gilg
	S. nitida G.Don
	(S. kerrii A.W. Hill*)*
	S. nux-blanda A.W. Hill
	S. nux-vomica Linn.
	S. polyantha Pierre ex Dop.
	(S. usitata Pierre ex Dop.*)*
	S. thorelii Pierre ex Dop.
	S. vanprukii Craib
Indo-china.....	*S. angustiflora* Benth.
	(S. usitata var.cirrosa Pierre ex Dop)
	S. axillaris Colebr.
	(S. armata A.W. Hill
	S. mucronata A.W. Hill*)*

Geographical Area	Species
Indo-china.....	*S. cathayensis* Merr.
	S. dinhensis Pierre ex Dop.
	S. ignatii Berg.
	(*S. balansae* A.W. Hill)
	S. minor Dennst.
	(*S. laurina* var.thorelii Wall ex DC.)
	S. nitida G.Don
	(*S. kerrii* A.W. Hill)
	S. nux-blanda A.W. Hill
	S. nux-vomica Linn.
	(*S. spireana* Pierre ex Dop.)
	S. ovata A.W. Hill
	S. polyantha Pierre ex Dop.
	S. rupicola Pierre ex Sauvan
	(*S. donnaiensis* Pierre ex Dop.
	S. usitata Pierre ex Sauvan)
	S. thorelii Pierre ex Dop.
	S. umbellata (Lour.)Merr.
	(*S. paniculata* Champ. ex Dop.)
	S. vanprukii Craib
	(*S. nitida* Gagnep)
	S. wallichiana Steud. ex DC.
	(*S. gauthierana*
	S. pierriana)

Geographical Area	Species
South china.....	*S.angustiflora* Benth
	S. cathayensis Merr.
	S. cheliensis HU
	S. henryi Merr. et Yamamoto ex Yamamoto
	S. ignatii Berg.
	(S. hainanensis Merr. et Chun*)*
	S. ovata A.W. Hill
	(S. confertiflora Merr. et Chun*)*
	S. umbellata (Lour.)Merr.
	(S. paniculata Champ. ex Benth*)*
	S. wallichiana Steud. ex DC.
	(S. gauthierana Pierre ex Dop
	S. pierriana A.W. Hill*)*
Philippines.....	*S. angustiflora* Benth.
	S. axillaris Colebr.
	(S. cenabrei Merrill
	S. impressinervis A.W. Hill
	S. tesseroidea DC.
	S. wenzelii Merr.*)*
	S. ignatii Berg.
	S. lanata A.W. Hill
	S. luzonensis Elmer
	S. minor Dennst.
	(S. dubia De Wild.
	S. forbesii A.W. Hill

Geographical Area	Species
	S. merrillii A.W. Hill
	S. multiflora Benth.
	S. similis A.W. Hill)
	S. oleifolia A.W. Hill
	S. ovata A.W. Hill
	(*S. panayensis*)
Malaysia(incl.Singapore)....	*S. axillaris* Colebr.
	(*S. malaccensis* Benth in Linn.
	S. penicillata A.W. Hill
	S. pubescens C.B. Clark
	S. quintuplinervis A.W. Hill
	S. scortechinii A.W. Hill)
	S. curtisii King et Gamble
	S. flavescens King et Gamble
	S. ignatii Berg.
	(*S. ovalifolia* Wall.)
	S. maingayi C.B. Clarke
	S. minor Dennst.
	(*S. septemnervis* C.B. Clarke)
	S. ridleyi King et Gamble
	S. rufa C.B. Clarke
	S. thorelii Pierre ex Dop.
	S. vanprukii Craib
	(*S. quadrangularis* A.W. Hill)

Geographical Area	Species
	S. villosa A.W. Hill
	(S. hirsutiflora A.W. Hill*)*
Borneo.....	*S. axillaris* Colebr.
	(S. pubescens C.B. Clarke*)*
	S. borneensis Leenh.
	S. flavescens King et Gamble
	S. ignatii Berg.
	(S. cuspidata A.W. Hill
	S. ovalifolia Wall*)*
	S. minor Dennst.
	(S. laurina Wall ex DC.*)*
	S. ovata A.W. Hill
	S. polytrichantha Gilg
	S. vanprukii Craib
	(S. maingayi subsp. borneensis C.B.Clarke)
	S. villosa A.W. Hill
Indonesia(incl. Borneo and western New Guinea).....	*S. axillaris* Colebr.
	(S. horsfieldiana Miq.
	S. monosperma Stokes
	S. palembanica Miq.
	S. robinsonii A.W. Hill*)*
	S. flavescens King et Gamble
	S. ignatii Berg.

Geographical Area	Species
Indonesia (incl. Borneo and western New Guinea).....	*S. lanceolaris* Miq.
	S. tieute Lesch.)
	S. lucida R. Br.
	(*S. ligustrina*)
	S. minor Dennst.
	(*S. barbata* A.W. Hill
	S. laurina Wall. ex DC.)
	S. ovata A.W. Hill
	(*S. lanceolaris* Miq.)
	S. villosa A.W. Hill
New Guinea and islands to the east.....	*S. axillaris* Colebr.
	(*S. oophylla* Gilg et Bened
	S. polytoma Gilg et Bened)
	S. ledermannii Gilg et Bened
	S. melanocarpa Gilg et Bened
	S. minor Dennst.
	(*S. barbata* A.W. Hill
	S. cinnamophylla Gilg et Bened
	S. kerstingii Gilg et K. Schum
	S. leuconeura Gilg et Bened
	S. myriantha Gilg et Bened
	S. pycnoneura Gilg et Bened)

Geographical Area	Species
Tropical Australia.....	*S. axillaris* Colebr.
	(S. arborea A.W. Hill
	S. psilosperma F.Muell
	S. lucida R. Br.)
	S. minor Dennst.
	(S. bancroftiana F.M. Bail*)*
Fiji Islands.....	*S. vitiensis* A.W. Hill

Plants belonging to the genus *Strychnos* have long been known as sources of powerfully acting alkaloids. Their physiological activities attracted the attention of chemists and pharmacists from early times, and as a result, many alkaloids have been found in the 100 years.

As the plant species in a single family or genus often produce bases of at least biogenetically similar structures, they have been conveniently classified by origin as well as by structural types. With the concept of biogenesis, another type of classification was developed. This is more useful in visualizing the relationship of groups already classified by structural types. A route biosynthetic view of alkaloids and related compounds is shown in Figure 1 (9).

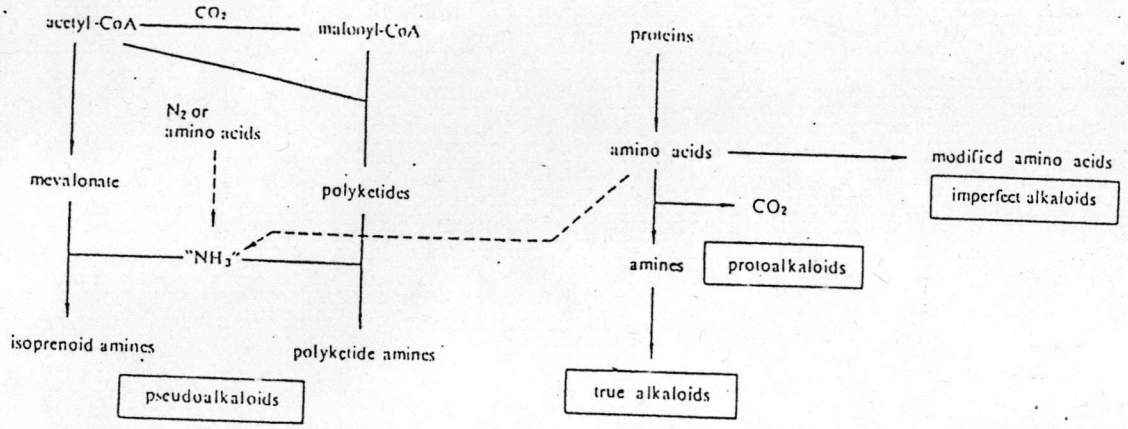


Figure 1 : Biosynthetic diagram of alkaloids and closely related compounds

The major constituents in the *Strychnos* plants are complex indole alkaloids, of which more than 350 alkaloids have been isolated (10). Many studies (3-5, 11-12) have been carried out to establish the types and structures of alkaloids responsible for correlate to their pharmacological and toxicological activities.

Strychnos Species in Thailand

Among 44 recorded Asian *Strychnos* species, at least 20 *Strychnos* species have been collected in Thailand. Bisset et al. (7) carried out the taxonomic revision of those Asian *Strychnos* species and adjusted them into 13 species. This is

due to the fact that they are including either synonyms or forms of the accepted known species. Smitinand(13) recorded the presence of 12 species of *Strychnos* in Thailand, ten of which are consistent with Bisset et al.' consideration (7,8). The two remaining species, *Strychnos colubrina* Linn. and *Strychnos kerrii* A.W. Hill with according to Bisset et al.(7) are the synonymous of *Strychnos wallichiana* Steud.Ex DC. and *Strychnos nitida* G.Don, respectively. In conclusion, there are at least 14 *Strychnos* species growing in Thailand and these currently accepted species are in accordance with 4 botanical sections : *Strychnos*, *Penicillatae*, *Brevitubae* and *Lanigerae* (14).

Table 3 (7, 13)

Strychnos Species Growing in Thailand

Section	Species	Well-known vernacular name
Strychnos	*Strychnos ignatii* Berg.	Phaya mue lek
	(*Strychnos krabiensis* A.W. Hill)	(พญามือเหล็ก)
	Strychnos lucida R.Br.	Phaya muun lek
	(*Strychnos roborans* A.W. Hill)	(พญามูลเหล็ก)
	Strychnos nitida G. Don	Kluai khieo
	(*Strychnos kerrii* A.W. Hill)	(กล้วยเขียว)
	Strychnos nux-blanda A.W. Hill	Tuumkaa khaao (ตูมกาขาว)
	Strychnos nux-vomica Linn.	Salaeng chi (แสลงใจ)

Table 3 (continue)

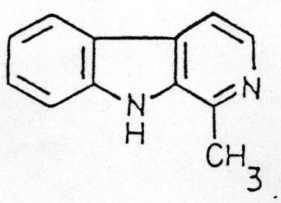
Section	Species	Well-known vernacular name
Strychnos	*Strychnos rupicola* Pierre ex Dop.	Kheekaa khruea
	(*Strychnos usitata* Pierre ex Dop.)	(ขี้กาเครือ)
	Strychnos wallichiana Steud. ex DC.	Thao plong
	(*Strychnos colubrina* Linn.)	(เถาปลอง)
Penicillatae	*Strychnos axillaris* Colebr.	Khwaak kai
	(*Strychnos chloropetala* A.W. Hill	(ขวากไก่)
	Strychnos kawbet A.W. Hill	
	Strychnos mucronata A.W. Hill	
	Strychnos plumosa A.W. Hill	
	Strychnos schmidtii Gilg	
	Strychnos viridiflora A.W. Hill)	
Brevitubae	*Strychnos vanprukii* Craib	Thao Chaang (เถาช้าง)
Lanigerae	*Strychnos curtisii* King et Gamble	
	Strychnos myrioneura Gilg	
	Strychnos minor Dennst.	Tum kaa daeng
	(*Strychnos beddomei* Clarke)	(ตูมกาแดง)
	(*Strychnos sivicola* A.W. Hill)	
	Strychnos polyantha Pierre ex Dop.	
	Strychnos thorelii Pierre ex Dop.	Sa-eng (สะเอ็ง)

The Strychnos Alkaloids

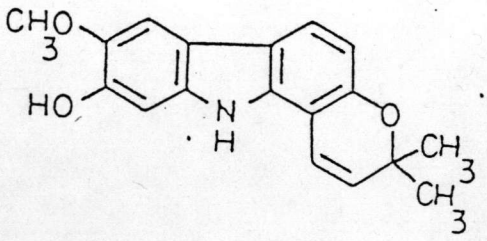
Strychnos, the largest of the four genera of the Loganiaceae have representative which contain indole alkaloids. The number of the structurally known indole alkaloids today amounts approximately to 1,200. The indole alkaloids are defined as the natural products containing either the indole nucleus, or an oxidized, reduced or substituted equivalent of it (15).

With respect to their structural features, the indole alkaloids can be divided into two main classes. The first class is that of the simple indole alkaloids. They do not present a structural uniformity, having only the indole nucleus or a direct derivative of it as a common feature. Depending upon the constitution of the rest of the molecule, their occurrences is either distributed in many plant families e.g. harman , or restricted to very few or only one family e.g. koenigine (Fig. 2).

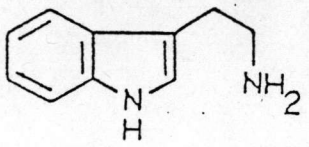
The indole bases of the second class contain two structure-elements: tryptamine with the indole nucleus and a C_9- or C_{10}-monoterpene moiety, derived from secologanin (Fig. 2). Very probably, because of both of the common components and the biogenetic relationships, the occurrence of this second class of indole alkaloids is more specific and thereby suitable for comparative chemotaxonomic considerations (16).



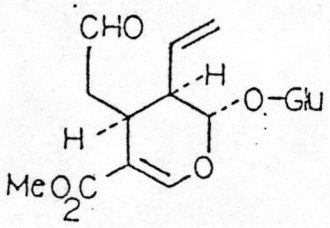
a Harman



b Koenigine



c Tryptamine



d Secologanin

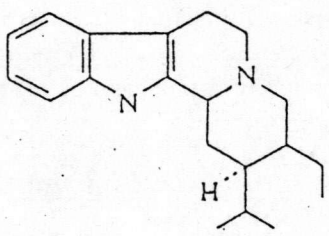
Figure 2 : Structural features of simple indole (a,b) together with precursors of the second class indole alkaloids (c,d)

The indole alkaloids derived from tryptamine and secologanin can be classified into 8 types, according to the structural characteristics of their skeletons. These types are (Fig.3): Corynanthean (C-type) e.g. sarpagine, yohimbine, ajmalicine, picraline; Vincosan (D-type) e.g. vincosidine, talbotine; Vallesiachotaman (V-type) e.g. vallesiachotamine; Strychnan (S-type) e.g. vomicine, akuammicine; Aspidospermatan (A-type) e.g. condylocarpine, aspidospermatine; Eburnan (E-type) e.g. vincamine, dichotine; Plumeran (P-type) e.g. kopsine, aspidospermidine, tabersonine; and Ibogan (J-type) e.g. voaluteine, ibogaine, pseudoasidospermine (16). In addition, the

combination between the two units of the same or the different indole alkaloid types would generate the bisindole alkaloid skeletons.

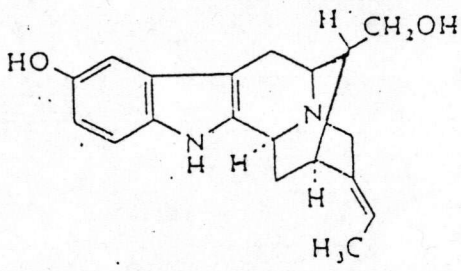
The indole alkaloids belonging to the *Strychnos* species are comprised with 5 types of alkaloids, they are the C-, D-, V-, S-, and A-types. The most abundant alkaloids in the genus are of the S-type and the lesser ones are of the C-type (10).

Alkaloid-type

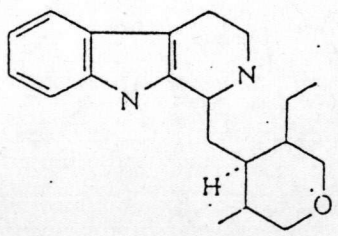


Corynanthean (C-type)

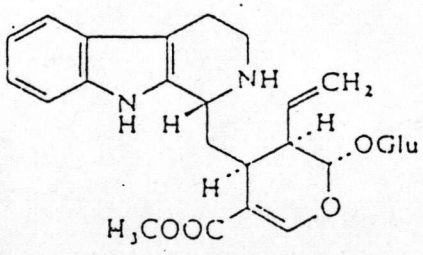
Examples



Sarpagine



Vincosan (D-type)

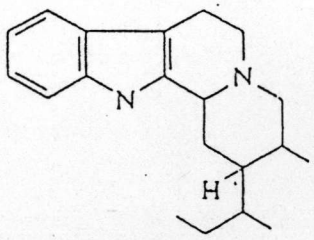


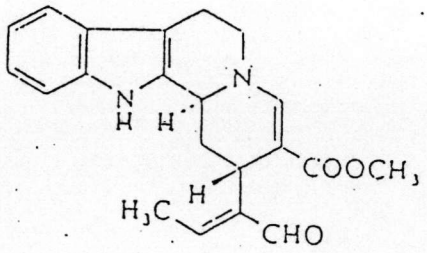
Vincoside

Figure 3 The skeletal types with corresponding examples of alkaloids

Alkaloid-types

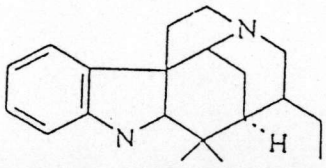
Examples

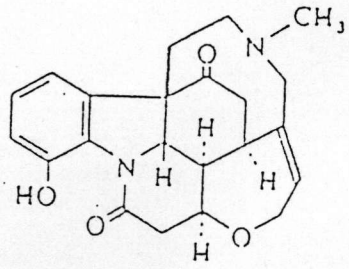




Vallesiachotaman (V-type)

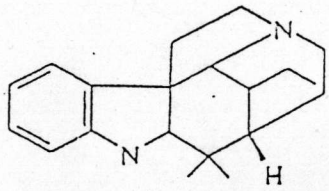
Vallesiachotamine

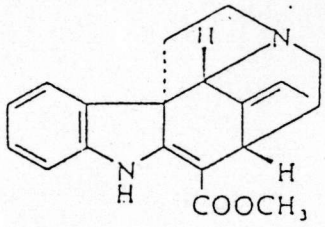




Strychnan (S-type)

Vomicine





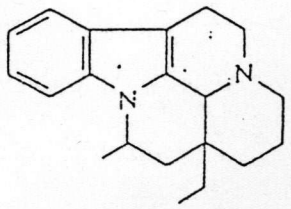
Aspidospermatan (A-type)

Condylocarpine

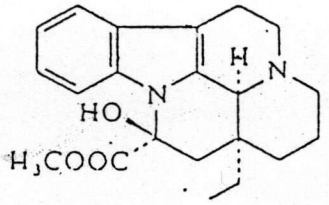
Figure 3 The skeletal types with corresponding examples of alkaloids (cont.)

Alkaloid-types

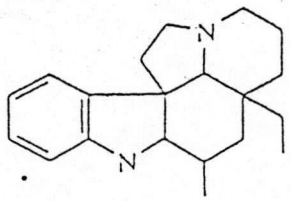
Examples



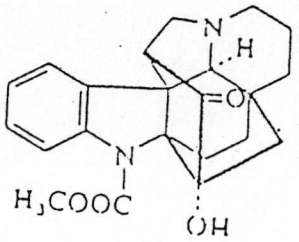
Eburnan (E-type)



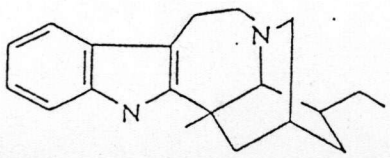
Vincamine



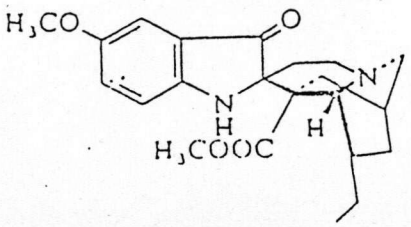
Plumeran (P-type)



Kopsine



Ibogan (J-type)



Voaluteine

Figure 3 The skeletal types with corresponding examples of alkaloids (cont.)

According to the above classifications (3,10,17) *Strychnos* alkaloids could be arranged into 2 main classes; monomeric indole alkaloids and bisindole alkaloids. Furthermore, monomeric indole alkaloids are subdivided into 6 types, five of which can be clearly differentiated while the rest is put in the miscellaneous alkaloids (M-type) (Table 4). Bisindole alkaloids which including the various combination products of monomeric indole alkaloids are subdivided into 2 types, there are symmetric bisindole alkaloids of the Strychnan-Strychnan type (S-S type) and asymmetric bisindole alkaloids of Strychnan-Corynanthean type (S-C type). All types of *Strychnos* alkaloids (as shown in Table 4) are further subdivided into two or more groups which are designed especially for the alkaloids of this genus. Basing on this division, it is hoped to give a more information covering their chemotaxonomic significant (14).

Table 4 Subdivision of the Main Types of Strychnos Alkaloids (14)

Class	Subdivision
Monomeric indole alkaloids	
Corynanthean (C-type)	Group C_1 : E-seco indole group
	Group C_2 : Ajmalicine group
	Group C_3 : Yohimbine group
	Group C_4 : Akagerine group
	Group C_5 : Mavacurine group
	Group C_6 : Sarpagine group
	Group C_7 : Oxindole group

Table 4 Subdivision of the Main Types of Strychnos Alkaloids

(cont.)

Class	Subdivision
Vincosan (D-type)	Group D_1 : Strictosidine group
	Group D_2 : Decussine group
Vallesiachotaman (V-type)	Group V_1 : Antirhine group
	Group V_2 : Angustine group
Strychnan (S-type)	Group S_1 : Retuline group
	Group S_2 : Diaboline group
	Group S_3 : Isostrychnine group
	Group S_4 : Strychnine group
	Group S_5 : Spermostrychnine group
	Group S_6 : Tsilanine group
Aspidospermatan (A-type)	Group A_1 : Condylocarpine group
Miscellaneous (M-type)	Group M_1 : Ngouniensine group
	Group M_2 : Olivacine group
Bisindole alkaloids	
	Group B_1 : Retuline-Retuline (S_1-S_1) group
Strychnan-Strychnan (S-S type)	Group B_2 : Diaboline-Diaboline (S_2-S_2) group
	Group B_3 : Retuline-Diaboline (S_1-S_2) group

Table 4 Subdivision of the Main Types of Strychnos Alkaloids

(cont.)

Class	Subdivision
Strychnan-Strychnan--------Group B_4 (S-S type)	: Isostrychnine-Isostrychnine (S_3-S_3) group
Strychnan-Corynanthean-----Group B_5 (S-C type)	: Diaboline-E-seco indole (S_2-C_1) group

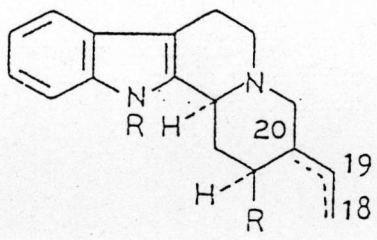
Various skeletons of *Strychnos* alkaloids together with their representatives are listed as follows.

Monomeric Indole alkaloids

1. Corynanthean type (C-type)

Group C_1 (E-seco indole group)

Geissoschizine and others



1 Geissoschizine

(R = $-C(CO_2CH_3)=CHOH$; Δ 19,20)

2 Geissoschizal

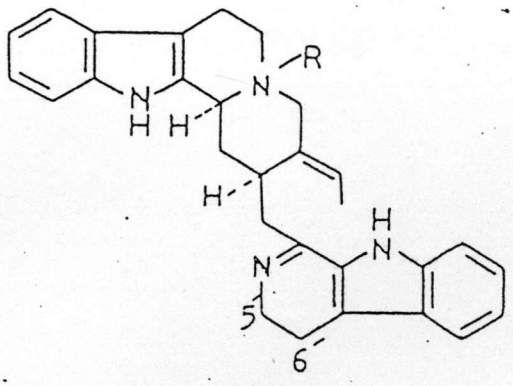
(R = $-CH_2-CHO$; Δ 19,20)

3 De-carbomethoxy-geissoschizine

(R = $=CH=CHOH$; Δ 19,20)

4 Normelinonine B

(R = $-CH_2-CH_2OH$; Δ 18,19)



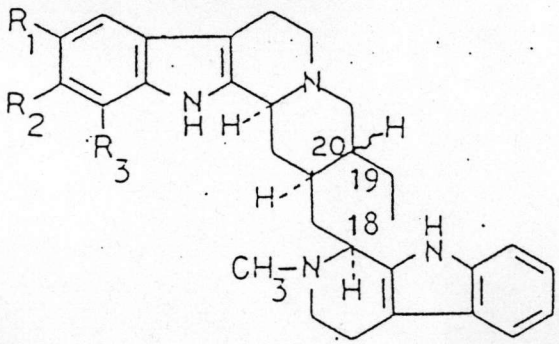
Usambarensine and others

5 Usambarensine

(R = H; 5',6')

6 N_b-Methyl-usambarensine

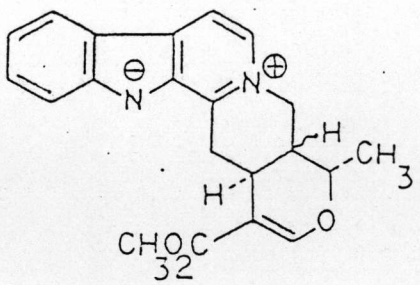
(R = CH_3; 5',6')



7 Usambarine

(R_1 = R_2 = R_3 = H; 20-β-H; Δ 18,19)

Group C_2 (Ajmalicine group)



Ajmalicine and others

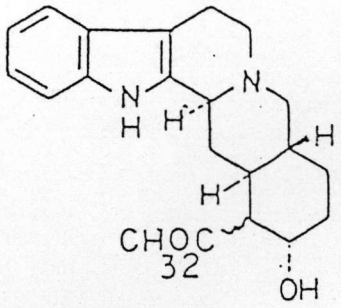
8 Alstonine

(20-α-H)

9 Serpentine

(20-β-H)

Group C_3 (Yohimbine group)



Yohimbine and others

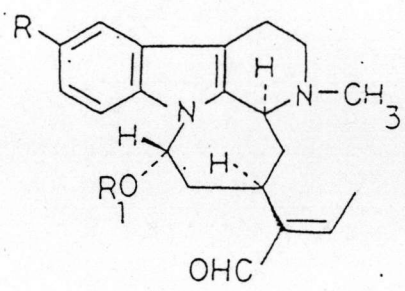
10 α-Yohimbine

(16-α-$COOCH_3$)

11 β-Yohimbine

(16-β-$COOCH_3$)

Group C_4 (Akagerine group)



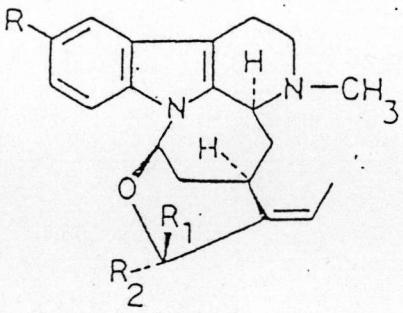
Akagerine and others

12 Akagerine

(R = R_1 = H)

13 17-*O*-Methyl-akagerine

(R = H, R_1 = CH_3)



Kribine and others

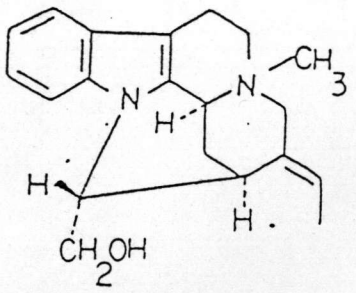
14 Kribine

(R = R_2 = H; R_1 = OH)

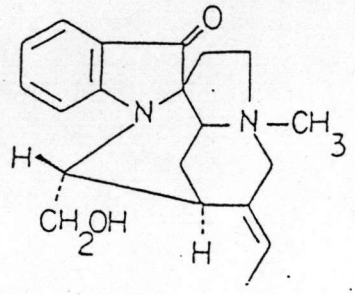
15 21-*O*-Methyl-kribine

(R = R_2 = H; R_1 = OCH_3)

Group C_5 (Mavacurine group)



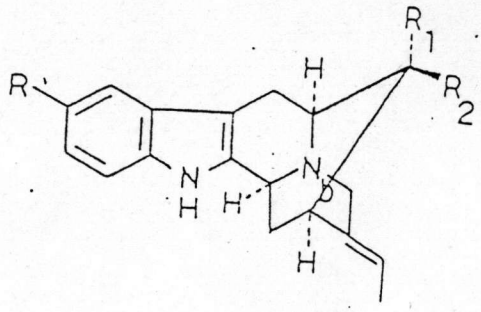
16 Mavacurine



17 C-Fluorocurine

(Pseudoindoxyl-mavacurine)

Group C_6 (Sarpagine group)



Sarpagine and others

18 Sarpagine

(R = OH, R_1 =H, R_2 = CH_2OH)

19 Macusine B

(R = R_1 = H, R_2 = CH_2OH; N_b^+-CH_3)

20 Normacusine B

(R = R_1 = H, R_2 = CH_2OH)

21 O-Methylmacusine B

(R = R_1 = H, R_2 = CH_2OCH_3; N_b^+-CH_3)

22 16-Epi-O-methyl macusine B

(R = R_2 = H, R_1 = CH_2OCH_3; N_b^+-CH_3)

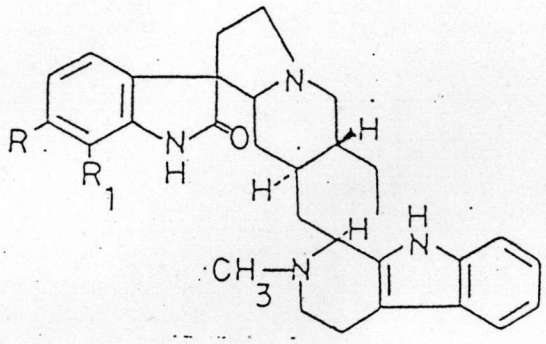
23 Akuammidine

(R = H, R_1 = CH_2OH, R_2 = CO_2CH_3)

24 Polyneuridine

(R = H, R_1 = CO_2CH_3, R_2 = CH_2OH)

Group C_7 (Oxindole group)



Strychnofoline and others

25 Strychnofoline

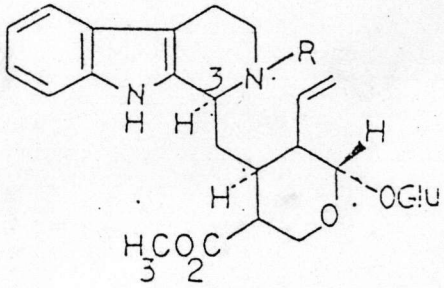
(R = OH, R_1 = H; Δ 18,19)

26 Oxindole I 7R

(R = R_1 = H; 19R)

2. Vincosan type (D-type)

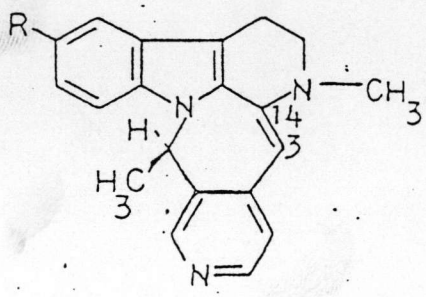
Group D_1 (Strictosidine group)



27 Dolichantoside

(R = CH_3 , 3-α-H)

Group D_2 (Decussine group)



Decussine and others

28 Decussine

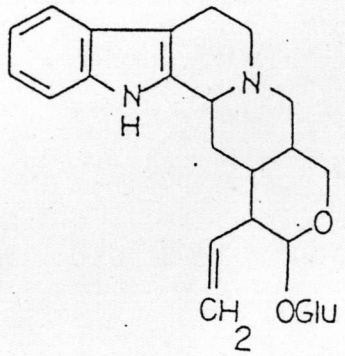
(R = H)

29 3,14-Dihydro-decussine

(R = H; 3,14-dihydro)

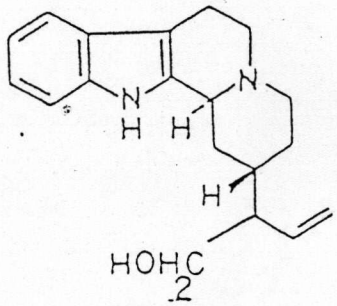
3. Vallesiachotaman type (V-type)

Group V_1 (Gluco alkaloids group)



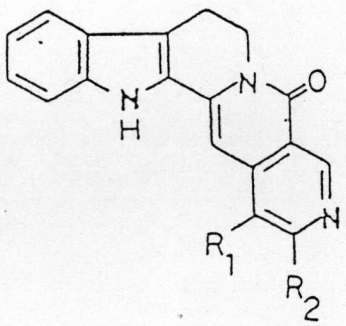
30 *Strychnos decussata* glucoalkaloid

Group V_2 (Antirhine group)



31 Antirhine

Group V_3 (Angustine group)



Angustine and others

32 Angustine

(R_1 = H, R_2 = $-CH=CH_2$)

33 Angustidine

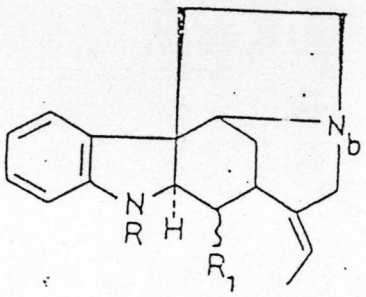
(R_1 = CH_3, R_2 = H)

34 Angustoline

(R_1 = H, R_2 = $-CH(OH)-CH_3$)

4. Strychnan type (S-type)

Group S_1 (Retulline)



Normal series

35 Retuline

(R = $COCH_3$, R_1 = α-CH_2OH)

36 Isoretuline

(R = $COCH_3$, R_1 = β-CH_2OH)

37 Acetyl-retuline

(R = $COCH_3$, R_1 = α-CH_2-$OCOCH_3$)

38 Retuline N-oxide

(R = $COCH_3$, R_1 = α-CH_2OH; N_b->O)

39 Akaummicine

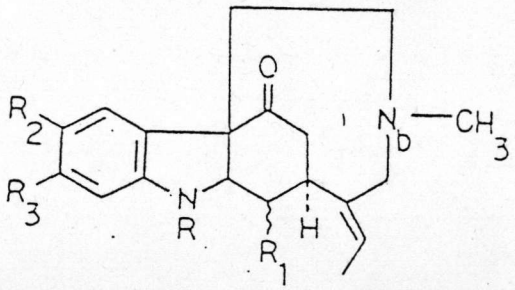
(R = H, R_1 = CO_2CH_3)

40 18-Desoxy-Wieland-Gumlich aldehyde

(R = H; R_1 = CHO; Δ 2,16;19-20-dih

41 Fluorocurarine

(R = H, R_1 = CHO; Δ2,16; N_b^+-CH_3)

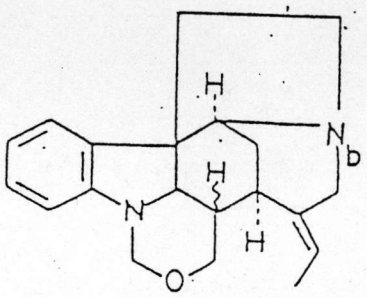


N-methyl-sec-pseudo series

42 Strychnosilidine

(R = $COCH_3$, R_1 = α-$CH_2CO_2CH_3$,

R_2 = R_3 = OCH_3)



Rosibiline and isomer

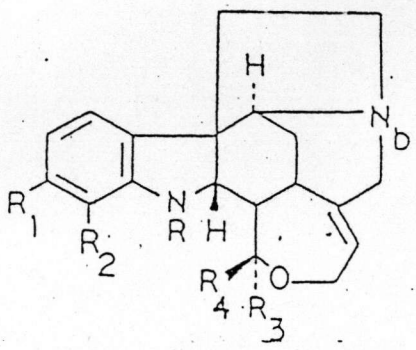
43 Rosibiline

(16-β-H)

44 Isorosibiline

(16-α-H)

Group S_2 (Diaboline group)



Diaboline and others

45 Wieland-Gumlich aldehyde (WGA)

($R = R_1 = R_2 = R_3 = H$, $R_4 = OH$)

46 Condensamine

($R = COCH_3$, $R_1 = OCH_3$, $R_2 = R_4 = H$, $R_3 = -OCOCH_3$)

47 Diaboline

($R = COCH_3$, $R_1 = R_2 = R_3 = H$, $R_4 = OH$)

48 Ethyldiaboline (Diaboline ethyleth

48a ($R = COCH_3$, $R_1 = R_2 = R_3 = H$, $R_4 = 17\text{-}\alpha\text{-}OEt$)

48b ($R = COCH_3$, $R_1 = R_2 = R_4 = H$, $R_3 = 17\text{-}\beta\text{-}OEt$)

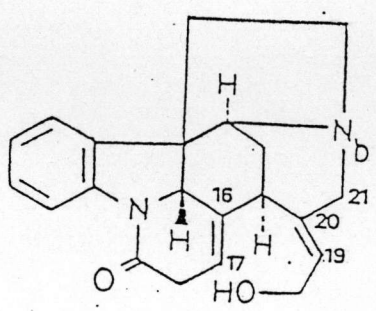
49 11-Methoxydiaboline

($R = COCH_3$, $R_1 = OCH_3$, $R_2 = R_3 = H$, $R_4 = OH$)

50 *O*-Acetyl diaboline

($R = COCH_3$, $R_1 = R_2 = R_3 = H$, $R_4 = -OCOCH_3$)

Group S_3 (Isostrychnine group)



Isostrychnine and others

51 Isostrychnine ($\Delta 19,20$)

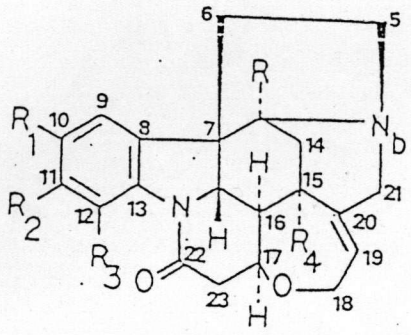
52 19,20-Dihydroisostrychnine

(19,20-dihydro)

53 Protostrychnine

(16-α-, 17-β-dihydro, 17-β-OH)

Group S_4 (Strychnine group)



[N-->O] = N-oxide series

3-α-H = normal series

3-α-OH =pseudo series

Normal and pseudo series

54 Strychnine ($R=R_1=R_2=R_3=R_4=H$)

55 Brucine ($R=R_3=R_4=H$, $R_1=R_2=OCH_3$)

56 α-Colubrine ($R=R_1=R_3=R_4=H$, $R_2=OCH_3$)

57 β-Colubrine ($R=R_2=R_3=R_4=H$, $R_1=OCH_3$)

58 10-Hydroxystrychnine ($R=R_2=R_3=R_4=H$, $R_1=OH$)

59 12-Hydroxystrychnine ($R=R_1=R_2=R_4=H$, $R_3=OH$)

60 15-Hydroxystrychnine ($R=R_1=R_2=R_3=H$, $R_4=OH$)

61 12-Hydroxy-11-methoxystrychnine ($R=R_1=R_4=H$, $R_2=OCH_3$, $R_3=OH$)

62 Strychnine N-oxide ($R=R_1=R_2=R_3=R_4=H$; N_b-->O)

63 12-Hydroxystrychnine N-oxide ($R=R_1=R_2=R_4=H$, $R_3=OH$; N_b-->O)

64 Brucine N-oxide ($R=R_3=R_4=H$, $R_1=R_2=OCH_3$; N_b-->O)

65 Pseudostrychnine ($R=OH$, $R_1=R_2=R_3=R_4=H$)

66 Pseudobrucine (R=OH, R_1=R_2=OCH_3, R_3=R_4=H)

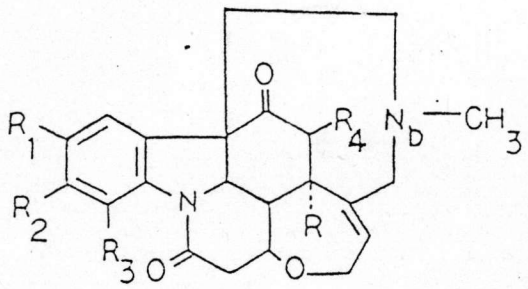
67 N-Methylstrychninium (R=R_1=R_2=R_3=R_4=H; N_b^+-CH_3)

68 3,12-Dihydroxystrychnine (R=R_3=OH, R_1=R_2=R_4=H)

69 3,12-Dihydroxy-11-methoxystrychnine (R=R_3=OH, R_1=R_4=H, R_2=OCH_3)

70 Pseudo-α-colubrine (R=OH, R_1=R_3=R_4=H, R_2=OCH_3)

71 Pseudo-β-colubrine (R=OH, R_1=OCH_3, R_2=R_3=R_4=H)



[N_b-CN] = N-cyano series

N-methyl-sec-pseudo series (3 keto-group)

72 Icajine (R=R_1=R_2=R_3=R_4=H)

73 Novacine (R=R_3=R_4=H, R_1=R_2=OCH_3)

74 Vomicine ($R=R_1=R_2=R_4=H$, $R_3=OH$)

75 14-Hydroxyicajine ($R=R_1=R_2=R_3=H$, $R_4=OH$)

76 14-Hydroxynovacine ($R=R_3=H$, $R_1=R_2=OCH_3$, $R_4=OH$)

77 15-Hydroxyicajine ($R=OH$, $R_1=R_2=R_3=R_4=H$)

78 15-Hydroxynovacine ($R=OH$, $R_1=R_2=OCH_3$, $R_4=H$)

79 11-Methoxyicajine ($R=R_1=R_3=R_4=H$, $R_2=OCH_3$)

80 N-Methyl-sec-pseudo-β-colubrine ($R=R_2=R_3=R_4=H$, $R_1=OCH_3$)

81 Icajine N-oxide ($R=R_1=R_2=R_3=R_4=H$, $N_b\text{-->}O$)

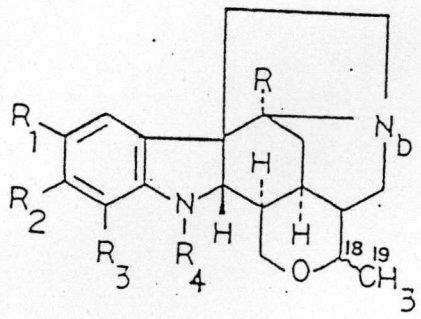
82 12-Hydroxy-11-methoxy-N-methyl-sec-pseudostrychnine
($R=R_1=R_4=H$, $R_2=OCH_3$, $R_3=OH$)

83 N-cyano-sec-pseudo-colubrine
($R=R_2=R_3=H$, $R_1=OCH_3$; N_b-CN),or
($R=R_1=R_3=H$, $R_2=OCH_3$; N_b-CN)

84 N-cyano-sec-pseudostrychnine ($R=R_1=R_2=R_3=H$; N_b-CN)

85 N-cyano-sec-pseudobrucine ($R=R_3=R_4=H$, $R_1=R_2=OCH_3$; N_b-CN)

Group S_5 (Spermostrychnine group)



normal and pseudo series

86 Spermostrychnine

($R = R_1 = R_2 = R_3 = H$;

$R_4 = COCH_3$; 18-β-CH_3)

87 Strychnospermine

($R = R_1 = R_2 = H$,

$R_3 = OCH_3$, $R_4 = COCH_3$;

18-β-CH_3)

88 Strychnosplendine

($R = OH$,

$R_1 = R_2 = R_3 = R_4 = H$;

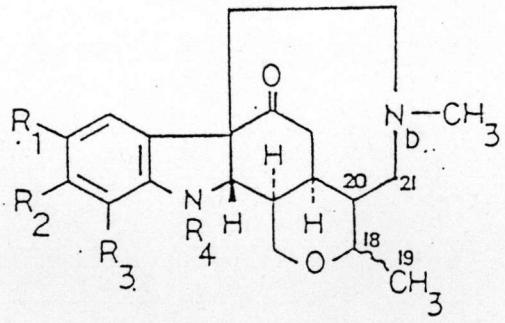
18-β-CH_3)

89 Isostrychnosplendine

($R = OH$,

$R_1 = R_2 = R_3 = R_4 = H$;

18-α-CH_3)



N-methyl-sec-pseudo series

90 Strychnofendlerine

($R_1 = R_2 = R_3 = R_4 = H$;

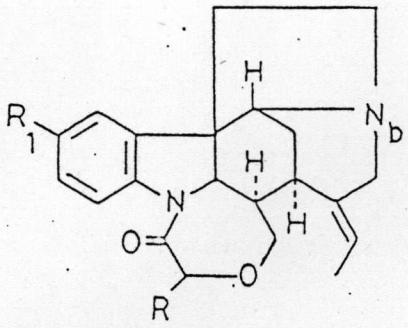
18-β-CH_3)

91 Strychnobresaline

($R_1 = R_2 = R_3 = R_4 = H$;

18-β-CH_3; Δ 20,21)

Group S_6 (Tsilanine group)



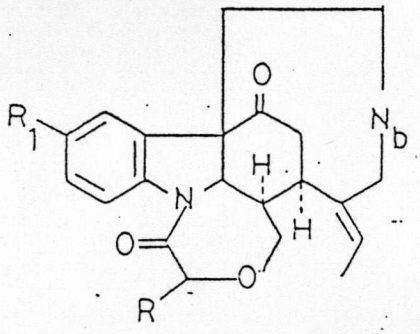
Normal series

92 Tsilanine

($R = OCH_3$, $R_1 = H$)

93 10-Methoxytsilanine

($R = R_1 = OCH_3$)



N-methyl-sec-pseudo series

94 Holstiine

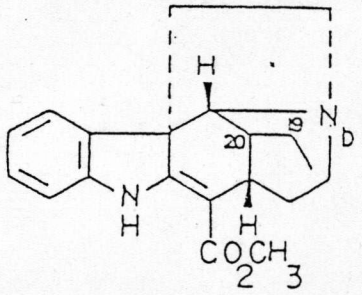
($R = OH$, $R_1 = H$)

95 Rindline

($R = R_1 = OCH_3$)

5. Aspidospermatan type (A-type)

Group A_1 (Condylocarpine group)



96 Condylocarpine

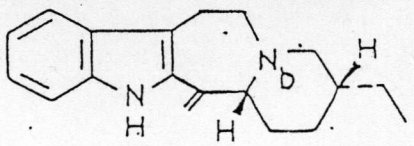
(Δ19,20)

97 Tubotaiwine

(19,20-dihydro)

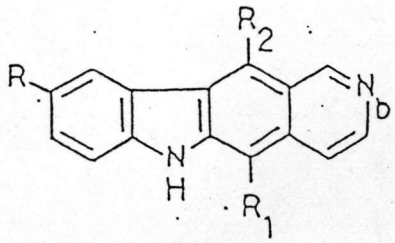
6. Miscellaneous type (M-type)

Group M_1 (Ngouniensine group)



98 Ngouniensine

Group M_2 (Olivacine group)



Ellipticine and others

99 Ellipticine

($R = H$, $R_1 = R_2 = CH_3$)

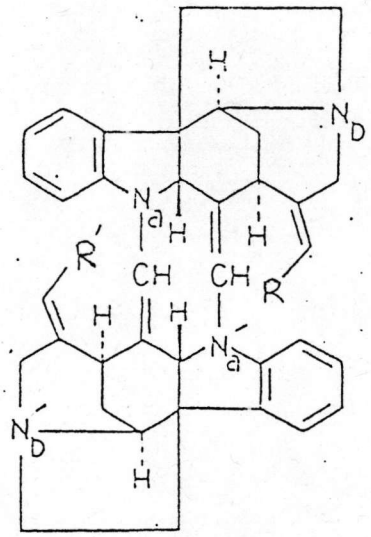
100 Ellipticine N_b-oxide

($R = H$, $R_2 = R_3 = CH_3$, $N_b \rightarrow O$)

Bisindole alkaloids

1. Strychnan-Strychnan type (S-S type)

Group B_1 (Retuline-Retuline group) (S_1-S_1)



Dihydrotoxiferine and derivatives (101-105)

101 Toxiferine

($R = R' = CH_2OH$; N_b^+-CH_3; N'_b-CH_3)

102 Dihydrotoxiferine

($R = R'$ CH_3; N_b^+-CH_3; $N'_b{}^+$-CH_3)

103 Bisnordihydrotoxiferine (R = R'= CH_3)

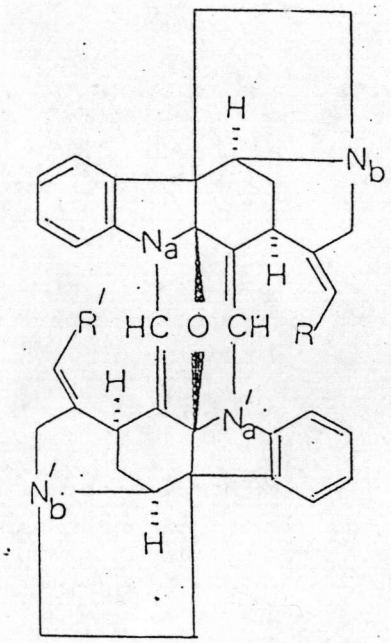
104 Bisnordihydrotoxiferine di N_b-oxide

(R =R'=CH_3; $\underline{N}_b$->O; $\underline{N}'_b$->O)

105 Bisnor-C-alkaloid H

(R = CH_2OH, R' = CH_3)

Only the part indicating the diffrence among the representatives alkaloids (106-110) will be shown here.



C-Curarine and derivatives

(106-108)

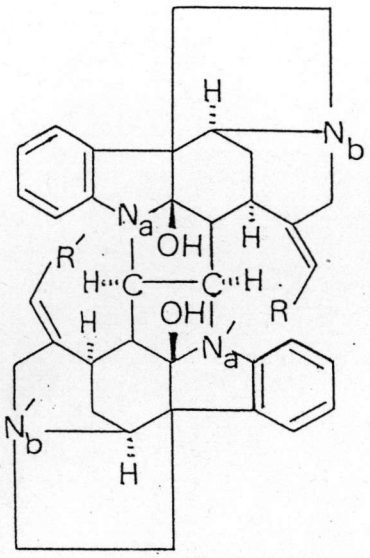
106 C-Curarine

(R = R' = CH_3; $\underline{N}_b^+$-CH_3; $\underline{N}_b^+$-CH_3)

107 Bisnor-C-Curarine (R = R' = CH_3)

108 C-alkaloid E

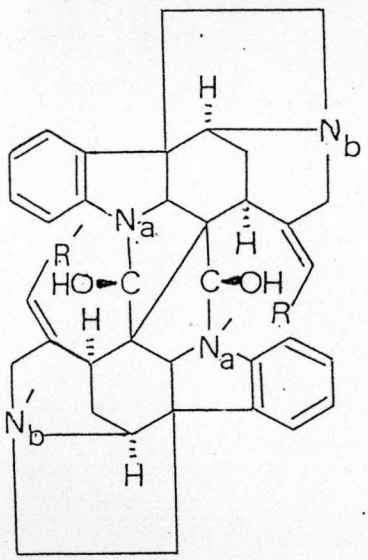
(R = R' = CH_2OH; $\underline{N}_b^+$-CH_3)



C-Calebassine (109)

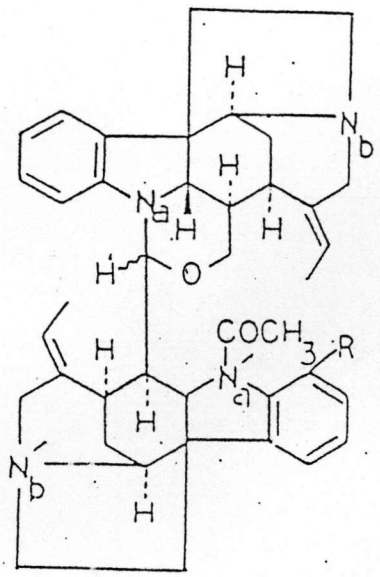
109 C-Calebassine

(R = R' = CH_3; $\underline{N}_b^+$-CH_3; $\underline{N}'_b{}^+$-CH_3)



Bisnor-C-Alkaloid D(110)

110 Bisnor-C-alkaloid D (R = R' = CH_3)



Strychnobiline and others

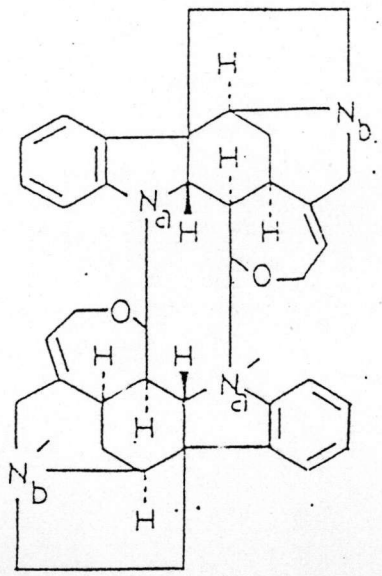
111 Strychnobiline

(R = H, 17-β-H)

112 Isostrychnobiline

(R = H, 17-α-H)

Group B_2 (Diaboline-Diaboline group) (S_2-S_2)



Caracurine and others

113 Caracurine V

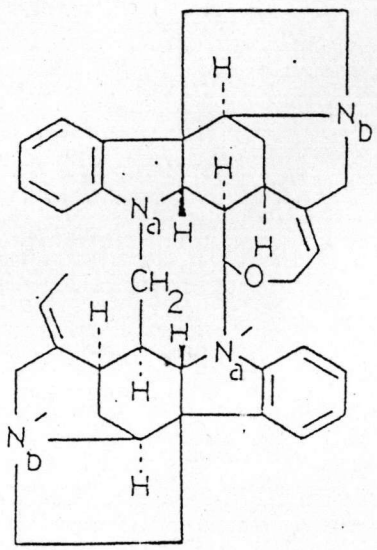
114 Caracurine V mono N-oxide

(N_b-->O)

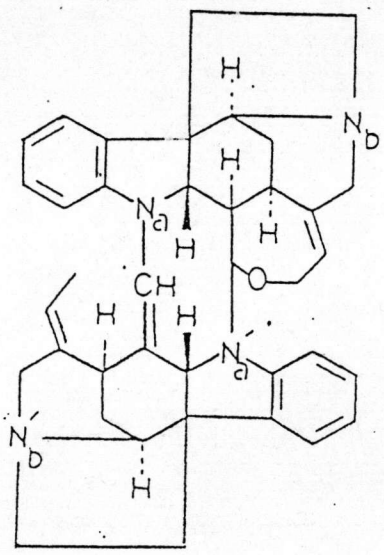
115 Caracurine V di N-oxide

(N_b-->O, N'_b--O)

Group B_3 (Retuline-Diaboline group) (S_1-S_2)

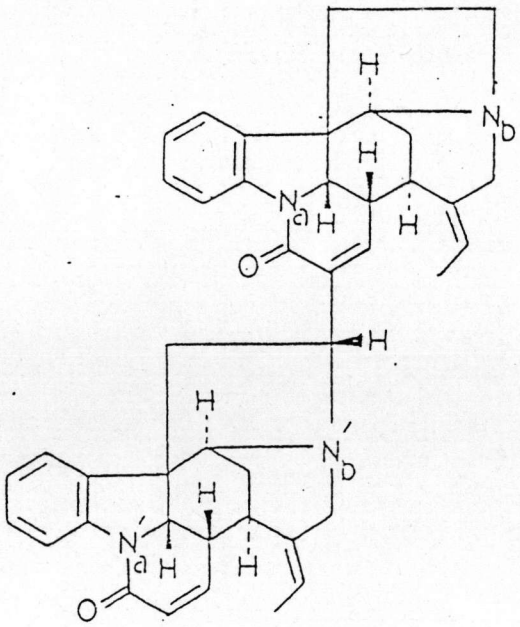


116 Dolichocurine



117 Dolichothyrine

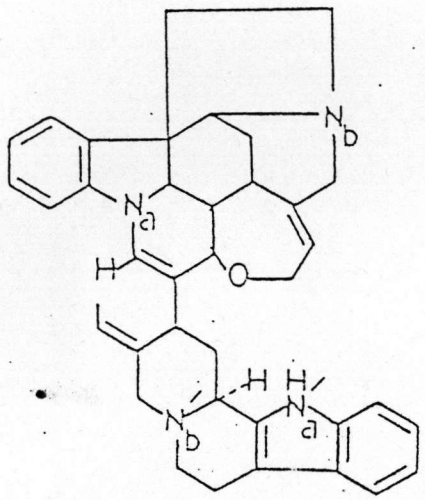
Group B_4 (Isostrychnine-Isostrychnine group) (S_3-S_3)



118 Sungucine

2. Strychnan-Corynanthean type (S-C type)

Group B_5 (Diaboline-E-seco indole group) (S_2-C_1)



119 Longicaudatine

Biosynthesis of Strychnos Alkaloids

Plants must synthesize secondary metabolites from primary ones. A knowledge of biosynthetic processes can permit us, at least in principle to manipulate the production of metabolites.

Classification of compounds from plants is usually on a structural basis, which in turn, consciously or unconsciously, has biogenetic connections. There are several good reasons for classification in this way, extending from the very simple fact that it is easier to remember formulae in relation to variations in a major theme, to the importance of considering natural assemblages of related substances such as plant indole alkaloids in terms of possible alternations in the nature or ratios of

components. Such knowledge assists the search for new and desirable plant varieties and for trace components of predictable types. It also assists in assigning structures to new compounds.

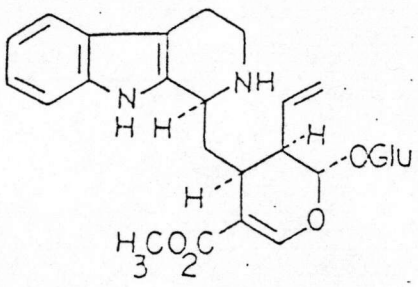
The simple basis for the biosynthesis of alkaloids in the plant cell is that a few common amino acids can be converted simply into reactive intermediates which may then condense spontaneously in variants of the Mannich reaction to yield, virtually at a stroke , the fully elaborated nuclei of the alkaloids(18).

The biogenetic pathway of *Strychnos* alkaloids is starting from tryptamine 120 and secologanin 121. The typical route of the alkaloid biosynthesis is *Strychnos* species has been indicated by Heimberger and Scott (19). The overall pathway has proceeded *via* strictosidine 122, geissoschizine 1, dehydro-preakuammicine 123 and Wieland-Gumlich aldehyde 45.

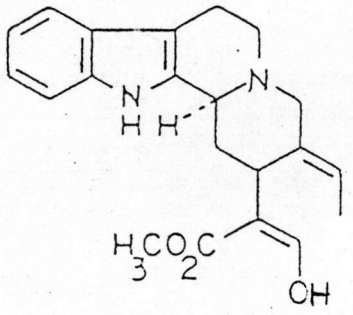
The important view of strictosidine 122 as being the key role intermediate of the biosynthetic pathway is emphasized by the isolation of N_b-methyl strictosidine, dolichantoside 124 from the root bark of African *S. gossweileri* Exell. (20).

The role of geissochizine 1 in the sequence of the heteroyohimbine alkaloids and several types of alkaloids biosynthesis have been demonstrated (21,22). However, more recent works (23-28) reveal that geissoschizine 1 seems to

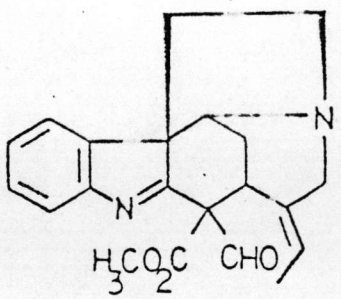
involve in the biosynthesis after two intermediates, 4,21-dehydrocorynantheine aldehyde 125 and 4,21-dehydrogeissoschizine 126. The alkaloid, 4,21-dehydrogeissoschizine 126 has been found naturally in *Guettarda eximia* Baill. (26) as well as isolate in a radioactive form from the incubations of [1-^{14}C] tryptamine 120 and secologanin 121 (27).



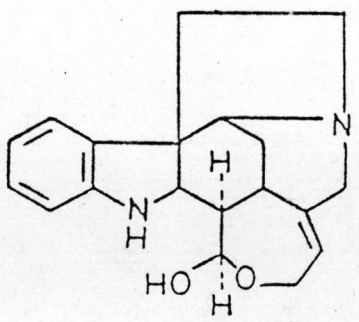
122 Strictosidine



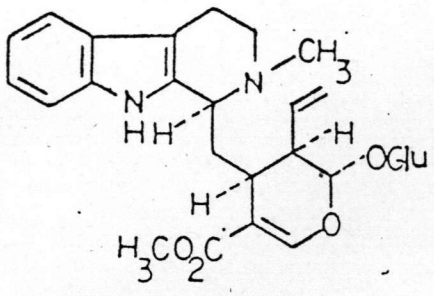
1 Geissoschizine



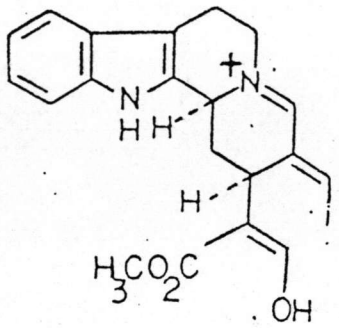
123 Dehydropreakuammicine



45 Wieland-Gumlich aldehyde



124 Dolichantoside



126 4,12-dehydrogeissoschizine

From these biosynthetic precursors, the biosynthesis of *Strychnos* alkaloids can be proposed as shown in (Fig. 4,page 44)

4,21-Dehydrogeissoschizine 126 is considered as the important branch point intermediate (27,28) in the biosynthesis of the Corynanthean, Ibogan, Aspidospermatan and also Strychnan type alkaloids. The relationships among the pathway intermediates in the biosynthesis of *Strychnos* alkaloids are demonstrated (Fig.4). Geissoschizine 1 is converted from 4,21-dehydrogeissoschizine 126 under NADPH-regenerating conditions (14,29).

The C-mavacurine group (C_3) of the corynanthean type alkaloid seems to be derived from 4,21-dehydrogeissoschizine 126 *via* geissoschizine 1 by C_{16} --> N_a ring closure (30). It is generally accepted that 4,21-dehydrogeissoschizine 126 produced the sarpagine group (C_6) alkaloids, however the pathway to form C_{16}-->C_5 bridge of sarpagine group is not clearly understood (14,28,30,31).

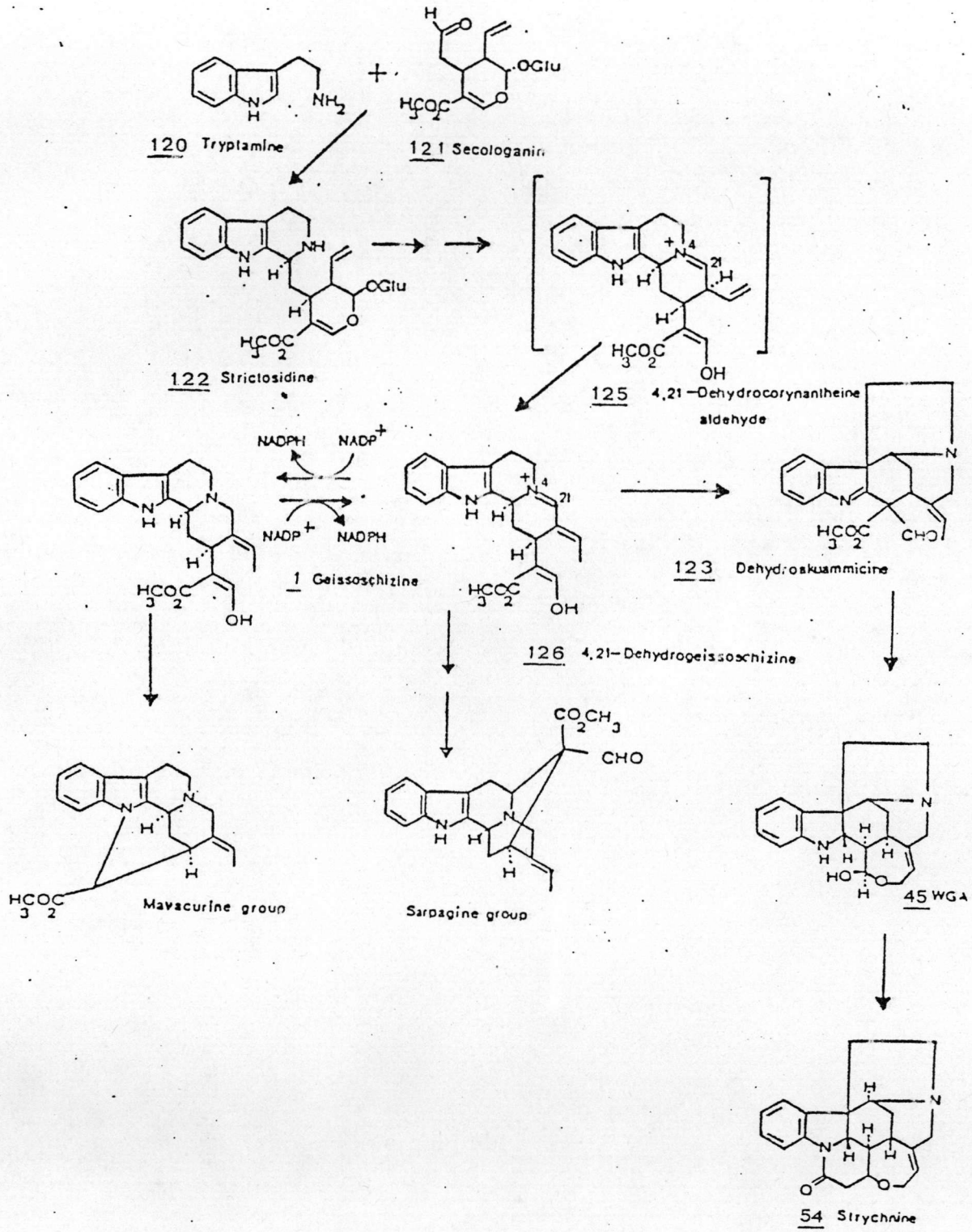
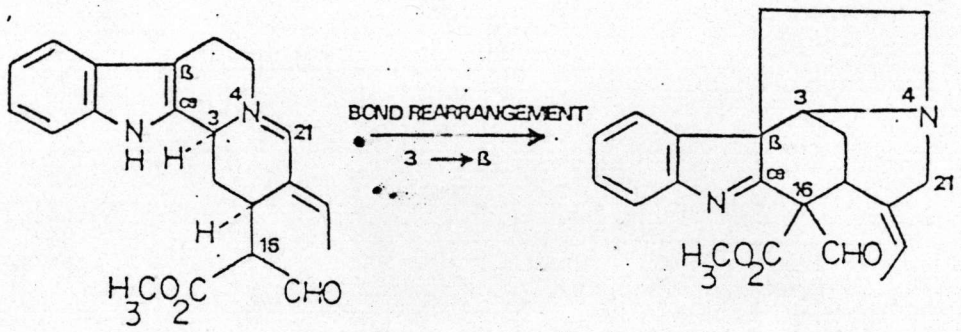


Figure 4 Overall view of the biosynthesis of *Strychnos* alkaloids

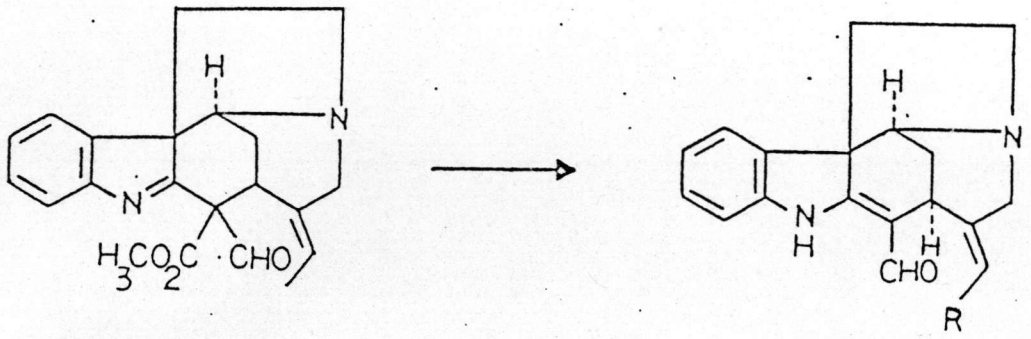
In the biosynthetic of strychnan type alkaloids (S-type), dehydropreakuammicine 123 of presumed to be the next stage intermediate after 4,21-dehydrogeissoschizine 126. The formation of dehydropreakuammicine 123 (32) has designed *via* the rearrangement of the C-3 bond of 4,21-dehydrogeissoschizine 126 from the α- to the β-position in the indole portion, follows by the bond formation between the α-position and C_{16} (Fig.5).



126 4,21-Dehydrogeissoschizine 123 Dehydropreakuammicine

Figure 5 Transformation of 4,21-Dehydrogeissoschizine 126 to Dehydropreakuammicine 123

By lossing the carbomethoxy group of dehydropreakuammicine 123 would lead to the next recognized intermediate for rather complicated rid, Nor-C-fluorocurarine 127 which then would hydroxylate to 18-Hydroxy-nor-C-fluorocurarine 128 (14,33) (Fig.6).



123 Dehydropreakuammicine 127 Nor-C-fluorocurarine; R = CH_3

128 18-Hydroxy-nor-C-fluorocurarine; R = CH_2OH

Figure 6 Alkaloids derived from Dehydropreakuammicine 123

The reduction of these two compounds, nor-C-fluorocurarine 127 and 18-hydroxy-nor-C-fluorocurarine 128 (33) would produce 18-dehydroxy Wieland-Gumlich aldehyde 129 and Wieland-Gumlich aldehyde (open form) 45a, respectively. These two aldehydes, 129 and 45a are the precursors of monomeric *Strychnos* alkaloids such as isoretuline 36, retuline 35 , 18-hydroxyisoretuline 130 and 18-hydroxy retuline 131 as well as bis-tertiary 132 or bis-quaternary 133 alkaloid (Fig.7 page 47). In conclusion, it is possible to indicate that 18-dehydroxy Wieland-Gumlich aldehyde 129 is hydroxylated to give Wieland-Gumlich aldehyde (open form) 45a and then the two molecules of either the same or different aldehydes of 129 and 45a are condensed to form bis-tertiary base 132 and also bis-quaternary base 133.

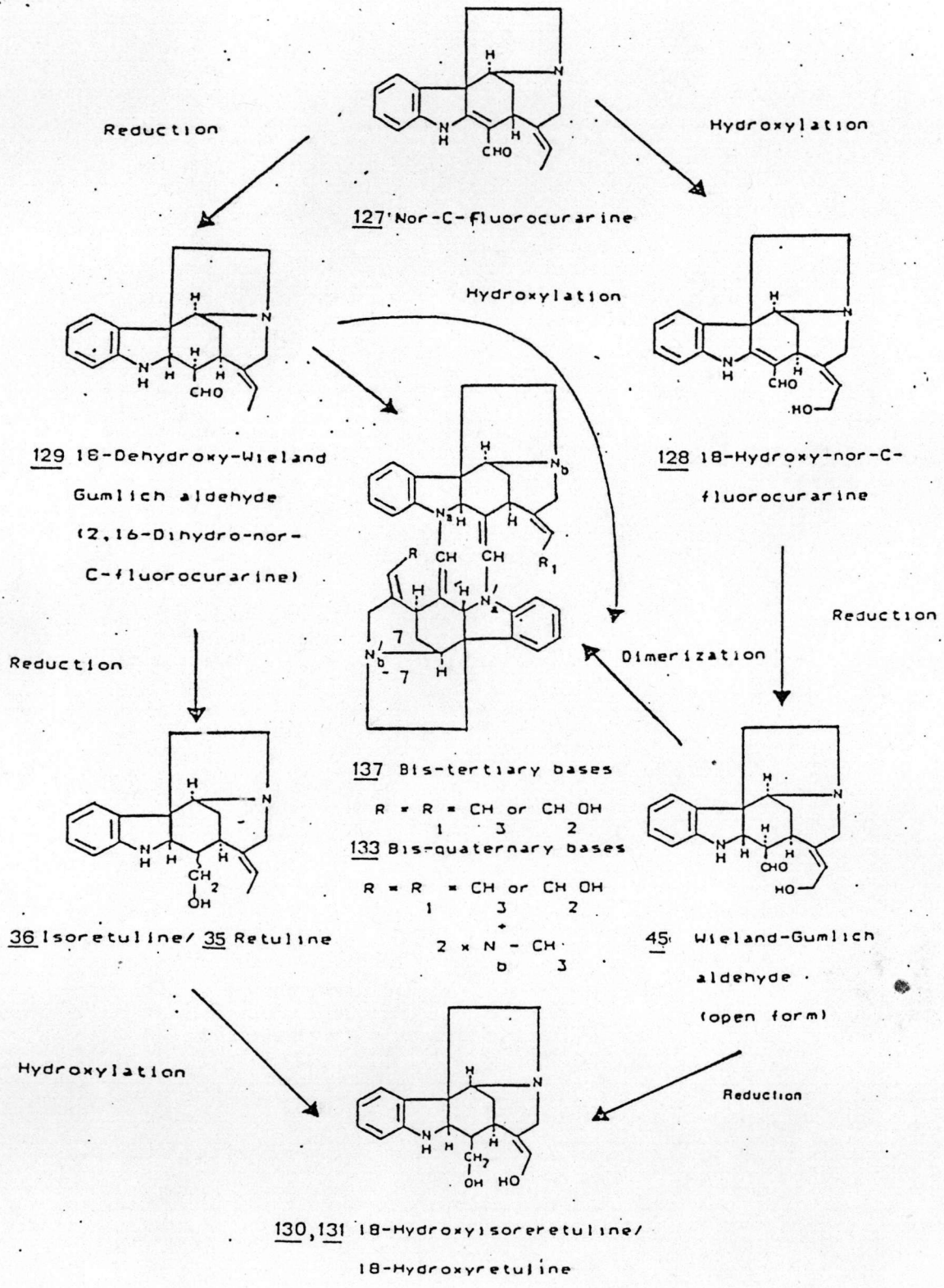
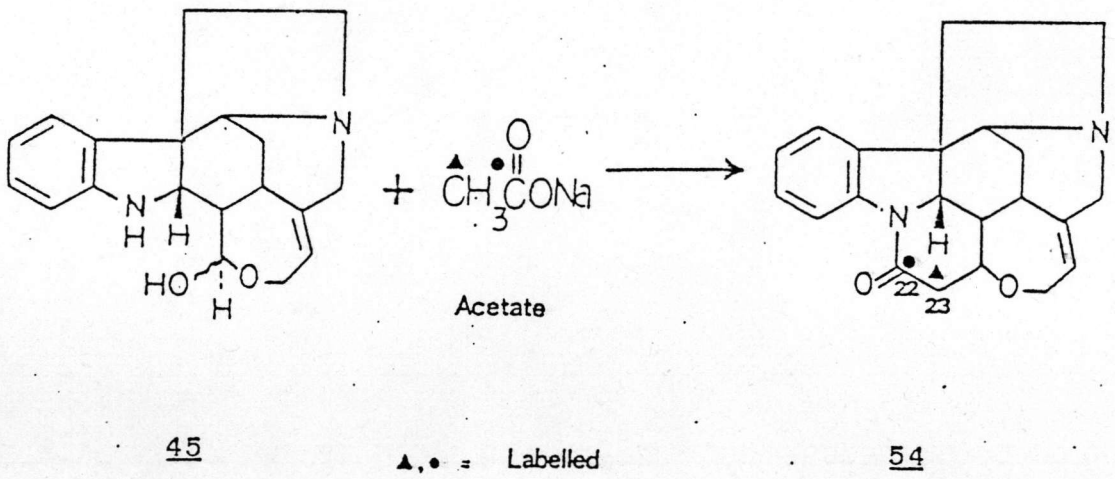


Figure 7 Alkaloids derived from Nor-F-fluorocurarine 127

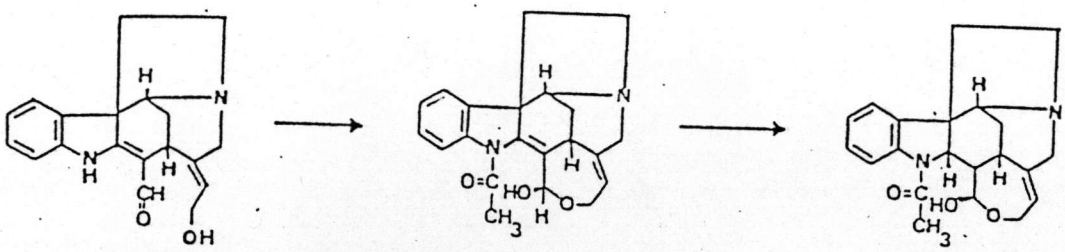
Heimberger and Scott (19), have proved that Wieland-Gumlich aldehyde 45 (close form) is a precursor of heterocyclic bases exemplified by strychnine 54. Although the N_a-acetyl derivative of Wieland-Gumlich aldehyde, diaboline 47 has been supposed to involve in the biosynthetic pathway to strychnine 54, it is failed to incorporate into strychnine 54 during the feeding experiment (19). This negative result leads to the suggestion that an extra two carbon atom C_{22} and C_{23} of strychnine 54 might be come from an acetate unit rather than the ring closure between C_{17} and N_a-acetyl group of diaboline 47. The condensation of the acetate unit at C_{17} and subsequent ring closure a N_a of Wieland-Gumlich aldehyde 45 to produce strychnine 54 have been proved (34) (Fig.8 page48).



45 ▲,● = Labelled 54

Figure 8 Formation of Strychnine 54 from Wieland-Gumlich aldehyde 45 and acetate unit

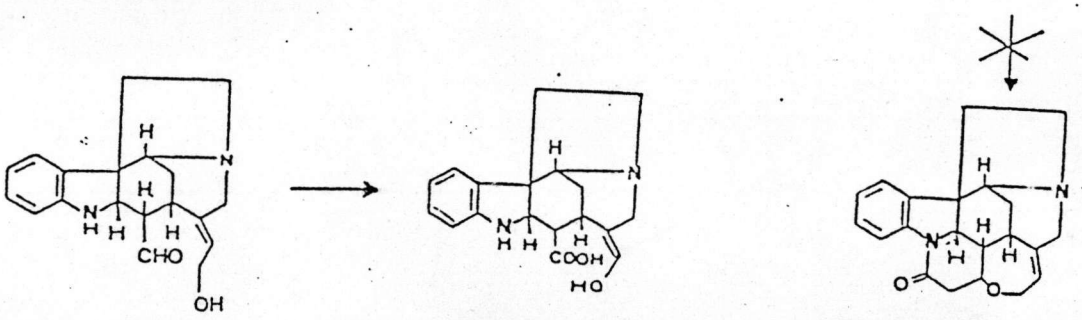
In addition, Heimberger and Scott (19) have predicted that there will be an aldol-acid compound called prestrychnine 134 which is placed at the last step in the biosynthesis next to strychnine 54. This proposal is supported by the isolation of protostrychnine 53 from the root bark of *S. nux-vomica* Linn. (35). Finally , protostrychnine 53 would be dehydrated to give strychnine 54. The metabolic grid at the final stage of the biosynthesis pathway to strychnine 54 has shown (Fig.9 page50).



129 18-Hydroxy-nor-C-fluorocurarine

135 2,16-Dehydrodiaboline

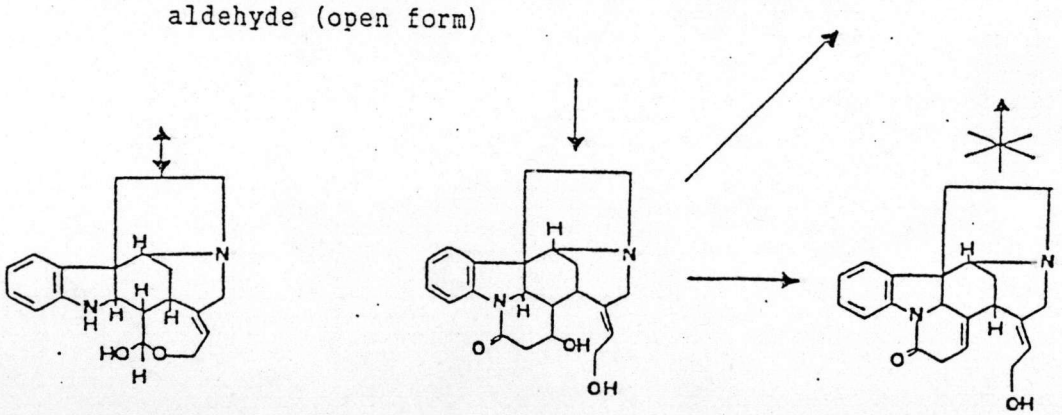
47 Diaboline



45a Wieland-Gumlich aldehyde (open form)

134 Prestrychnine

54 Strychnine



45 Wieland-Gumlich aldehyde (closed form)

53 Protostrychnine

51 Isostrychnine

Figure 9 The final stage in the biosynthesis pathway of Strychnine 54

Pharmacology of Strychnos Alkaloids

Strychnos species have long been known as sources of powerfully acting alkaloids. The first *Strychnos* alkaloids to be isolated were strychnine 54 and brucine 55 obtained from the seed of both *S. ignatii* and *S. nux-vomica* L. in 1819 (36). Pharmacologically, strychnine 54 excites all portions of the central nervous system. It is a powerful convulsant and death results from asphyxia. Strychnine 54 has no therapeutic uses in Western medicine, but Chinese traditional doctors have described the use of strychnine nitrate in the treatment of chronic aplastic anemia (37).

The two main type of activity exhibited by *Strychnos* species from various parts of the world are convulsant (CNS stimulating) and muscle-relaxant (more precisely, curarizing). American species mainly posses alkaloids which are muscle-relaxants, while the alkaloids of the Asian species generally exhibit convulsant activity. The alkaloids of the African species have both muscle-relaxant and convulsant activities (36). Moreover, a number of other pharmacological activities which have been demonstrated are antimicrobial (38,39), antitumor and anticancer activities (40,41), hypotensive effect (42-46), reserpine like activities (47), cardiac depressant action (40) and cardiotoxic effect (48).

The strong central nervous system stimulant action of *Strychnos* alkaloids is major cause of clonic and tonic convulsions.Clonic convulsion occurs when having an alternating

contraction and relaxation of the muscles, where as a sustained rigidity of the muscles occurs (3) in tonic convulsion (14).

Muscle relaxant effect may also be subdivided into truly curarizing and muscle relaxant activities (3). Curarizing activity represents by the neuro-muscular blockage of impulse transmission of the motor end-plates as a result of inhibition of acetylcholine. The result possesses the complete paralysis of the skeletal or striated muscle apparatus. It is generally accepted that inhibitors of neuro-muscular transmission exerts their principal action either presynaptically or postsynaptically or a combination of both, while muscle relaxant activity refers to the term of being only a weak action on neuro-muscular junctions (14).

In general, non-polar fractions of the crude alkaloids from *Strychnos* species, always show strong convulsant activity of the both clonic and tonic types while the polar fractions show the muscle relaxant activity (14,49).

The chemical structures of these alkaloids can be related to their pharmacological activities (42,50) and the arrangements of the *Strychnos* alkaloids structures are recently described (3, 38-41, 43-44, 51) to correlate either to convulsant of muscle relaxant activities. However, only some structural types of *Strychnos* alkaloids can be related to this arrangement due to the insufficient pharmacological investigation of these alkaloids (3,14,52).

1. Alkaloids with convulsant activity

The *Strychnos* alkaloids that responsible for the activity are described as follows.

1.1 Strychnine group (5)

This alkaloid type can be rearranged to 3 groups.

a. Normal series

The well-known alkaloid strychnine 54 is prototype.Strychnine 54 and 12-hydroxy strychnine 59 are the strongest convulsive activity *Strychnos* alkaloids. The phenolic hydroxyl group in 12-hydroxystrychnine 59 is of minor importance for the pharmacological effect but it strongly forms hydrogen-bond to the amide carbonyl. The effect is such as to give absorptive properties of 12-hydroxy strychnine 59 similar to those of strychnine 54.

b. Pseudo series

The pseudo series are slightly less action than strychnine 54. Because their 3-α-hydroxyl group get a lesser fitness with the receptor.

c. *N*-methyl-*sec*-pseudo series

This series are less active than strychnine 54. Because the 3-keto group extrudes from the back of the molecule causing a less satisfactory fitness with the receptor. They show only clonic convulsive action.

1.2 Diaboline group

This group has the molecular structure respected to strychnine 54. But the opening amide lactam ring decreases the

potency and shows only clonic convulsive action (5).

1.3 Spermostrychnine group

This group has the same convulsive activity as the diaboline group (5).

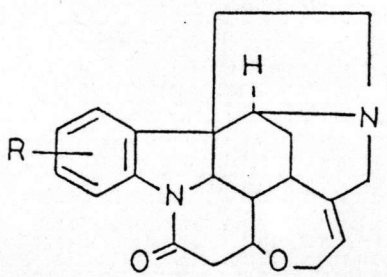
1.4 Other type alkaloids

a. Akagerine group alkaloids, akagerine 12 and its congeners are the potent convulsant agents. They also posses the tonic convulsion effect which is less activity than strychnine 54 (53-55).

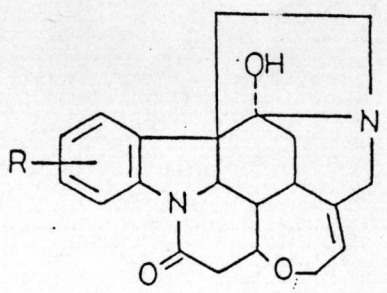
b. Sarpagine group alkaloids such as macusine B 19 show clonic convulsant effect *in vivo* (45).

c. Tubotaiwine 97, shows only weak clonic convulsion *in vivo* (56).

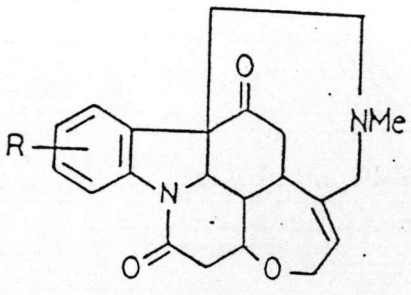
Strychnine group



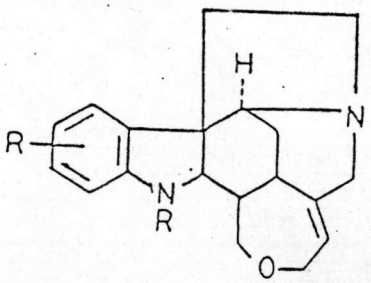
Normal series



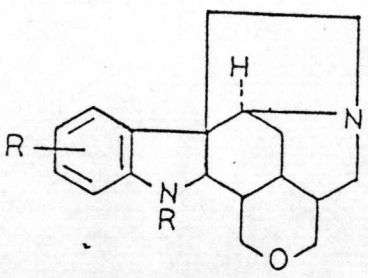
Pseudo series



N-methyl-*sec*-pseudo series



Diaboline group



Spermostrychnine group

2. Alkaloids with muscle-relaxant activity

Muscle-relaxant effect of *Strychnos* species may be subdivided into muscle-relaxant and truly curarizing(3).Muscle-relaxant is a weak action on neuro-muscular junctions while curarizing activity is phenomenological term describing neuro-muscular block of impulse transmission of the motor end-plates as a result of inhibition of acetylcholine, the result is complete paralysis of the skeletal or striated muscle apparatus. This effect is the main activity of American *Strychnos* species. Many bis-quarternary indole alkaloids have been detected corresponding to this action(11).Up till now, other type of *Strychnos* alkaloids are studied to have this activity too.

2.1 Bis-quaternary indole alkaloids

These alkaloids are potent curarizing agents,the presence of two quaternary nitrogens in a single molecule being responsible for the high activity. The activity depends on the distance between the quartenary nitrogens (3). For optimal activity the distance must be about 14 A. Whereas the distance decrease, the activity decrease. The presence of hydroxyl group at C-18 will increase the activity. The more polar alkaloids have greater neuro-muscular activity than less polar alkaloids.

This curarizing activity of bis-quaternary indole alkaloids from *Strychnos* species is similar to the well-known bis-benzylisoquinoline alkaloid, d-tubocurarine 136 isolated from the tube curare and from *Chondrodendron tomentosum* Ruiz. et Pav. of family Menispermaceae. Their mechanism are non-polarizing

competitive antagonism of acetylcholine for post synaptic receptors and a weak activity for presynaptic receptor at the neuro-muscular junctions. The effect is antagonized by a small dose of neostigmine, but in large doses, it will prolong of paralytic action.

The bis-quaternary indole alkaloids may be divided into three groups according to the transformation at the central eight-membered ring between the monomers of the molecule(3).

2.1.1 Toxiferine group

Alkaloids in this group show slowly progressive onset of paralysis but the effect is long duration. The representatives of the group are toxiferine 101, C-dihydro-toxiferine 102 and C-alkaloid H 137. Toxiferine 101, is the most potent member of this group which possesses even more potent than d-tubocurarine 136.

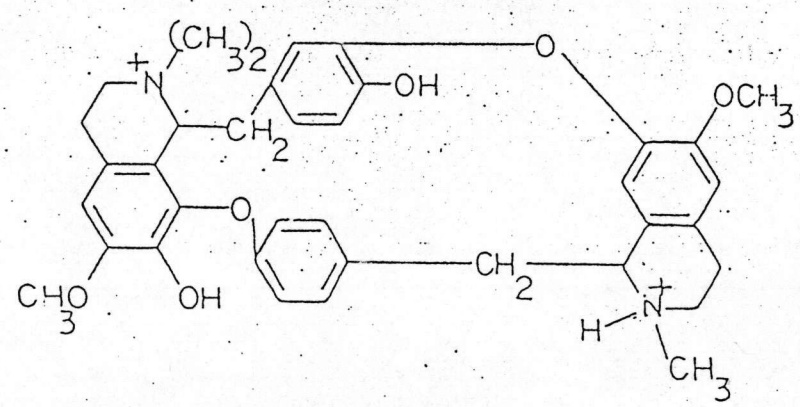
2.1.2 Curarine group

The action of alkaloids in this group is sustained in moderate duration. The representatives of this group are C-curarine 106, C-alkaloid E 108 and C-alkaloid G 138. C-curarine 106 is the potent member of this group and being more potent than d-tubocurarine 136. The most active effect of the Curarine group posses by ether oxygen in the central eight membered ring.

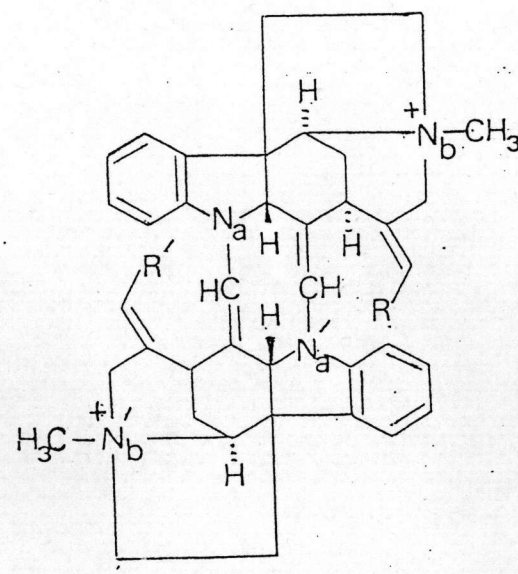
2.1.3 Calebassine group

The action of this group is less potent than d-tubocurarine 136 and has a short duration. The low activity may be explained by the fact that the presence of the C-C bridge

in the central eight-membered ring such representative by C-Calebassine 109, C-alkaloid A 139 and C-alkaloid F 140 would reduce the distance between the two quaternary nitrogens down to 8.6 A.



136 d-Tubocurarine

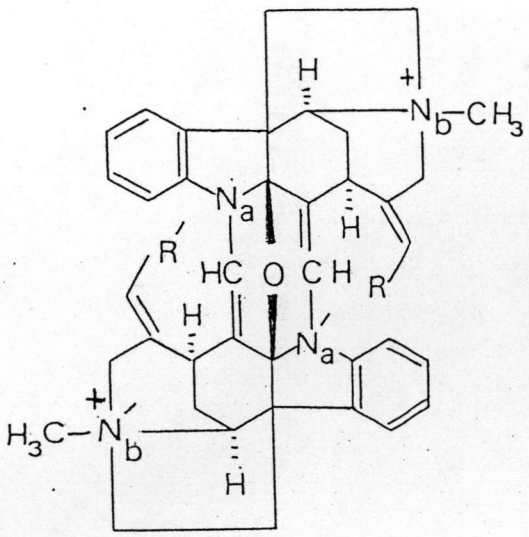


Toxiferine group

101 Toxiferine; R=R'=OH

102 C-Dihydrotoxiferine; R = R'= H

137 C-Alkaloid H; R = H, R'= OH



Curarine group

108 C-Alkaloid E;

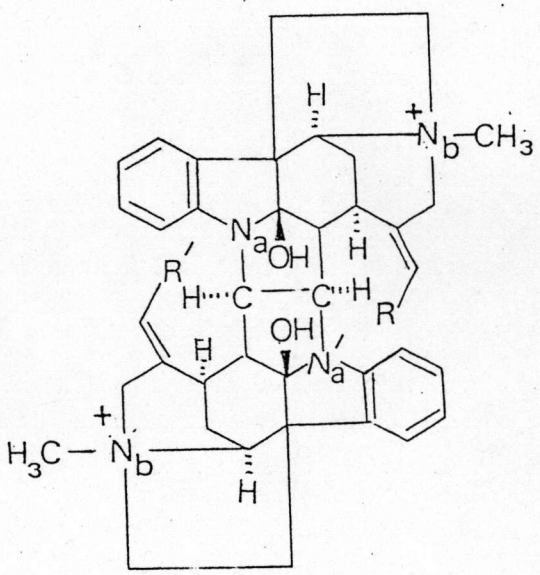
R = R'= OH

106 C-Curarine;

R = R'= H

138 C-Alkaloid G;

R = H, R'= OH



Calebassine group

139 C-Alkaloid A;

R = R'= OH

109 C-Calebassine;

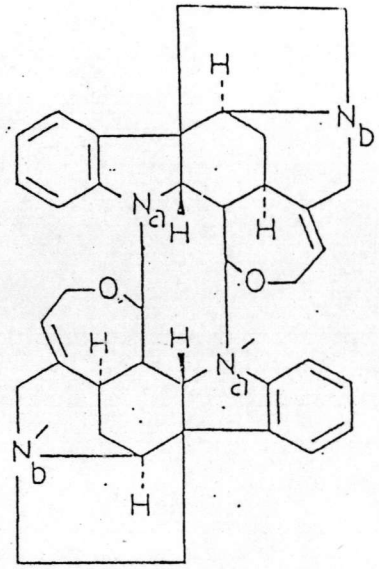
R = R'= H

140 C-Alkaloid F;

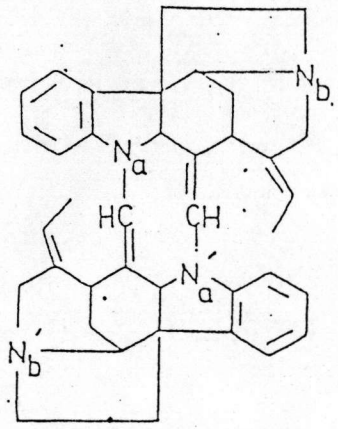
R = H, R'= OH

2.2 Bis-tertiary indole alkaloids

The alkaloids that have been studied are caracurine V 113 (57) and bisnor-dihydrotoxiferine 103 (3). Caracurine V 113 showed a weak muscle-relaxant activity which was not antagonized by choline esterase inhibitors.Bisnor-dihydrotoxiferine 103 also had a muscle-relaxant activity.



113 Caracurine V

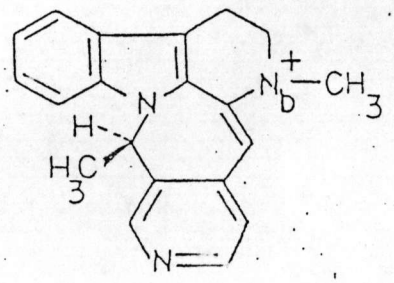


103 Bisnor-dihydrotoxiferine

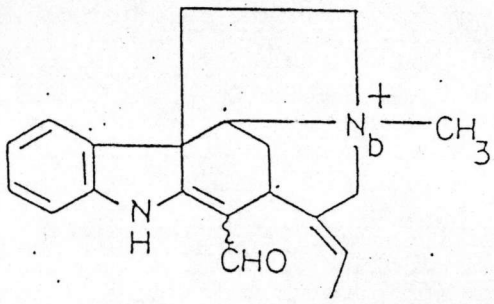
2.3 Other alkaloid types

Decussine 28 , the alkaloid of the vicosan type had pronounced muscle-relaxant effect.It is probably due to the 13,14 double bond of the molecule being responsible for their muscle-relaxant activities (58-59).

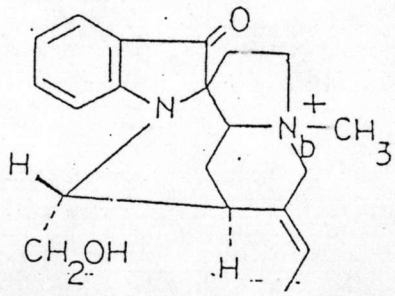
Some monoquaternary alkaloids, Fluorocurarine 41, C-fluorocurine 17 and C-mavacurine 16 give only a weak curare activity too (45).



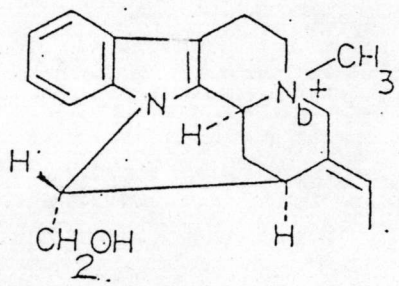
28 Decussine



41 Fluorocurarine



17 C-Fluorocurine



16 C-Mavacurine

3.Alkaloids with cytotoxic activity

3.1 Usambarane skeleton alkaloids

Usambarane skeleton is the skeleton type of E-seco indole group and oxindole group of corynanthean type alkaloid (14).These alkaloids have high cytotoxic activity (60). This fact can be related to the relationship between the structure of these alkaloids and emetine 141 which has well-known for cytotoxicity. All of which result from condensation of a monoterpenoid unit and an amino unit. Strychnopentamine 142 is the most active compound.

The structure-activity-relationships of these usambarane skeleton are discussed as follows:

(a) The N-methyl-pyrrolidine group on C-12 increase the activity (41). This reason causes strychnopentamine 142 and strychnophylline 143 to have more activity than 11-hydroxyusambarine 144 and strychnofoline 25 respectively.

(b) The quaternization of the alkaloids strongly decrease the cytotoxic activity.

(c) The 5',6'-dihydro derivative is more active than the one with the extra double bond.

3.2 Other alkaloids

3.2.1 Non-terpenoid indole alkaloids : Melinonine F 145 (61-63), Harmine 146, Harmol 147, Harmaline 148, N_b-Methyl-harmalane 149 (60).

3.2.2 Monomeric alkaloids

(a) Corynanthean type

-E-*seco* indole group : 4,21-Dehydrogeissoschizine 126 (60)

-Akagerine group : Akagerine 12 (60)

-Ajamalicine group : Alstonine 8 , Serpentine 9 (3)

(b) Vincosan type

-Strictosidine group : Dolichantoside 124, Iso-dolichantoside 150 (60)

(c) Vallesiachotaman type

- Anterhine group : Methylantirhine 151 (60)

(d) Strychnan type

- Diaboline group : Diaboline 47 , Henningsoline 152 (64)

- Tsilanine group : Holstiine 94 (64)

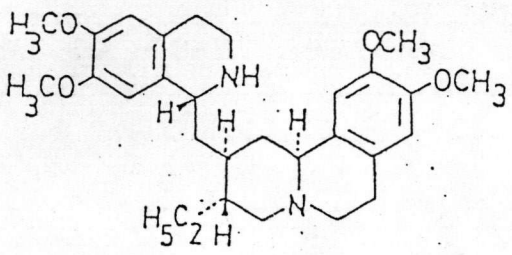
(e) Miscellaneous type

- Olivacine group : Ellipticine 99 and 9-methoxy-ellipticine 153 (40)

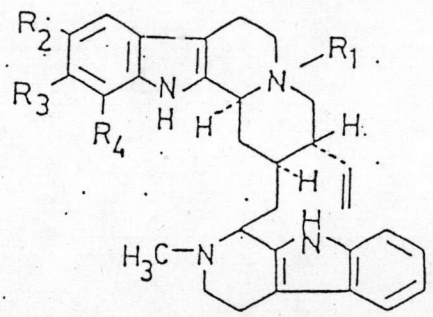
3.2.3 Bis-indole alkaloids : Bisnordihydrotoxiferine 103 (65)

There are not any discussion about the structure-activity-relationships of these alkaloids. And some of them are inactive in other report or very less active in the report, such as strychnan type, ajamalicine and bis-indole alkaloids. The only alkaloids that have certain activity are melinonine F 145 and ellipticine alkaloids 99,153 which are

the well-known cytotoxic agents. These alkaloids have a planar heterocyclic ring which can be inserted between DNA base pairs. Inhibition of DNA , RNA or protein synthesis (40, 61-63).



141 Emetine



142 Strychnopentamine

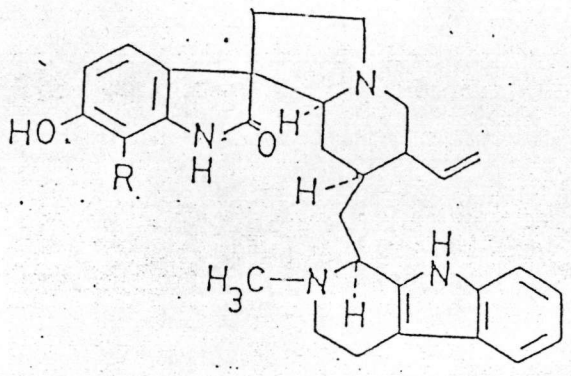
R_1 = - , R_2 = H, R_3 = OH

R_4 = H_3C-N

144 11-Hydroxyusambarine

R_1 = -, R_2 = H,

R_3 = OH, R_4 = H

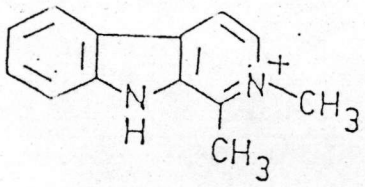


143 Strychnophylline

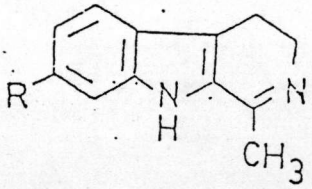
R= H_3C-N

25 Strychnofoline

R=H



145 Melinonine F



146 Harmine

R=OCH_3, 5,6-dehydro

147 Harmol;

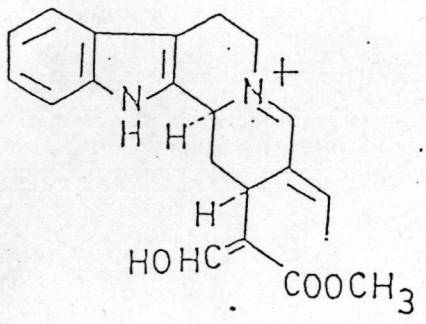
R=OH, 5,6-dehydro

148 Harmaline;

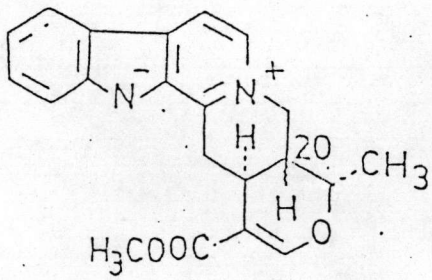
R=OCH_3

149 N_b-Methyl-harmalane;

R=H, N_b-CH_3

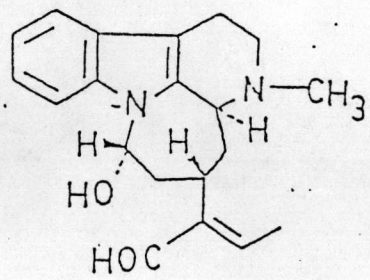


126 4,21-Dehydro-geissoschizine

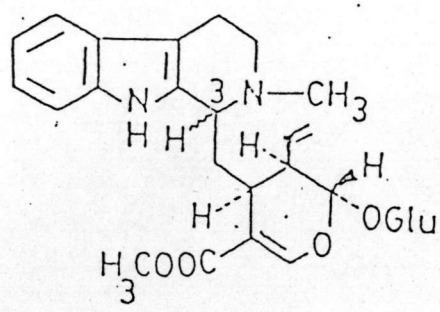


8 Alstonine; 20-α-H

9 Serpentine; 20-β-H

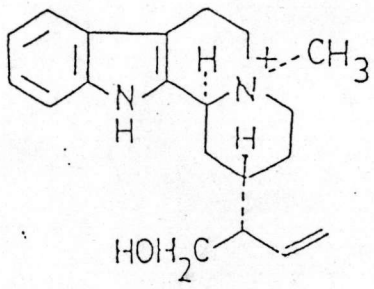


12 Akagerine

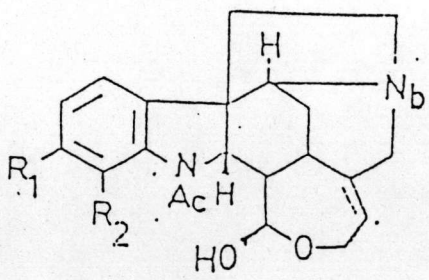


124 Dolichantoside; 3-α-H

150 Isodolichantoside; 3-β-H

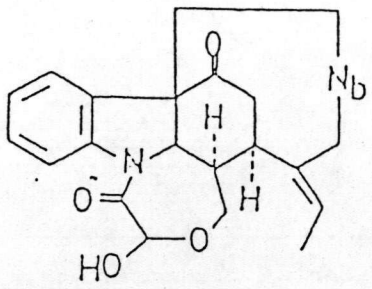


151 Methylantirhine

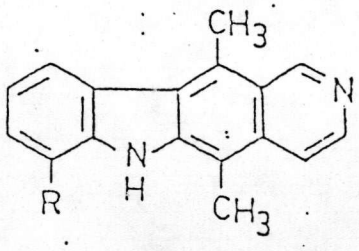


47 Diaboline; $R_1=R_2=H$

152 Henningsoline; $R_1=OCH_3, R_2=OH$

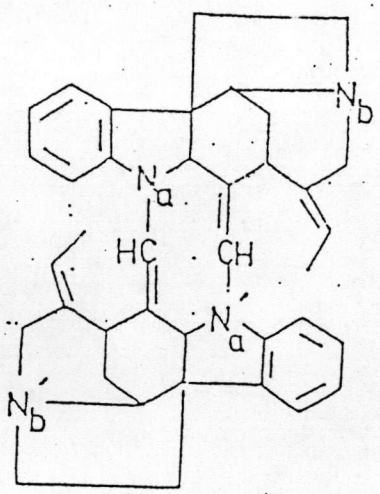


94 Holstiine



99 Ellipticine; R=H

153 9-Methoxyellipticine; R=OCH_3



103 Bisnor-dihydrotoxiferine

4. Alkaloids with antimicrobial activity

In the screening of antimicrobial activity of some plants belonging to the Apocynaceae and Loganiaceae, some *Strychnos* species were showed to have this activity. The alkaloids that posses for the action are bis-tertiary indole alkaloids and ellipticine type alkaloids.(51)

4.1 Bis-tertiary indole alkaloids

The alkaloids that exhibit antimicrobial activity are bisnor-dihydrotoxiferine 103, bisnor-C-alkalois H 105 and caracurine 113. The di-*N*-oxides of bis-nordihydrotoxiferine 104 and caracurine V 113 have a little activity.It was concluded that these alkaloids exhibit a bacteriostatic effect rather than a bactericidal effect (57).

For their antimicrobial spectra, caracurine V 113 is active against *Escherichia coli*, *Pseudomonas aeruginosa* and *Staphylococcus* species (57). Bisnordihydrotoxiferine 103 is a board antimicrobial spectrum against gram-positive, gram-negative, acid-fast bacteria and fungi but relatively weak (65).

4.2 Ellipticine type alkaloids

It has not any discussion about the structure and activity for ellipticine type alkaloids 99 . But they are found as a major component of *Strychnos dinklagei* which was a species

among active species during the screening of antimicrobial activity of some plants belonging to the Apocynaceae and Loganiaceae (51).

4.3 Usambarane skeleton alkaloids

Some of these alkaloids are found in *Strychnos dali* De Wild. which was one of the most active species during the screening (51). The alkaloids show antimicrobial activity against *Staphylococcus aureus, Mycobacterium smegmatis, Bacillus subtilis* and *Escherichia coli*. 5',6'-Dihydrousambarensine 154 posses amoebicide property *in vitro* against *Entamoeba histolytica* (3). The structure-activity-relationships of these skeleton alkaloids are concluded as follows (66).

(a) The introduction of a 3,4- or 17,4'-double bond in a carboline moiety lowers the activity.

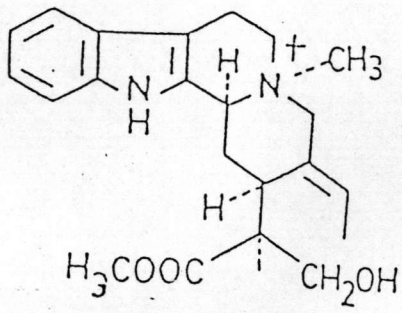
(b) The oxygenated substitutions on benzene ring of indole moiety reduce the activity. But introduction on N-methyl group will counteract the activity.

(c) The stereochemistry of C/D ring junction is important for the activity.

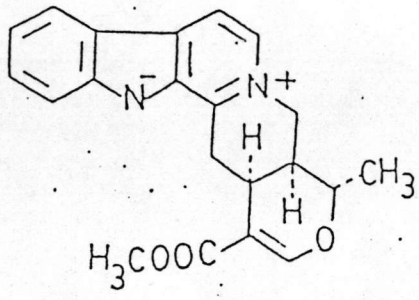
4.4 Corynanthean type alkaloids

Diploceline 155, the E-seco indole group, shows a weak antimicrobial activity towards *Staphylococcus aureus* and *Staphylococcus haemolyticus*. Alstonine 8 was isolated from the more active portion than that contained diploceline 155. But no

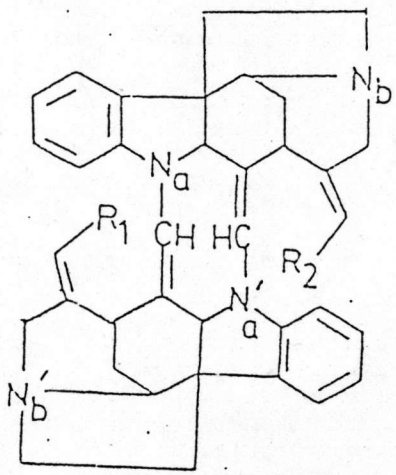
tests could be performed owing to lack of material (17).



155 Diploceline



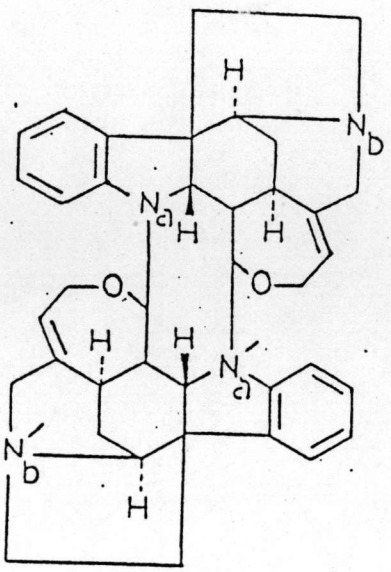
8 Alstonine



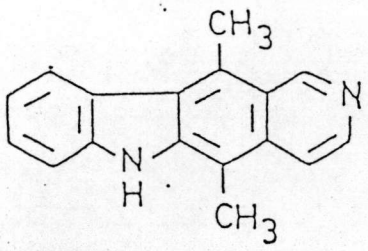
103 Bisnor-dihydrotoxiferine;
$R_1 = R_2 = H$

104 Bisnor-dihydrotoxiferine di-*N*-oxide

105 Bisnor-*C*-alkaloid H;
$R_1 = H$, $R_2 = OH$



113 Caracurine V



99 Ellipticine

5. Alkaloids with hypotensive activity

5.1 Corynanthean type

5.1.1 Ajmalicine group:

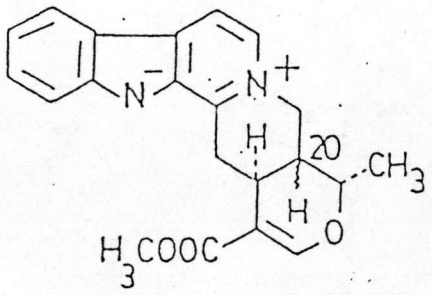
Alstonine 8, Serpentine 9 (46).

5.1.2 Sarpagine group:

Macusine B 19, Normacusine B 20 (3).

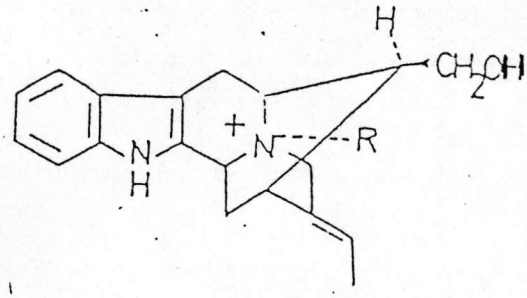
5.2 Strychnan type : Diaboline 47 (67)

5.3 Bis-indole alkaloids : Longicaudatine 119 (68)



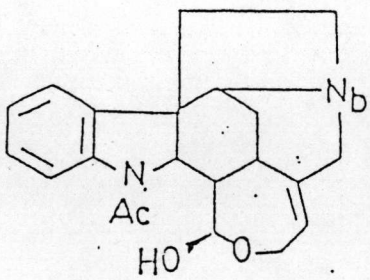
8 Alstonine ; 20-α-H

9 Serpentine ;20-β-H

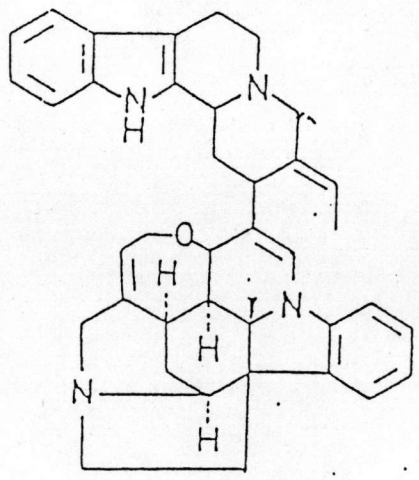


19 Macusine B; R =CH

20 Normacusine B; R =CH_2OH



47 Diaboline



119 Longicaudatine

6. Alkaloids with other activities

6.1 Bisnor-dihydrotoxiferine 103 : sedative (3)

6.2 Normacusine B 20 : sedative in vivo in mice (3)

6.3 Strychnocarpine 156 : stimulator of the central 5 HT receptor (58)

6.4 Harman 122 and its derivatives : inhibitors of mono-amin oxidase (46)

6.5 Usambarensine 5 : atropine-like and spasmolytic activities (3).