

## CHAPTER II



## HISTORICAL

### Alkaloids Isolated from Species of *Stephania*

The *Stephania* alkaloids were firstly studied by Kondo and Sanada in 1925 from stems and roots of *Stephania japonica* Miers. Recently, there are about 144 alkaloids of known structures from 25 *Stephania* species. Most of them were isolated from the tubers. Zhu *et al.* (1983) reported the total amount of alkaloids from roots or tubers of some *Stephania* species in China as shown in Table 1.

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Table 1 Total amount of the alkaloids from some *Stephania* species in China

Plant	Total alkaloids (%)
<i>Stephania brachyandra</i> Diels	6.65
<i>S. cepharantha</i> Hayata	1.52
<i>S. delavayi</i> Diels	3.10
<i>S. dicentrinifera</i> H.S. Lo et M. Yang	4.20
<i>S. dielsiana</i> Wu	2.62
<i>S. epigeae</i>	2.96
<i>S. excentrica</i>	19.65
<i>S. hainanensis</i>	2.44
<i>S. japonica</i> (Thunb.) Miers	0.19
<i>S. kwangsiensis</i> H.S. Lo	2.62
<i>S. longa</i> Lour.	0.86
<i>S. mashanica</i>	2.00
<i>S. micrantha</i>	1.00
<i>S. sinica</i>	2.04
<i>S. succifera</i>	2.32
<i>S. tetrandra</i> S. Moore	2.96
<i>S. viridiflavens</i>	6.00
<i>S. yunnanensis</i>	5.16

The distribution of alkaloids in the genus *Stephania* are summarized in Table 2

Table 2 Distribution of *Stephania* alkaloids

Plant	Alkaloid	Reference
<i>Stephania abyssinica</i> Walp. (roots)	6-dihydroepistephamine-6-acetate neostephanine oxoxylophine	Waal and Weideman, 1962; Kupchan <i>et al.</i> , 1970, Van, 1975
<i>S. brachyandra</i> Diels (roots)	corytuberine dehydrodicentrine dicentrine 8,14-dihydrosalutaridine isoboldine isocorydine N-methyl-laurotetanine sinoacutine sinomenine 1-tetrahydropalmatine	Chen <i>et al.</i> , 1982
<i>S. capitata</i> Sprengel (roots)	crebanine cycleanine d-dicentrine phanostenine stephanine	Tomita and Shirai, 1942, 1943 b; Shirai, 1944; Shirai and Oda, 1956; Tomita and Hirai, 1957, 1958

Table 2 (Continued)

Plant	Alkaloid	Reference
<i>Stephania cepharantha</i> Hayata (roots)	berbamine cephamine cepharanoline cepharanthine cycleanine homoaromoline isotetrandrine	Kondo <i>et al.</i> , 1934, 1938; Kondo and Keimatsu, 1935 a, b; Tomita and Kozuka, 1966 a, 1967; Tomita <i>et al.</i> , 1969
<i>S. cepharantha</i> Hayata (seeds)	berbamine crebanine dehydrocrebanine dehydrostephanine isotetrandrine O-nornuciferine stephanine stesakine	Kunitomo <i>et al.</i> , 1981 b
<i>S. delavayi</i> Diels (leaves, stems, roots)	delavaine isostephodeline 16-oxodelavaine	Fadeeva <i>et al.</i> , 1970 b, 1971 b; Il' inskaya <i>et al.</i> , 1972; Perel'son <i>et al.</i> , 1975
<i>S. dicentrinifera</i> H.S. Lo et M. Yang (roots)	dehydrodicentrine dehydrostephanine dicentrine	Min and Zheng, 1984

Table 2 (Continued)

Plant	Alkaloid	Reference
<i>Stephania</i> <i>dicentrinifera</i> H.S. Lo et M. Yang (roots)	isocorydine sinoacutine sinomenine stephanine	
<i>S. dielsiana</i> Wu (roots)	crebanine dehydrostephanine sinoacutine stephanine 1-tetrahydropalmatine xylopinine	Min, 1983
<i>S. dinklagei</i> Diels (roots)	corydine dicentrine isocorydine N-methylcorydine N-methylglucine norcorydine roemerine stephalagine stepharine steporphine	Debray <i>et al.</i> , 1967; Quevauviller and Sarrazin, 1967; Tackie <i>et al.</i> , 1974; Dwuma <i>et al.</i> , 1980

Table 2 (Continued)

Plant	Alkaloid	Reference
<i>Stephania elegans</i> Hook.f. et Thoms. (roots)	cyclanoline isosinoacutine magnoflorine sinoacutine tetrahydropalmatine	Khosa <i>et al.</i> , 1980 a,b
<i>S. elegans</i> Hook.f. et Thoms. (leaves, stems, roots)	aknadinine cyclanoline cycleanine epihernandolinol hasubanone isochondrodendrine isotetrandrine magnoflorine N-methylcorydalmine	Singh <i>et al.</i> , 1981
<i>S. epigeae</i> (roots)	cepharanthine curine cycleanine isocorydine	Huang and Chen, 1979
<i>S. erecta</i> Craib (roots)	cepharanthine homoaromoline	Prawat <i>et al.</i> , 1982

Table 2 (Continued)

Plant	Alkaloid	Reference
<i>Stephania glabra</i> (Roxb.) Miers (roots)	capaurine columbamine corydalmine corynoxidine cycleanine dehydrocorydalmine jatrorrhizine magnoflorine N-methylcycleanine palmatine palmatrubine (+)-pronuciferine stephaglabrine (+)-stepharanine (+)-stepharine stepholidine 1-tetrahydropalmatine	Chaudhry and Siddiqui, 1950; Chaudhry <i>et al.</i> , 1952; Cava <i>et al.</i> , 1964; Shchelchkova <i>et al.</i> , 1965; Rabinovich <i>et al.</i> , 1965; Doskotch <i>et al.</i> , 1967; TinWa <i>et al.</i> , 1967; Berezhin- skaya <i>et al.</i> , 1977; Patra <i>et al.</i> , 1980; Bhakuni and Gupta, 1982
<i>S. hernandifolia</i> (Willd.) Walp. (roots)	aknadine aknadicine (4-desmethyl- norhasubanonine) aknadinine (4-desmethyl hasubanonine)	Tomita and Ueda, 1959; Kupchan <i>et al.</i> , 1961; Moza, 1967; Moza and Basu, 1967 a,b; Fadeeva <i>et al.</i> ,

Table 2 (Continued)

Plant	Alkaloid	Reference
<i>Stephania</i> <i>hernandifolia</i> (Willd.) Walp. (roots)	fangchinoline hernandoline hernandolinol d-isochondrodendrine isotriline stephisoferuline d-tetrandrine dl-tetrandrine	1967, 1970 a,c; Kupchan <i>et al.</i> , 1968; Moza <i>et al.</i> , 1969, 1970; Kupchan and Suffness, 1970
<i>S. hernandifolia</i> (Willd.) Walp. (aerial parts)	aknadinine 3-O-dimethyl- hernandifoline epistephanine hernandifoline hernandine magnoflorine methylhernandine	Fadeeva <i>et al.</i> , 1971 a, 1972; Fesenko <i>et al.</i> , 1971; Il'inskaya <i>et al.</i> , 1971; Ray <i>et al.</i> , 1979
<i>S. intermedia</i> (roots)	1-corydalmine dehydrocorydalmine dehydrodiscretamine 1-discretamine jatrorrhizine palmatine stepharanine	Chen <i>et al.</i> , 1985



Table 2 (Continued)

Plant	Alkaloid	Reference
<i>Stephania intermedia</i> (roots)	stepharine 1-stepholidine 1-tetrahydropalmatine	
<i>S. japonica</i> (Thunb.) Miers (whole plants)	stephadiamine	Taga <i>et al.</i> , 1984
<i>S. japonica</i> (Thunb.) Miers (roots)	cyclanoline epistephamiarsine epistephanine hasubanone homostephanoline hypoepistephanine insularine lanuginosine metaphanine oxoepistephamiarsine 16-oxohasubanone 16-oxoprometaphanine oxostephamiarsine oxostephanine oxostephasunoline prometaphanine protostephanine	Kondo and Sanada, 1923, 1927 a,b, 1928, 1931; Kondo and Watanabe, 1938, 1950; Kondo and Nozoye, 1943; Kondo and Tanaka, 1943; Tanaka, 1944; Kondo <i>et al.</i> , 1951, 1952, 1953; Satomi, 1952, 1955; Kondo and Takeda, 1953, 1954, 1955, 1956, 1958; Takeda, 1956, 1960, 1963;

Table 2 (Continued)

Plant	Alkaloid	Reference
<i>Stephania japonica</i> (Thunb.) Miers (roots)	stebisimine stephamiersine stephanine stephanoline stepharine stephasunoline stepholine (obamegine) steponine stepinonine	Tomita and Watanabe, 1956; Tomita <i>et al.</i> , 1957, 1964, 1965 a,b, c, 1967 b; Watanabe 1957, 1960; Watanabe <i>et al.</i> , 1957, 1975a,b; Nozoye, 1957; Tomita and Ibuka, 1963a,b, 1965; Barton <i>et al.</i> , 1966a, b; Ibuka and Kitano, 1967a, b; Thornber, 1970; Ibuka <i>et al.</i> , 1975; Matsui <i>et al.</i> , 1975, 1984; Matsui and Watanabe, 1984.

Table 2 (Continued)

Plant	Alkaloid	Reference
<i>Stephania japonica</i> (Thunb.) Miers (leaves)	16-oxoprometaphanine oxostephamiersine stebisimine	Matsui <i>et al.</i> , 1982
<i>S. japonica</i> (Thunb.) Miers (fruits)	stephabenine	Kondo <i>et al.</i> , 1983
<i>S. kwangsiensis</i> H.S.Lo (roots)	1-capaurine dehydroroemerine dehydrostephanine dihydropalmatine d-isocorydine palmatine 1-roemerine stephanine tetrahydropalmatine	Min and Zhong, 1980 Cheng <i>et al.</i> , 1981
<i>S. longa</i> Lour. (Stems and roots)	longanine longanone prostephabyssine stephaboline stephabyssine	Lao <i>et al.</i> , 1980, 1981, 1982
<i>S. mahanica</i> (roots)	1-dicentrine dicentrinone sinoacutine	Wang and Wei, 1983

Table 2 (Continued)

Plant	Alkaloid	Reference
<i>Stephania mashanica</i> (roots)	1-tetrahydrocolumbamine 1-tetrahydrojatrorrhizine 1-tetrahydropalmatine	
<i>S. micrantha</i> (roots)	1-capaurine corypalmine dehydrooemerine dehydrostephanine d-isocorydine sinoacutine sinomenine stephanine tetrahydrocolumbanine 1-tetrahydropalmatine xylopinine	Min <i>et al.</i> , 1981
<i>S. rotunda</i> Lour. (roots)	pronuciferine stepharine stepharotine tetrahydropalmatine tuduramine	Tomita <i>et al.</i> , 1965 d, 1966; Tomita and Kozuka, 1966 b
<i>S. rotunda</i> Lour. (leaves and stems)	cepharamine	Kozuka <i>et al.</i> , 1985



Table 2 (Continued)

Plant	Alkaloid	Reference
<i>Stephania sasakii</i>	N-acetylstepharine	Kondo and Tomita
Hayata ex	aknadilactam	1939; Tomita,
Yamamoto (roots)	aknadinine	and Shirai 1943
	berbamine	a; Tomita and
	bisaknadinine	Kishikita, 1944;
	cepharadione-A	Kunitomo <i>et al.</i> ,
	cepharamine	1966, 1967,
	cepharanthine	1969 a,b, 1972,
	crebanine	1980 a,b, 1981
	dehydrocrebanine	a,c, 1985
	dehydrophanostenine	
	dehydroroemerine	
	dehydrostesakine	
	dihydrosecocepharanthine	
	4,5-dioxodehydrocrebanine	
	4-hydroxycrebanine	
	d-isocorydine	
	lanuginosine	
	liriodinine	
	lysicamine	
	N-methyl-6,7-dimethoxy-	
	1-isoquinolone	
	N-methylpapaveraldinium	
	O-methyldeoxopunjabine	

Table 2 (Continued)

Plant	Alkaloid	Reference
<i>Stephania sasakii</i> Hayata ex Yamamoto (roots)	O-methylpunjabine nuciferine obaberine 7-oxocrebanine phanostenine pronuciferine roemerine (R)-roemeroline secocepharanthine steponine steporphine stesakine 1-tetrahydropalmatine thalrugosine tuduranine	
<i>S. suberosa</i> Forman (roots)	(-)-capaurimine (-)-coreximine (-)-corytenchine (-)-discretine (-)-kikemanine 8-oxypseudopalmatine (-)-8-oxoxylopinine pseudopalmatine (-)-stephabinamine	Patra <i>et al.</i> , unpublished at this time



Table 2 (Continued)

Plant	Alkaloid	Reference
<i>Stephania suberosa</i> Forman (roots)	stephabine stepholidine (-)-tetrahydropalmatine (-)-tetrahydropalma- trubine (-)-tetrahydrostephabine (-)-xylopinine (-)trans-xylopinine N-oxide (-)cis-xylopinine N-oxide	
<i>S. tetrandra</i> S.Moore (roots)	cyclanoline fangchinoline tetrandrine	Kondo and Yano, 1928, 1929; Tomita <i>et al.</i> , 1967 c
<i>S. venosa</i> Spreng. (roots)	ayuthianine d-corydine (-)-crebanine stephanine sukhodianine tetrahydropalmatine thailandine ushinsunine uthongine	Tomita <i>et al.</i> , 1967 a; Guinaudeau <i>et al.</i> , 1981, 1982; Pharadai, <i>et al.</i> , 1981

Table 2 (Continued)

Plant	Alkaloid	Reference
<i>Stephania venosa</i> Spreng. (leaves)	(-)O-acetylsukhodianine (-)-crebanine dehydrocrebanine (-)-kikemanine liriodenine oxocrebanine oxostephanine oxostephanosine (-)-sukhodianine (-)-tetrahydropalmatine (-)-ushinsunine	Pharadai <i>et al.</i> , 1985
<i>S. viridiflavens</i> (roots)	jatrorrhizine palmatine l-tetrahydropalmatine l-xylopinine	Fang <i>et al.</i> , 1981



### Chemistry of *Stephania* alkaloids

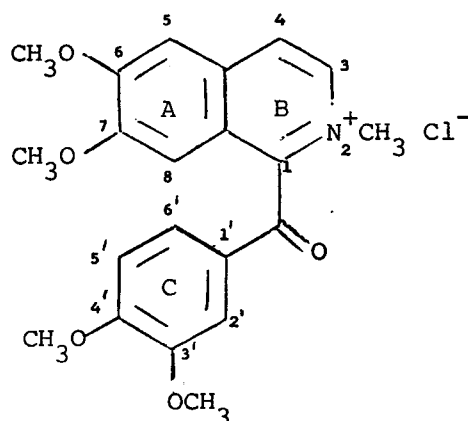
Most of alkaloids found in the *Stephania* species are isoquinolines as benzyloisoquinolines proaporphines, aporphines, oxoaporphines, dioxoaporphines, dehydroaporphines, morphinandienones, tetrahydroprotoberberines, quaternary protoberberines, dihydroprotoberberines, hasubanans, oxo-hasubanans, dioxohasubanans, hasubanalactams, hasubanan esters, C-norhasubanans, bisbenzyloisoquinolines, secobisbenzyloisoquinolines, benzyl-rheadans, isoquinolones and dibenzazonines

The numbering and structure of the alkaloids are as follows :-

#### I. Benzyloisoquinolines

The benzyloisoquinolines occupy a paramount position in alkaloid chemistry because they act as *in vivo* precursors to so many of the other naturally occurring isoquinoline alkaloids. Ring A in the benzyloisoquinoline alkaloids may possess two or three oxygenated substituents, which ring C has only one or two (Shamma, 1972b).

In genus *Stephania* it was found only one benzyloisoquinoline, N-methylpapaveraldinium chloride, isolated from *Stephania sasakii* Hayata (Kunitomo *et al.*, 1966).

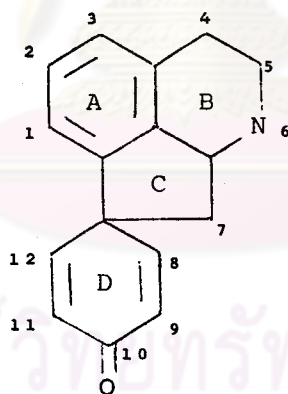


N-methylpapaveraldinium chloride

## II. Proaporphines

The proaporphine alkaloids occur in a variety of oxidation states. (+)-Pronuciferine possesses a cyclohexadienone system which is present in many other proaporphines such as (+)-crotonosine and (-)-orientalinone. The proaporphine numbering system is as indicated for (+)-pronuciferine. Because of the asymmetry at C-6a, one side of the dienone system is not equivalent to the other. The lower numbers (C-8 and C-9) are assigned to the side of the dienone above the mean plane of the molecule, and the higher numbers (C-11 and C-12) to the side below, as shown for (+)-linearisine (Shamma, 1972d).

There are three proaporphines isolated from genus *Stephania* and shown below :-



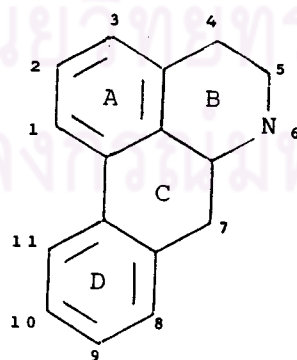
Alkaloid	Substitution			
	1	2	6	11
N-Acetylstepharine	OCH <sub>3</sub>	OCH <sub>3</sub>	COCH <sub>3</sub>	
Pronuciferine	OCH <sub>3</sub>	OCH <sub>3</sub>	H	CH <sub>3</sub>
Stepharine	OCH <sub>3</sub>	OCH <sub>3</sub>	H	

### III Aporphines

The aporphines are the large group of *Stephania* alkaloids, being second only to the tetrahydroprotoberberines. A methyl group is usually attached to the nitrogen and formed tertiary nitrogen atom. If the nitrogen is secondary, the alkaloid is called noraporphine.

Position 1 and 2 are always substituted with hydroxyl, methoxyl or methylenedioxy. Other substitutions may be found on the position 9,10,11 and less often on the position 3,8. In a few cases, a hydroxyl may locates at position 7, while steporphine is the only aporphine alkaloid known to be oxygenated at C-4 (Shamma, 1972e). Kunitomo *et al.* (1981c) isolated 4-hydroxycrebanine, a new 4-hydroxyaporphine alkaloid from *Stephania sasakii* Hayata.

The basic structure, the substitution of this alkaloidal type of *Stephania* species are shown below.

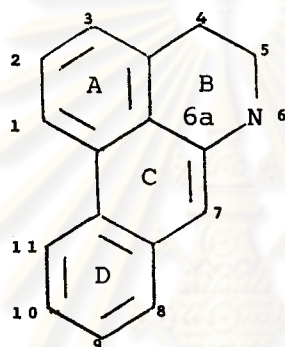


Alkaloid	Substitution										
	1	2	3	4	6	7	8	9	10	11	
Stephalagine	OCH <sub>2</sub> O		OCH <sub>3</sub>		CH <sub>3</sub>						
Steporphine	OCH <sub>2</sub> O			OH	CH <sub>3</sub>						
4-Hydroxycrebanine	OCH <sub>2</sub> O			OH	CH <sub>3</sub>		OCH <sub>3</sub>	OCH <sub>3</sub>			
Roemerine					CH <sub>3</sub>						
Ushinsunine	OCH <sub>2</sub> O				CH <sub>3</sub>	OH					
Ayuthianine	OCH <sub>2</sub> O				CH <sub>3</sub>	OH	OCH <sub>3</sub>				
Sukhodianine	OCH <sub>2</sub> O				CH <sub>3</sub>	OH	OCH <sub>3</sub>	OCH <sub>3</sub>			
O-Acetyl sukhodianine	OCH <sub>2</sub> O				CH <sub>3</sub>	OAc	OCH <sub>3</sub>	OCH <sub>3</sub>			
Stephanine	OCH <sub>2</sub> O				CH <sub>3</sub>		OCH <sub>3</sub>				
Crebanine	OCH <sub>2</sub> O				CH <sub>3</sub>		OCH <sub>3</sub>	OCH <sub>3</sub>			
Stesakine	OCH <sub>2</sub> O				CH <sub>3</sub>		OCH <sub>3</sub>	OH			
Roemeroline	OCH <sub>2</sub> O				CH <sub>3</sub>			OH			
Dicentrine	OCH <sub>2</sub> O				CH <sub>3</sub>			OCH <sub>3</sub>	OCH <sub>3</sub>		
Phanostenine	OCH <sub>2</sub> O				CH <sub>3</sub>			OCH <sub>3</sub>	OH		
Norcorydine	OH	OCH <sub>3</sub>			H				OCH <sub>3</sub>	OCH <sub>3</sub>	
Corytuberine	OH	OCH <sub>3</sub>			CH <sub>3</sub>				OCH <sub>3</sub>	OH	
Corydine	OH	OCH <sub>3</sub>			CH <sub>3</sub>				OCH <sub>3</sub>	OCH <sub>3</sub>	
Magnoflorine	OH	OCH <sub>3</sub>			(CH <sub>3</sub> ) <sub>2</sub>				OCH <sub>3</sub>	OH	
N-methyl corydine	OH	OCH <sub>3</sub>			(CH <sub>3</sub> ) <sub>2</sub>				OCH <sub>3</sub>	OCH <sub>3</sub>	
Tuduranine	OCH <sub>3</sub>	OCH <sub>3</sub>			H				OH		
Nuciferine	OCH <sub>3</sub>	OCH <sub>3</sub>			CH <sub>3</sub>						
N-methyl-lauro- tetanine	OCH <sub>3</sub>	OCH <sub>3</sub>			CH <sub>3</sub>			OH	OCH <sub>3</sub>		
Isocorydine	OCH <sub>3</sub>	OCH <sub>3</sub>			CH <sub>3</sub>				OCH <sub>3</sub>	OH	
N-methyl glaucine	OCH <sub>3</sub>	OCH <sub>3</sub>			(CH <sub>3</sub> ) <sub>2</sub>			OCH <sub>3</sub>	OCH <sub>3</sub>		
Isoboldine		OCH <sub>3</sub>			CH <sub>3</sub>			OH	OCH <sub>3</sub>		

#### IV. Dehydroaporphines

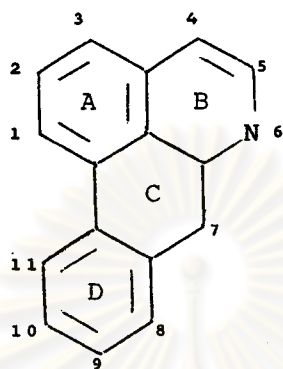
The dehydroaporphines are optically inactive and classified as a subgroup of the aporphine alkaloids (Shamma, 1972e). From the basic structure, there are two types of this subgroup.

a) 6a,7-Dehydroaporphines. In this subgroup, dehydrodicentrine was first reported to be isolated from natural sources. The unsaturation is on the C-6a,7. The details of their structures isolated from *Stephania* species are shown below :-



Alkaloid	Substitution					
	1	2	6	8	9	10
Dehydrostephanine	OCH <sub>2</sub> O	CH <sub>3</sub>	OCH <sub>3</sub>			
Dehydrocrebanine	OCH <sub>2</sub> O	CH <sub>3</sub>	OCH <sub>3</sub>	OCH <sub>3</sub>		
Dehydrostesakine	OCH <sub>2</sub> O	CH <sub>3</sub>	OCH <sub>3</sub>	OH		
Dehydrodicentrine	OCH <sub>2</sub> O	CH <sub>3</sub>			OCH <sub>3</sub>	OCH <sub>3</sub>
Dehydrophanostenine	OCH <sub>2</sub> O	CH <sub>3</sub>			OCH <sub>3</sub>	OH

b) 4,5-Dehydroaporphines. The unsaturation is on the C-4,5. Only one alkaloid of this subgroup in *Stephania* species is dehydroroemerine.



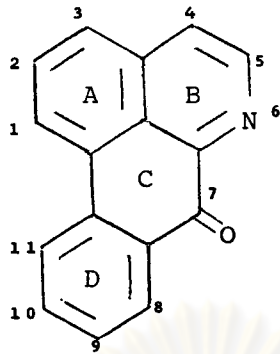
Alkaloid	Substitution		
	1	2	6
Dehydroroemerine	OCH <sub>2</sub> O		CH <sub>3</sub>

#### V. Oxoaporphines

Oxoaporphine alkaloids are probably derived in plant by oxidation of the corresponding aporphine alkaloids. The free bases possess a bright yellow or orange color which will be turned to pink or red upon the addition of mineral acids.

W.I. Taylor, in 1961, described the structural elucidation and synthesis of liriodenine, the first oxoaporphine to be fully characterized (Shamma, 1972f).

The structures of this alkaloidal group in *Stephania* species are summarized and shown below :-

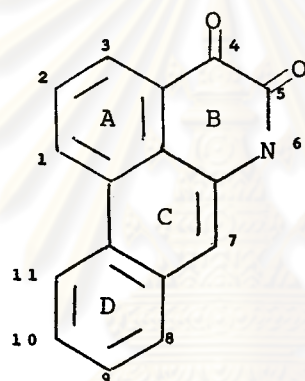


Alkaloid	Substitution					
	1	2	6	8	9	10
Liriodenine		OCH <sub>2</sub> O	-			
Thailandine		OCH <sub>2</sub> O	CH <sub>3</sub>	OCH <sub>3</sub>		
Uthongine		OCH <sub>2</sub> O	CH <sub>3</sub>	OCH <sub>3</sub>	OCH <sub>3</sub>	
Oxostephanine		OCH <sub>2</sub> O	-	OCH <sub>3</sub>		
7-oxocrebanine		OCH <sub>2</sub> O	-	OCH <sub>3</sub>	OCH <sub>3</sub>	
Lanuginosine		OCH <sub>2</sub> O	-		OCH <sub>3</sub>	
Dicentrinone		OCH <sub>2</sub> O	-		OCH <sub>3</sub>	OCH <sub>3</sub>
Oxoxylopine		OCH <sub>2</sub> O	-			OCH <sub>3</sub>
Lysicamine	OCH <sub>3</sub>		OCH <sub>3</sub>	-		

## VI. 4,5-Dioxoaporphines

It is only recently that the reddish-orange 4,5-dioxoaporphines have been recognized as a distinct group of isoquinoline alkaloids. This group includes cepharadione-A and -B, norcepharadione-B and pontevedrine which was previously believed to be a 5,7-dioxoaporphine (Shamma and Moniot, 1978b).

For *Stephania* species, this group of alkaloid was only isolated from *Stephania sasakii* Hayata as cepharadione-A and 4,5-dioxodehydrocrebanine (Kunitomo *et al.*, 1980a, 1981a).



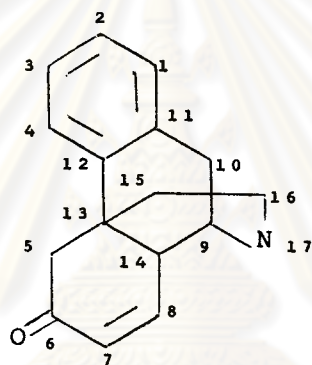
Alkaloid	Substitution				
	1	2	6	8	9
Cepharadione-A	OCH <sub>2</sub> O		CH <sub>3</sub>		
4,5-Dioxodehydrocrebanine	OCH <sub>2</sub> O		CH <sub>3</sub>	OCH <sub>3</sub>	OCH <sub>3</sub>



## VII. Morphinandienones

The morphinandienone alkaloids are more limited in numbers and distribution. There are fewer than a dozen of them distributed in Family Papaveraceae, the genus *Papaver* and several genera of the Menispermaceae (Robinson, 1981).

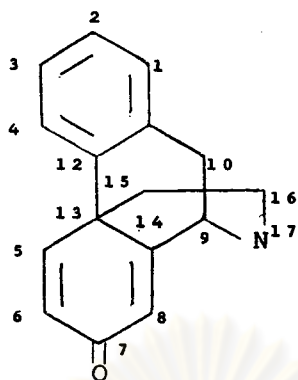
The basic structure of the morphinandienone alkaloids found in genus *Stephania* are occurred in three formulae; A, B and C. The summarization of the structures and their substitutions are shown in the following tables.



Formula A

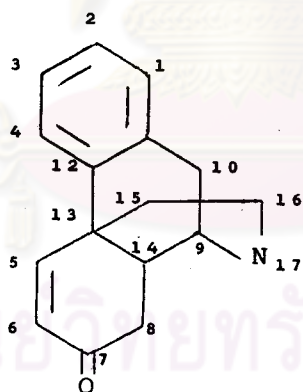


Alkaloid	Substitution						
	2	3	4	7	8	16	17
Sinomenine		OCH <sub>3</sub>	OH	OCH <sub>3</sub>			CH <sub>3</sub>
Isostephodeline	OCH <sub>3</sub>	OCH <sub>3</sub>		OCH <sub>3</sub>	OCH <sub>3</sub>		H
Delavaine		OCH <sub>2</sub> O		OCH <sub>3</sub>	OCH <sub>3</sub>		CH <sub>3</sub>
16-Oxodelavaine		OCH <sub>2</sub> O		OCH <sub>3</sub>	OCH <sub>3</sub>	O	CH <sub>3</sub>



Formula B

Alkaloid Formula B	Substitution			
	3	4	6	17
Sinoacutine	OCH <sub>3</sub>	OH	OCH <sub>3</sub>	CH <sub>3</sub>



Formula C

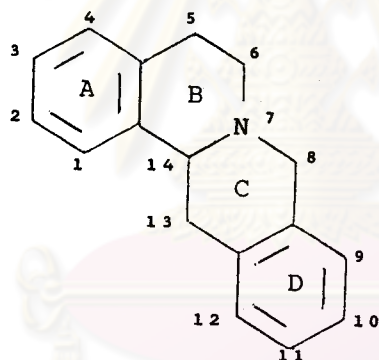
Alkaloid Formula C	Substitution			
	3	4	6	17
8,14-dihydrosalutaridine	OCH <sub>3</sub>	OH	OCH <sub>3</sub>	CH <sub>3</sub>

### VIII. Protoberberines

Most of protoberberine alkaloids exist in nature as tetrahydroprotoberberine and quaternary protoberberine salts, but some dihydroprotoberberines are also known. Substitutions are usually present at C-2 and C-3, C-9 and C-10, or C-10 and C-11. In some instances a hydroxyl or methyl substitution may be presented at C-1 (Shamma, 1972g).

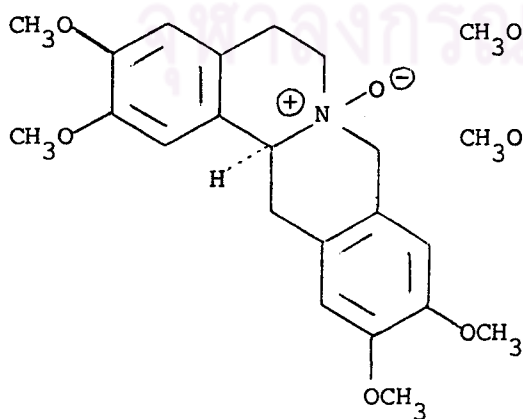
The basic structure, the substitutions and the list of alkaloids are summarized in three subgroups as was mentioned above.

#### a) Tetrahydroprotoberberines and its N-oxides

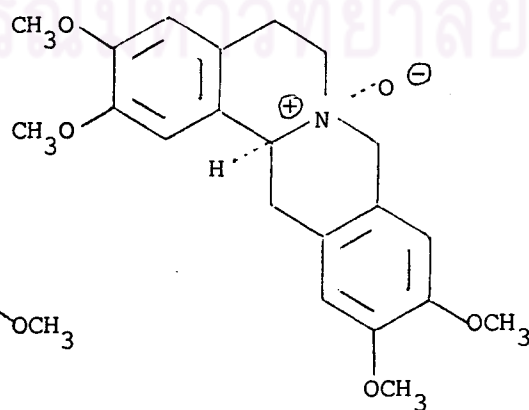


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Alkaloid	Substitution								
	1	2	3	7	8	9	10	11	
Capaurine	OH	OCH <sub>3</sub>	OCH <sub>3</sub>	-		OCH <sub>3</sub>	OCH <sub>3</sub>		
Capaurimine	OH	OCH <sub>3</sub>	OCH <sub>3</sub>	-		OCH <sub>3</sub>	OH		
Stephabinamine	OH	OCH <sub>3</sub>	OCH <sub>3</sub>	-			OCH <sub>3</sub>	OH	
Tetrahydrostephabine	OH	OCH <sub>3</sub>	OCH <sub>3</sub>	-			OCH <sub>3</sub>	OCH <sub>3</sub>	
Kikemanine	CH <sub>3</sub>	OCH <sub>3</sub>	OCH <sub>3</sub>	-		OCH <sub>3</sub>	OH		
Isocorypalmine		OH	OCH <sub>3</sub>	-		OCH <sub>3</sub>	OCH <sub>3</sub>		
Stepholidine		OH	OCH <sub>3</sub>	-		OCH <sub>3</sub>	OH		
Tetrahydrocolumbamine		OH	OCH <sub>3</sub>	-		OCH <sub>3</sub>	OCH <sub>3</sub>		
Coreximine		OH	OCH <sub>3</sub>	-			OCH <sub>3</sub>	OH	
Tetrahydropalmatine		OCH <sub>3</sub>	OCH <sub>3</sub>	-		OCH <sub>3</sub>	OCH <sub>3</sub>		
Corydalmine		OCH <sub>3</sub>	OCH <sub>3</sub>	-		OCH <sub>3</sub>	OH		
Tetrahydropalmatrubine		OCH <sub>3</sub>	OCH <sub>3</sub>	-		OH	OCH <sub>3</sub>		
Tetrahydrojatrorrhizine		OCH <sub>3</sub>	OH	-		OCH <sub>3</sub>	OCH <sub>3</sub>		
Corypalmine		OCH <sub>3</sub>	OH	-		OCH <sub>3</sub>	OCH <sub>3</sub>		
Discretamine		OCH <sub>3</sub>	OH	-		OCH <sub>3</sub>	OH		
Xylopinine		OCH <sub>3</sub>	OCH <sub>3</sub>	-			OCH <sub>3</sub>	OCH <sub>3</sub>	
Corytenchine		OCH <sub>3</sub>	OCH <sub>3</sub>	-			OCH <sub>3</sub>	OH	
Discretine		OCH <sub>3</sub>	OH	-			OCH <sub>3</sub>	OCH <sub>3</sub>	
Cyclanoline		OH	OCH <sub>3</sub>	CH <sub>3</sub>		OH	OCH <sub>3</sub>		
Steponine		OCH <sub>3</sub>	OH	CH <sub>3</sub>		OH	OCH <sub>3</sub>		
N-methyl corydalmine		OCH <sub>3</sub>	OCH <sub>3</sub>	CH <sub>3</sub>		OCH <sub>3</sub>	OH		
Corynoxidine		OCH <sub>3</sub>	OCH <sub>3</sub>	β-OH		OCH <sub>3</sub>	OCH <sub>3</sub>		
8-Oxoxylopinine		OCH <sub>3</sub>	OCH <sub>3</sub>	-	O		OCH <sub>3</sub>	OCH <sub>3</sub>	

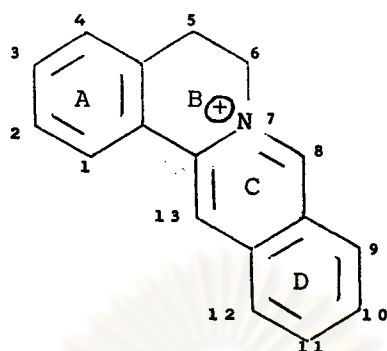


(-)-trans-xylopinine N-oxide



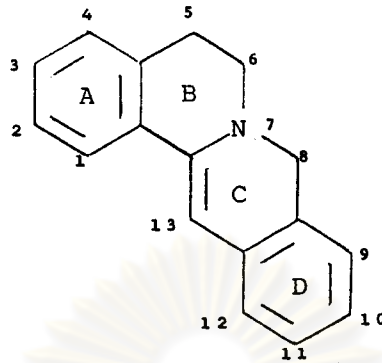
(-)-cis-xylopinine N-oxide

## b) Quaternary protoberberines



Alkaloid	Substitution					
	1	2	3	9	10	11
Berberine		OCH <sub>2</sub> O		OCH <sub>3</sub>	OCH <sub>3</sub>	
Palmatine		OCH <sub>3</sub>	OCH <sub>3</sub>	OCH <sub>3</sub>	OCH <sub>3</sub>	
Columbamine		OH	OCH <sub>3</sub>	OCH <sub>3</sub>	OCH <sub>3</sub>	
Jatrorrhizine		OCH <sub>3</sub>	OH	OCH <sub>3</sub>	OCH <sub>3</sub>	
Dehydrodiscretamine		OCH <sub>3</sub>	OH	OCH <sub>3</sub>	OH	
Dehydrocorydalmine		OCH <sub>3</sub>	OCH <sub>3</sub>	OCH <sub>3</sub>	OH	
Stepharanine		OH	OCH <sub>3</sub>	OCH <sub>3</sub>	OH	
Palmatrubine		OCH <sub>3</sub>	OCH <sub>3</sub>	OH	OCH <sub>3</sub>	
Stephantine	OH	OCH <sub>3</sub>	OCH <sub>3</sub>		OCH <sub>3</sub>	OCH <sub>3</sub>

## c) Dihydroprotoberberines



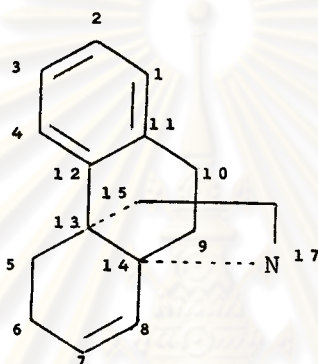
Alkaloid	Substitution				
	2	3	8	9	10
Dihydropalmatine	OCH <sub>3</sub>	OCH <sub>3</sub>		OCH <sub>3</sub>	OCH <sub>3</sub>
8-Oxypseudopalmatine	OCH <sub>3</sub>	OCH <sub>3</sub>	O	OCH <sub>3</sub>	OCH <sub>3</sub>

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## IX. Hasubanans

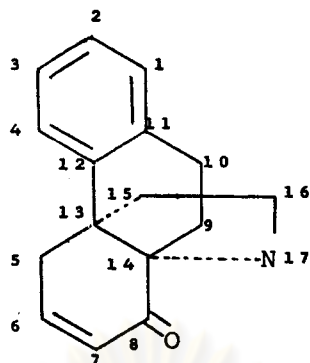
The hasubanan alkaloids are limited in distribution to the genera *Menispermum*, *Sinomenium* and *Stephania* in the family Menispermaceae. The numbering system of the skeleton is suggested by Tomita (Cordell, 1981b).

The basic structures and substitutions of the alkaloids found in *Stephania* species are summarized in five formulae in the following tables.



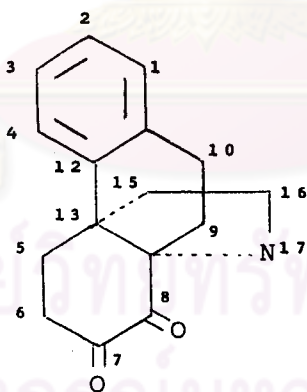
Formula A

Alkaloid	Substitution						
	3	4	6	7	8	16	17
Homostephanoline	OH	OCH <sub>3</sub>	O	OCH <sub>3</sub>	OCH <sub>3</sub>		CH <sub>3</sub>
Cepharamine	OCH <sub>3</sub>	OH	O	OCH <sub>3</sub>			CH <sub>3</sub>
4-Desmethylhasubanonine (aknadinine)	OCH <sub>3</sub>	OH	O	OCH <sub>3</sub>	OCH <sub>3</sub>		CH <sub>3</sub>
4-Desmethylnorhasubanonine (aknadicine)	OCH <sub>3</sub>	OH	O	OCH <sub>3</sub>	OCH <sub>3</sub>		H
Hasubanonine	OCH <sub>3</sub>	OCH <sub>3</sub>	O	OCH <sub>3</sub>	OCH <sub>3</sub>		CH <sub>3</sub>
Hernandoline	OCH <sub>3</sub>	OH	O	OCH <sub>3</sub>	OCH <sub>3</sub>		CH <sub>3</sub>
Hernandolinol	OCH <sub>3</sub>	OH	OH	OCH <sub>3</sub>	OCH <sub>3</sub>		OH
16-oxohasubanonine	OCH <sub>3</sub>	OCH <sub>3</sub>	O	OCH <sub>3</sub>	OCH <sub>3</sub>	O	CH <sub>3</sub>
Aknadilactam	OCH <sub>3</sub>	OH	O	OCH <sub>3</sub>	OCH <sub>3</sub>	O	CH <sub>3</sub>



Formula B

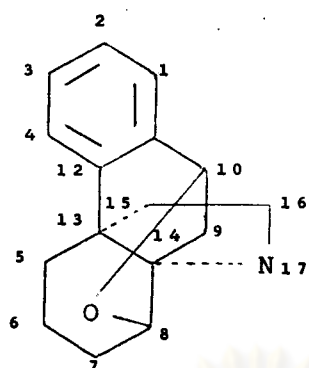
Alkaloid	Substitution					
	3	4	7	10	16	17
Formula B						
Prometaphanine	OCH <sub>3</sub>	OCH <sub>3</sub>	OCH <sub>3</sub>	OH		CH <sub>3</sub>
16-oxoprometaphanine	OCH <sub>3</sub>	OCH <sub>3</sub>	OCH <sub>3</sub>	OH	O	CH <sub>3</sub>



Formula C

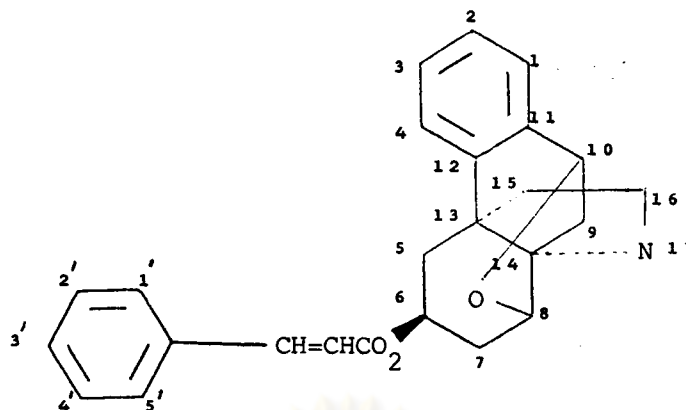
Alkaloid	Substitution			
	3	4	10	17
Formula C				
Metaphanine	OCH <sub>3</sub>	OCH <sub>3</sub>	OH	CH <sub>3</sub>





Formula D

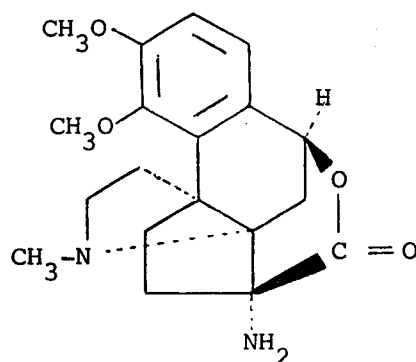
Alkaloid Formula D	Substitution							
	2	3	4	6	7	8	16	17
Stephabenine	OCH <sub>2</sub> O							CH <sub>3</sub>
Hernandine		OCH <sub>3</sub>	OH	OH	OH	OCH <sub>3</sub>		CH <sub>3</sub>
Methylhernandine		OCH <sub>3</sub>	OH	OH	OCH <sub>3</sub>	OCH <sub>3</sub>		CH <sub>3</sub>
Stephaboline		OCH <sub>3</sub>	OH		OH	OH		CH <sub>3</sub>
Longanine		OCH <sub>3</sub>	OH	OH	OCH <sub>3</sub>	OH		CH <sub>3</sub>
Stephasunoline		OCH <sub>3</sub>	OCH <sub>3</sub>	OH	OCH <sub>3</sub>	OH		CH <sub>3</sub>
Longanone		OCH <sub>3</sub>	OH	O	OCH <sub>3</sub>	OCH <sub>3</sub>		CH <sub>3</sub>
Stephamiersine		OCH <sub>3</sub>	OCH <sub>3</sub>	O	OCH <sub>3</sub>	OCH <sub>3</sub>		CH <sub>3</sub>
Stephabyssine		OCH <sub>3</sub>	OH		O	OH		CH <sub>3</sub>
Oxostephasunoline		OCH <sub>3</sub>	OCH <sub>3</sub>	OH	OCH <sub>3</sub>	OH	O	CH <sub>3</sub>
Oxostephamiersine		OCH <sub>3</sub>	OCH <sub>3</sub>	O	OCH <sub>3</sub>	OCH <sub>3</sub>	O	CH <sub>3</sub>
6-dihydroepistepha- miersine-6 acetate		OCH <sub>3</sub>	OCH <sub>3</sub>	OAc	OCH <sub>3</sub>	OCH <sub>3</sub>		CH <sub>3</sub>



Formula E

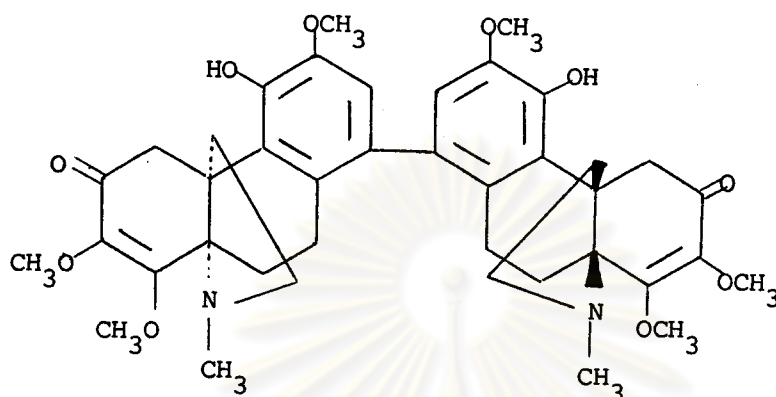
Alkaloid Formula E	Substitution						
	3	4	7	8	17	3'	4'
Hernandifoline	OCH <sub>3</sub>	OH	OCH <sub>3</sub>	OCH <sub>3</sub>	H	OCH <sub>3</sub>	OH
Stephisoferuline	OCH <sub>3</sub>	OH	OCH <sub>3</sub>	OCH <sub>3</sub>	H	OCH <sub>3</sub>	OH
3-O-demethyl- hernandifoline	OH	OH	OCH <sub>3</sub>	OCH <sub>3</sub>	H	OCH <sub>3</sub>	OH

Stephadiamine, a new skeletal alkaloid from *Stephania japonica* (Thunb.) Miers is the first example of a C-Norhasubanan alkaloid. The ethanolic extract of the whole plant collected in Taiwan was previously reported to yield many alkaloids such as metaphanine. Taga *et al.* (1984) isolated a novel skeletal lactonic alkaloid, stephadiamine. The structure of stephadiamine has a hasubanan-like pentacyclic skeleton, which has not previously been found in nature.



Stephadiamine

Bisaknadinine is a new dimeric hasubanan type alkaloid containing biphenyl linkage, isolated from *Stephania sasakii* Hayata. The structure is shown below :-

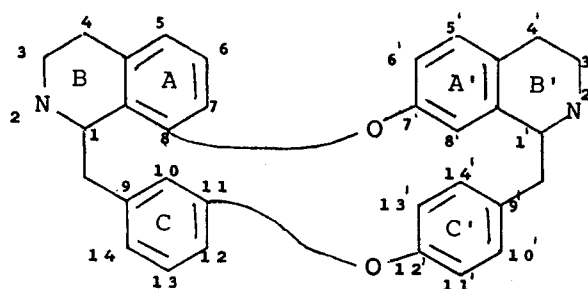


Bisaknadinine

#### X. Bisbenzylisoquinolines

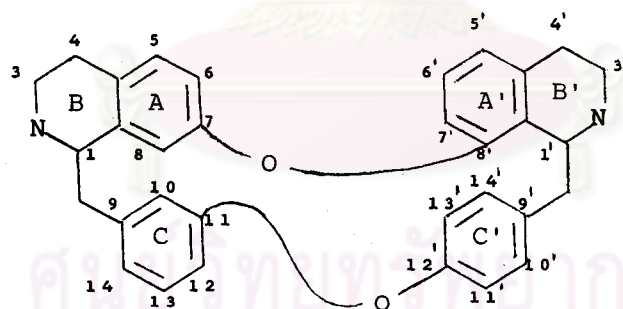
Bisbenzylisoquinoline alkaloids have been classified into 28 types. An asterisk (\*) or other symbol (+ or †) on the upper right of a number indicated the diarylether terminals. Numbers in parentheses are used to indicate aryl-aryl bonds. Square brackets are used to indicate the terminals of a methylene dioxy bridge (Shamma and Moniot, 1978a). Among 28 types of them, the alkaloids in genus *Stephania* distribute in 5 types of bisbenzylisoquinolines as follows.

a) Bisbenzylisoquinolines; Berbamine type; 6,7,8<sup>\*</sup>,11<sup>+</sup>, 12-6,7<sup>\*</sup>,12<sup>+</sup>



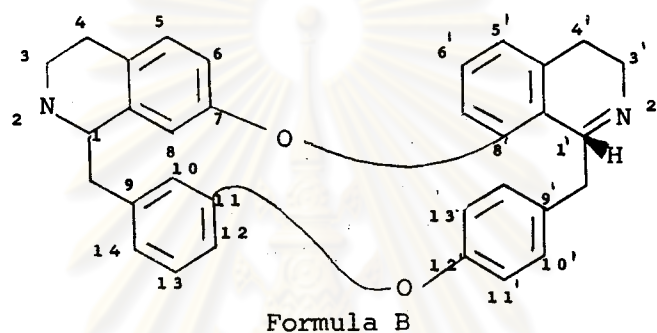
Alkaloid	Substitution									
	2	6	7	12	2'	5'	6'	7'	11'	
Berbamine	CH <sub>3</sub>	OCH <sub>3</sub>			CH <sub>3</sub>		OCH <sub>3</sub>	OCH <sub>3</sub>		
Tetrandrine	CH <sub>3</sub>	OCH <sub>3</sub>		OCH <sub>3</sub>	CH <sub>3</sub>		OCH <sub>3</sub>	OCH <sub>3</sub>		
Isotetrandrine	CH <sub>3</sub>	OCH <sub>3</sub>		OCH <sub>3</sub>	CH <sub>3</sub>		OCH <sub>3</sub>	OCH <sub>3</sub>		
Fangchinoline	CH <sub>3</sub>	OCH <sub>3</sub>		OCH <sub>3</sub>	CH <sub>3</sub>		OCH <sub>3</sub>			
Obamegine (= Stepoline)	CH <sub>3</sub>	OCH <sub>3</sub>			CH <sub>3</sub>		OCH <sub>3</sub>			
Stephanoline	CH <sub>3</sub>				CH <sub>3</sub>	OCH <sub>3</sub>	OCH <sub>3</sub>	OCH <sub>3</sub>	OCH <sub>3</sub>	
Thalrugosine	CH <sub>3</sub>	OCH <sub>3</sub>	OH	OCH <sub>3</sub>	CH <sub>3</sub>		OCH <sub>3</sub>			

b) Bisbenzylisoquinolines; Oxycanthine type; 6,7<sup>\*</sup>,11<sup>+</sup>,  
12-6,7,8<sup>\*</sup>,12<sup>+</sup>

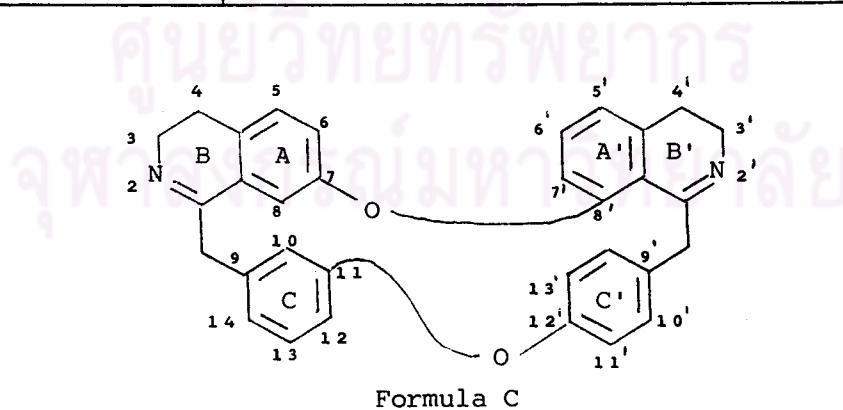


Formula A

Alkaloid Formula A	Substitution					
	2	6	12	2'	6'	7'
Cepharanoline	CH <sub>3</sub>	OCH <sub>3</sub>		CH <sub>3</sub>	-OCH <sub>2</sub> O-	
Cepharanthine	CH <sub>3</sub>	OCH <sub>3</sub>	OCH <sub>3</sub>	CH <sub>3</sub>	-OCH <sub>2</sub> O-	
Homoaromoline	CH <sub>3</sub>	OCH <sub>3</sub>	OCH <sub>3</sub>	CH <sub>3</sub>	OCH <sub>3</sub>	
Obaberine	CH <sub>3</sub>	OCH <sub>3</sub>	OCH <sub>3</sub>	CH <sub>3</sub>	OCH <sub>3</sub>	OCH <sub>3</sub>



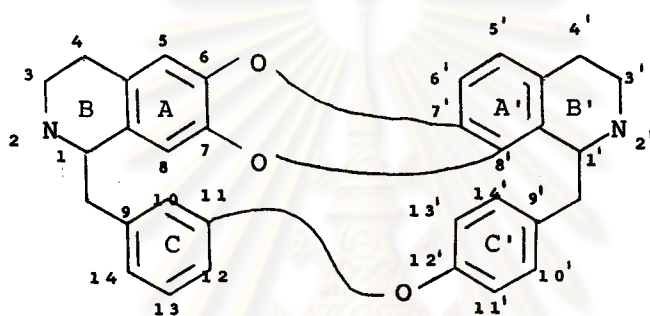
Alkaloid Formula B	Substitution				
	2	6	12	6'	7'
Epistephanine	CH <sub>3</sub>	OCH <sub>3</sub>	OCH <sub>3</sub>	OCH <sub>3</sub>	OCH <sub>3</sub>
Hypoepistephanine	CH <sub>3</sub>	OCH <sub>3</sub>	OH	OCH <sub>3</sub>	OCH <sub>3</sub>



Alkaloid	Substitution			
	6	12	6'	7'
Formula C				
Stebisimine	OCH <sub>3</sub>	OCH <sub>3</sub>	OCH <sub>3</sub>	OCH <sub>3</sub>

c) Bisbenzylisoquinolines; Dibenzo-p-dioxin type;

6<sup>\*</sup>, 7<sup>+</sup>, 11<sup>+</sup>, 12-6, 7<sup>\*</sup>, 8<sup>+</sup>, 12<sup>+</sup>

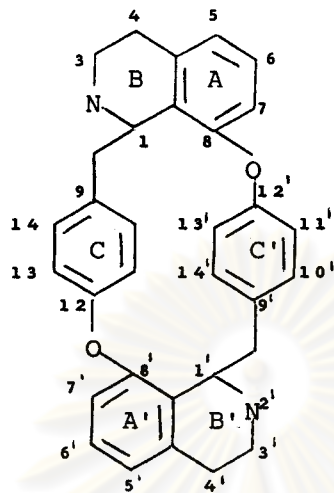


Alkaloid	Substitution			
	2	12	2'	6'
Isotrilobine	CH <sub>3</sub>	OCH <sub>3</sub>	CH <sub>3</sub>	OCH <sub>3</sub>

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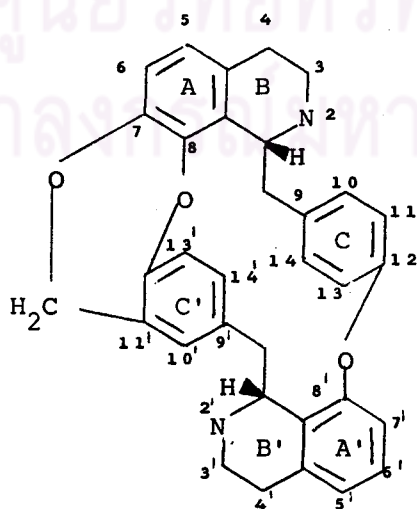
d) Bisbenzylisoquinolines; Isochondodendrine type;

6,7,8<sup>\*</sup>,12<sup>±</sup>-6,7,8<sup>+</sup>,12<sup>\*</sup>



Formula A

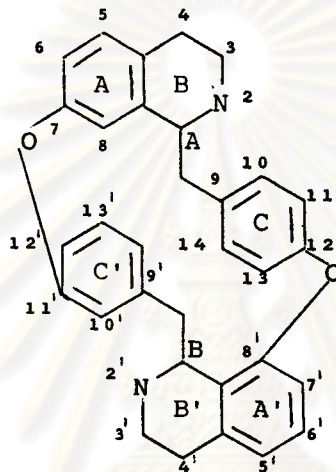
Alkaloid	Substitution					
	2	6	7	2'	6'	7'
Formula A						
Isochondodendrine	CH <sub>3</sub>	OCH <sub>3</sub>		CH <sub>3</sub>	OCH <sub>3</sub>	
Cycleanine	CH <sub>3</sub>	OCH <sub>3</sub>	OCH <sub>3</sub>	CH <sub>3</sub>	OCH <sub>3</sub>	OCH <sub>3</sub>
N-desmethyl cycleanine	CH <sub>3</sub>	OCH <sub>3</sub>	OCH <sub>3</sub>	H	OCH <sub>3</sub>	OCH <sub>3</sub>



Formula B

Alkaloid	Substitution				
	2	6	2'	6'	7'
Insularine	CH <sub>3</sub>	OCH <sub>3</sub>	CH <sub>3</sub>	OCH <sub>3</sub>	OCH <sub>3</sub>

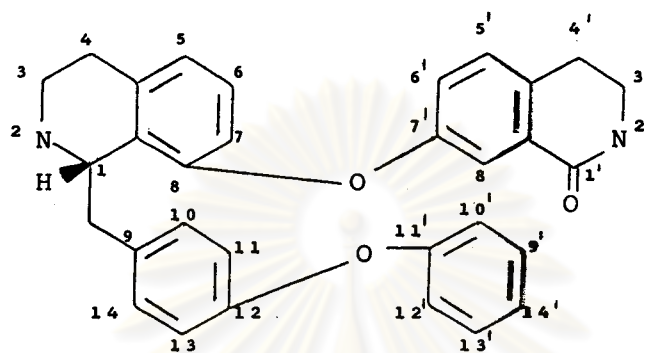
e) Bisbenzylisoquinoline; Curine type; 6,7,8<sup>\*</sup>,11<sup>+</sup>,  
12-6,7<sup>+</sup>,12<sup>\*</sup>



Alkaloid	Substitution						Configuration	
	2	6	2'	6'	7'	13'	A	B
d-Curine	CH <sub>3</sub>	OCH <sub>3</sub>	CH <sub>3</sub>	OCH <sub>3</sub>	OH	OH	L	L
l-Curine	CH <sub>3</sub>	OCH <sub>3</sub>	CH <sub>3</sub>	OCH <sub>3</sub>	OH	OH	D	D

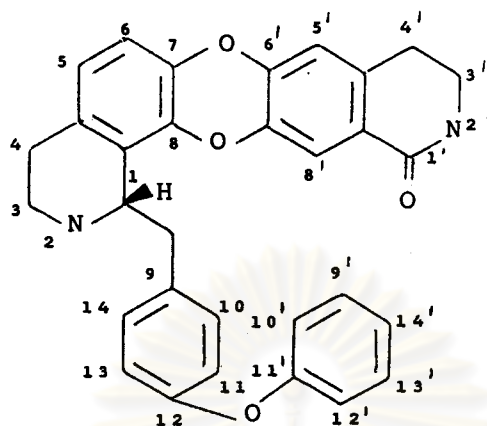


Four secobisbenzylisoquinoline alkaloids, dihydrosecocepharanthine, secocepharanthine, O-methyldeoxypunjabine and O-methylpunjabine were isolated from *Stephania sasakii* Hayata. Their structures were established as formula A or B.



Formula A

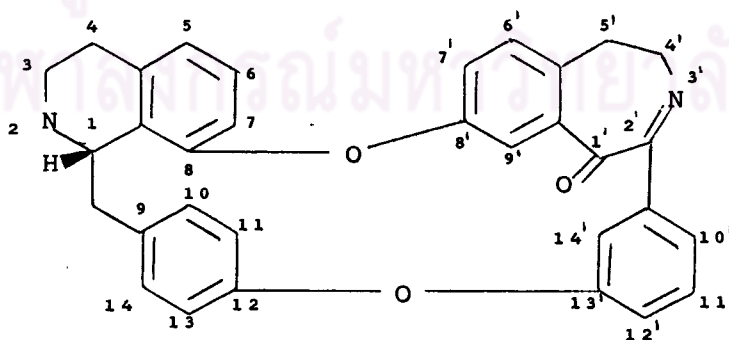
Alkaloid	Substitution						
	2	6	7	2'	6'	9'	12'
Formula A							
dihydrosecocepharanthine	CH <sub>3</sub>	OCH <sub>2</sub> O	CH <sub>3</sub>	OCH <sub>3</sub>	CHO	OCH <sub>3</sub>	
secocepharanthine	CH <sub>3</sub>	OCH <sub>2</sub> O	CH <sub>3</sub>	OCH <sub>3</sub>	CH <sub>2</sub> OH	OCH <sub>3</sub>	



Formula B

Alkaloid	Substitution				
	2	6	2'	9'	12'
O-methyldeoxopunjabine	CH <sub>3</sub>	OCH <sub>3</sub>	CH <sub>3</sub>	CH <sub>3</sub>	OCH <sub>3</sub>
O-methylpunjabine	CH <sub>3</sub>	OCH <sub>3</sub>	CH <sub>3</sub>	CHO	OCH <sub>3</sub>

## XI. Benzyl-Rheadans



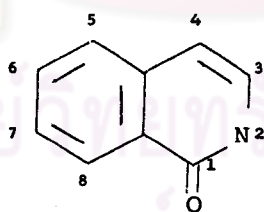
Alkaloid	Substitution				
	2	6	7	7'	12'
Stepinonine	CH <sub>3</sub>	OCH <sub>3</sub>	OCH <sub>3</sub>	OCH <sub>3</sub>	OH

Stepinonine is an unusual bisbenzylisoquinolines, isolated from *Stephania japonica* Miers (Shamma and Moniot, 1978a).

## XII. Isoquinolones

The isoquinolone alkaloids are a small group of alkaloids present in plants only in minor amounts. They can be subdivided into two categories : those with a totally aromatic nucleus such as doryanine, thalactamine and those which incorporate a C-3,4 single bond (Shamma, 1972b).

In *Stephania* species, it was found only one isoquinolone, N-methyl-6, 7-dimethoxy-1-isoquinolone, from *Stephania sasakii* Hayata (Kunitomo *et al.*, 1981a).

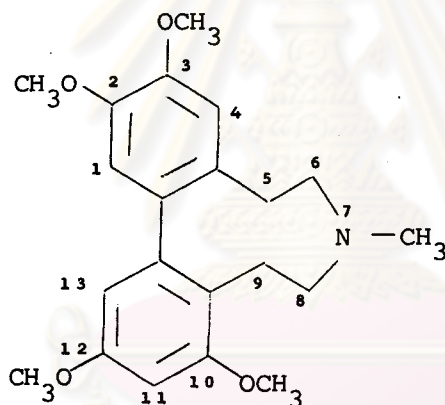


Alkaloid	Substitution		
	2	6	7
N-Methyl-6, 7-dimethoxy-1-isoquinolone	CH <sub>3</sub>	OCH <sub>3</sub>	OCH <sub>3</sub>

### XIII. Dibenzazonine

The dibenzazonine alkaloids are the small group of isoquinoline alkaloids. It can be divided into two types, the fully oxygenated bases such as erybidine, and those which have undergone a net deoxygenation with respect to their precursors, for example, protostephanine, laurifinine, laurifine and laurifonine (Shamma and Moniot, 1978c).

In *Stephania* species, it was found only protostephanine from *Stephania japonica* Miers. by Kondo and Sanada (1972a). The structure of the alkaloid is shown below :-



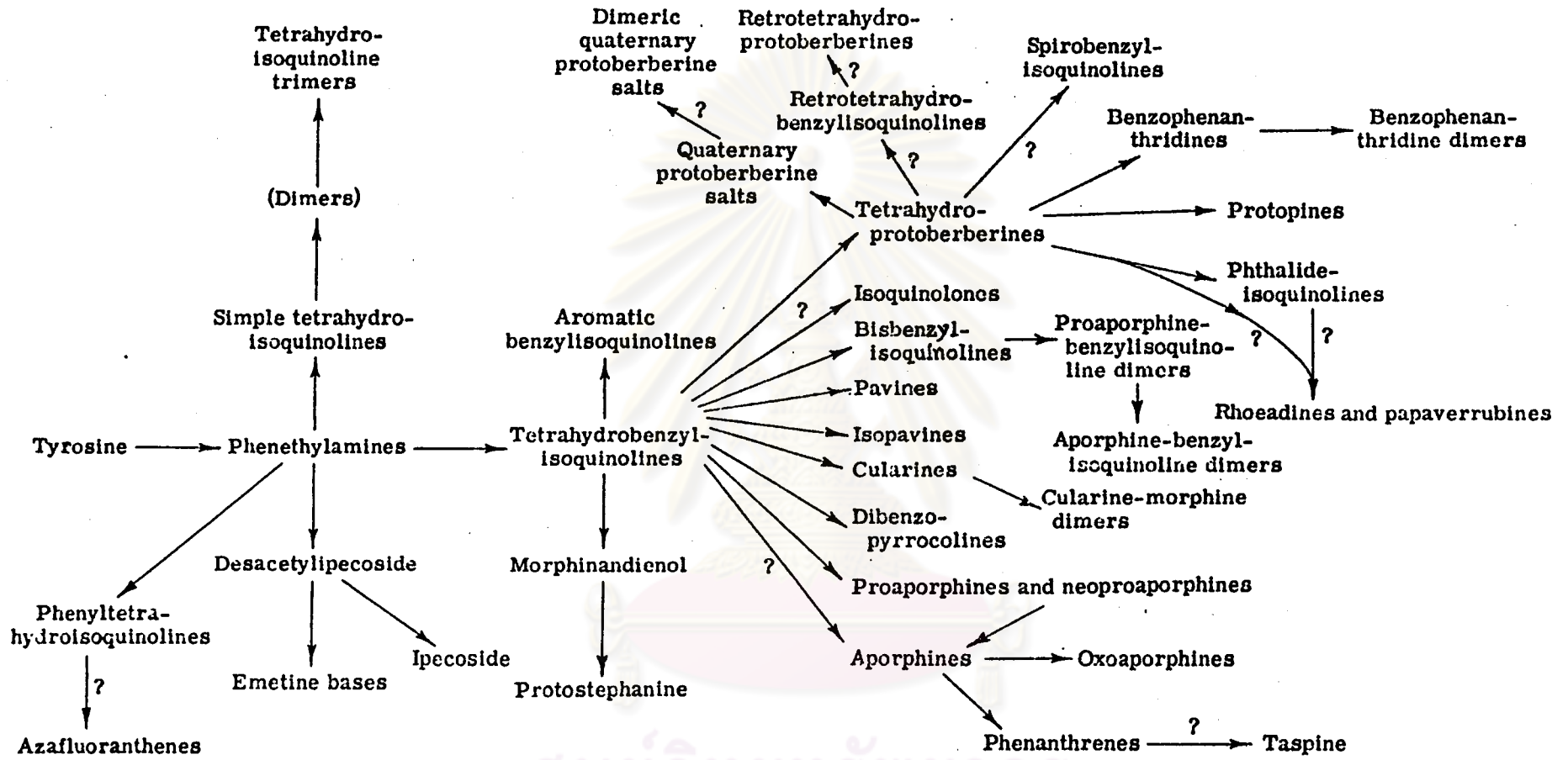
Protostephanine



## Biosynthesis

The biosynthetic routes of isoquinoline alkaloids which, generally accepted are started from the essential amino acid, tyrosine as shown in Scheme 1 (Shamma, 1972a). It is conveniently treated the alkaloids in two parts, starting with the generation of simple isoquinoline structures, then elaborating to more complicated structures (Staunton, 1979).

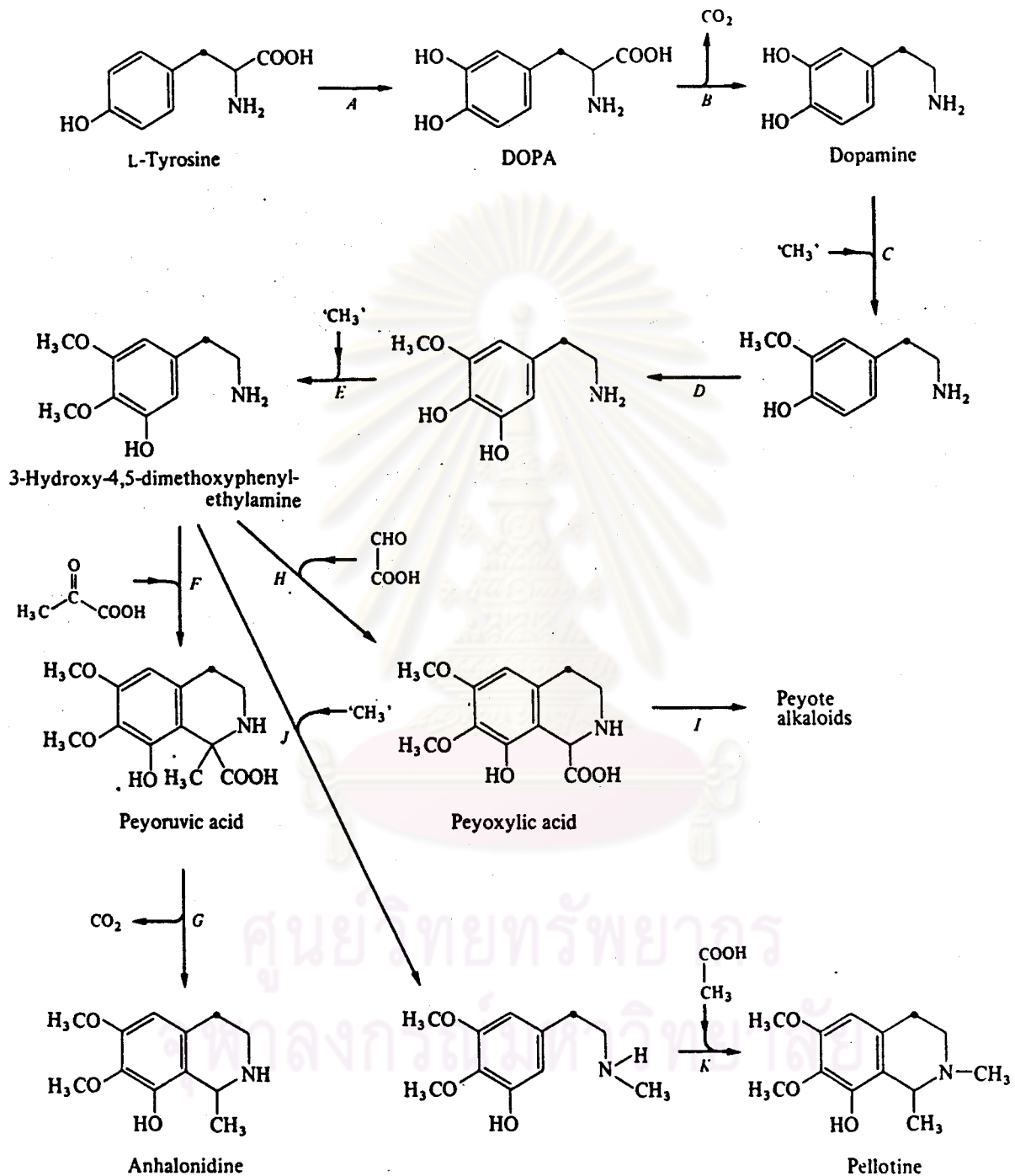
The formation of the simple tetrahydroisoquinoline alkaloids involves the hydroxylation of the aromatic ring of L-tyrosine followed by decarboxylation and then ring closure with another compound, which provides an additional one or two carbon units, occurs. A typical example of this procedure is seen in the formation of anhalonidine by the peyote cactus (Scheme 2). It is assumed that 3,4-dihydroxyphenylalanine (DOPA), formed by 3-hydroxylation of L-tyrosine, is converted into 3-hydroxy-4,5-dimethoxyphenylethylamine, known to be present in the peyote cactus *Lophophora williamsii* (Lam.) Coulter, by a series of steps (steps B,C,D and E). The 3-hydroxy-4,5-dimethoxyphenylethylamine then undergoes ring closure (step F) with pyruvate to form peyoruvic acid which is then decarboxylated (step G) to anhalonidine. The proposed intermediate, peyoruvic acid, has been isolated from *L. williamsii*. The analogue of peyoruvic acid, peyoxylic acid, is formed by the condensation of the precursor amine with glyoxylic acid (step H); peyoxylic acid can also be incorporated into peyote alkaloids (step I). The N-methylated isoquinoline alkaloids are formed by N-methylation of a precursor amine (step J,K) (Goodwin and Mercer, 1983).



Scheme 1

Proven or Probable Biogenetic Loci for the Formation of the Isoquinoline Alkaloids

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Scheme 2

The formation of peyote alkaloids from L-tyrosine

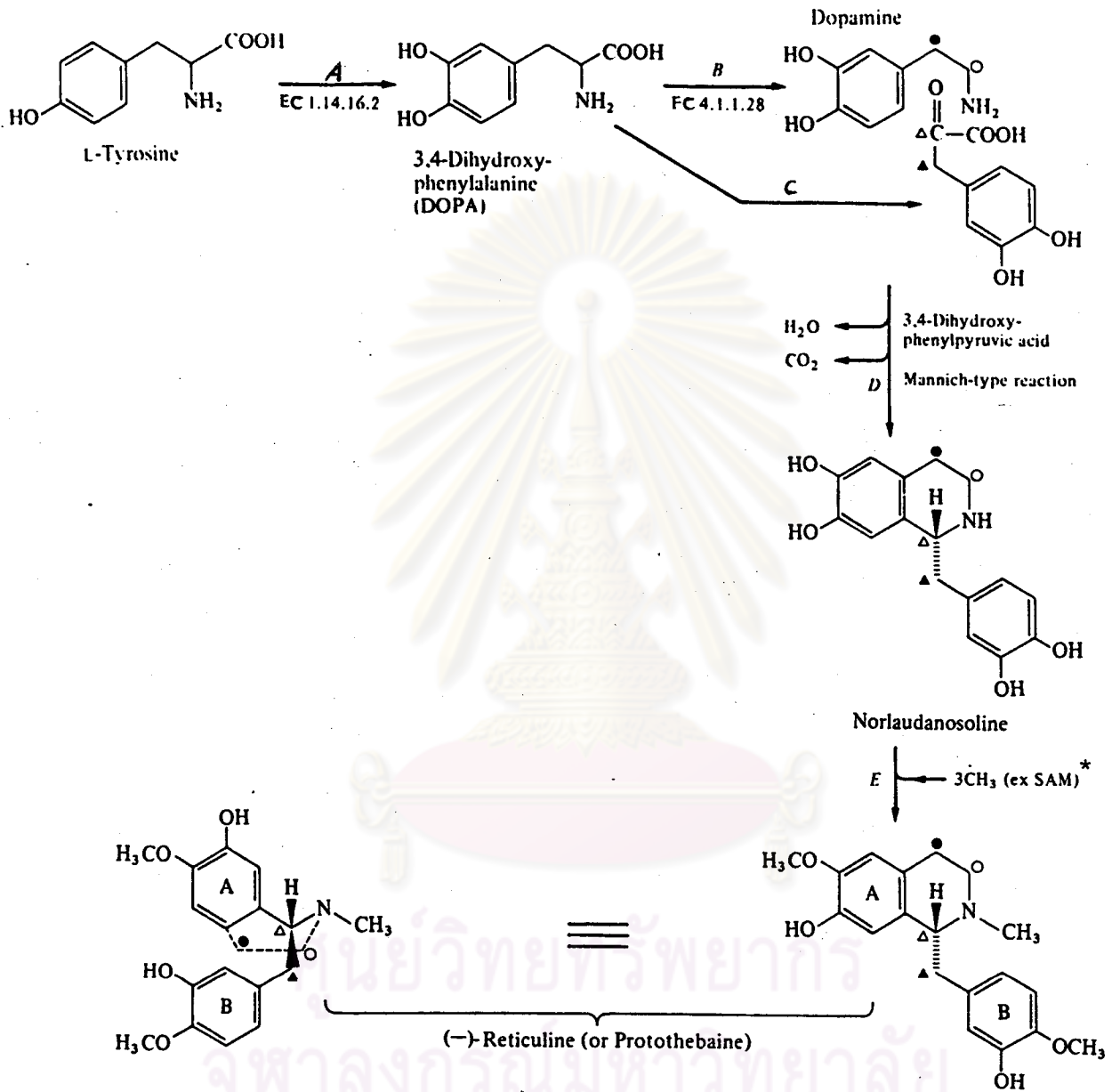


The benzyloquinolines are biosynthesised from L-tyrosine by way of DOPA. From Scheme 3 the first step (step A) involves the conversion of two molecules of L-tyrosine into two molecules of DOPA. One molecule of DOPA is converted into dopamine (step B) whilst the other is converted into 3,4-dihydroxyphenylpyruvate (step C). These two compounds then combine with the elimination of water and carbon dioxide in a Mannich-type reaction to yield a molecule of norlaudanosoline (step D) O- and N-methylation (step E) then lead to (-)-reticuline (sometimes called protothebaine) (Goodwin and Mercer, 1983).

The benzyloquinoline alkaloids are the precursors of a large array of polynuclear structures including simple benzyloquinolines, bisbenzyloquinoline dimers, proaporphines, aporphines, aporphine-benzyloquinoline dimers, oxoaporphines, protoberberines, benzophenanthridines, protopines, phthalideisoquinolines and hasubanan derivatives. Some biogenetic relationships of these alkaloid groups are shown in Scheme 4 (Cordell, 1981a).

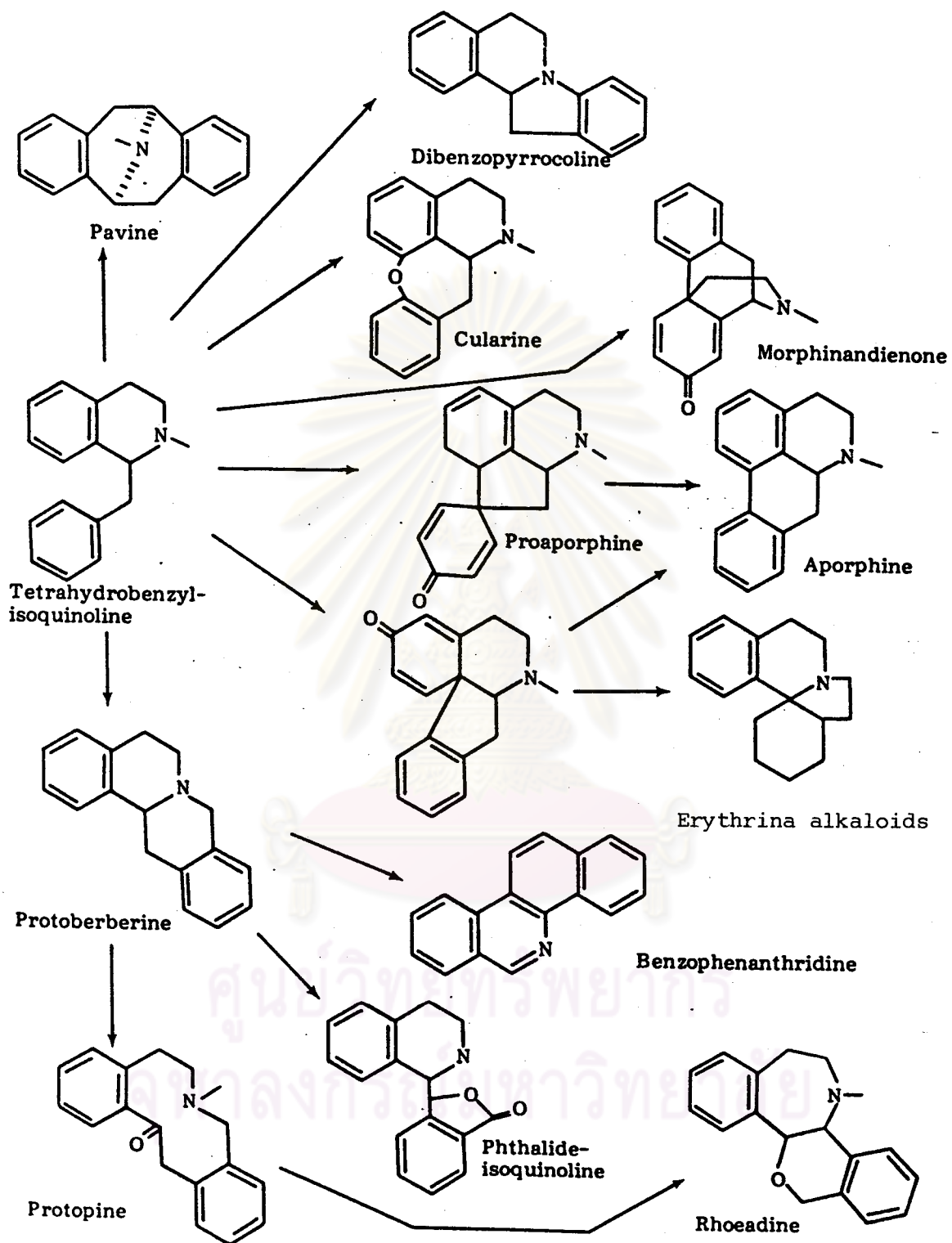
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**Scheme 3** The formation of 1-benzyl-1,2,3,4-tetrahydroisoquinolines

\* SAM = S-adenosylmethionine



Scheme 4

Biogenetic relationships of the major alkaloid groups derived from a tetrahydrobenzylisoquinoline precursor

According to biogenetic theory, the tetrahydroprotoberberine and quaternary protoberberine bases of *Stephania glabra* could be derived in nature from norlaudanoline (1) derivatives. Reticuline (2) could be oxidised to give the iminium salt (6) which would then cyclise to yield scoulerine (13), the key intermediate. The bases 11, 12 and 15 could then be formed from 13 by unexceptional steps. The tetrahydroprotoberberines (11-15) and the quaternary protoberberines (22-26), however, could also be formed in nature from orientalinaline (3), protosinomenine (4) and laudanidine (5) via the iminium intermediates 9, 7 and 8 respectively. The dienone intermediate (10) derived from 12 could undergo dienone-phenol rearrangement as shown in 10 to give corydalmine (12). The tetrahydroprotoberberine alkaloid capaurine (16) could be formed in the plants from tetrahydropalmatine (15) by nuclear hydroxylation at position 1 in ring A and corynoxidine by N-oxidation of 15.

The quaternary protoberberine alkaloids (22-26) of *S. glabra* could be formed in nature by dehydrogenation of the corresponding tetrahydroprotoberberines.

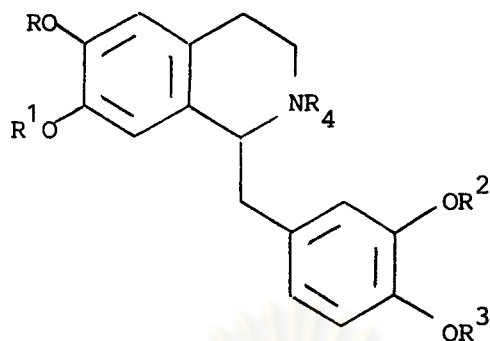
The proaporphine alkaloids pronuciferine (20) and stepharine (19) of *S. glabra* could be formed in the plant from coclaurine (21) via the dienone (18) intermediate.

The bisbenzylisoquinoline alkaloids cycleanine (30) and N-desmethylcycleanine (29) could be derived in nature from coclaurine derivatives. Oxidative dimerization of (R)-coclaurine (17, R=H) could give the dimeric base (27). O-Methylation of the phenolic

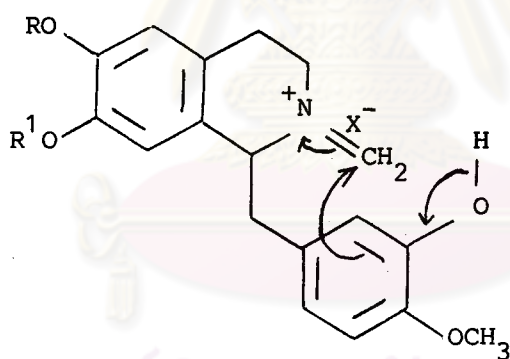
groups in 27 could give norcycleanine (28). Finally N-methylation could yield cycleanine (30). Selective N-methylation of the secondary amine functions in (28) could give N-desmethylcycleanine (29). Cycleanine could also be formed by direct oxidation dimerization of (R)-N-methylcoclaurine (17, R=Me) via (31) (Bhakuni *et al.*, 1983).



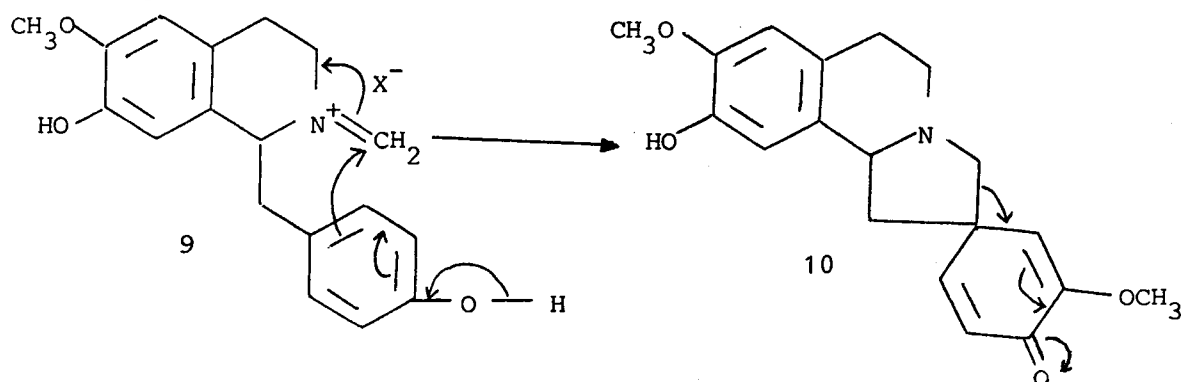
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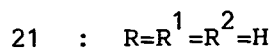
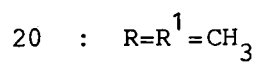
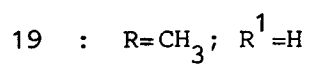
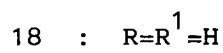
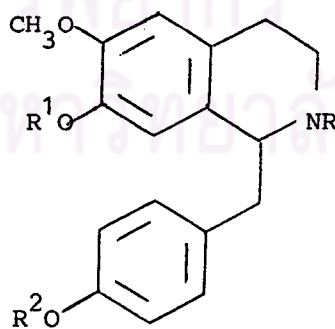
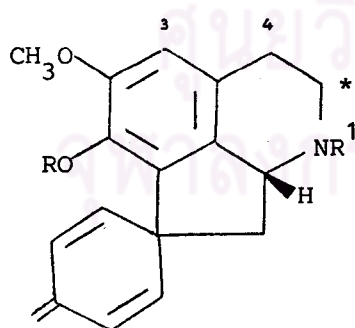
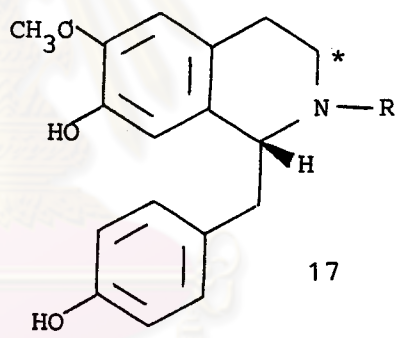
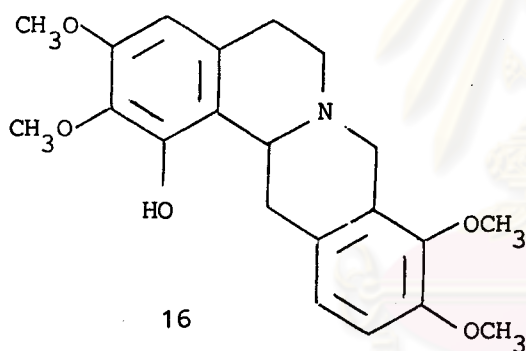
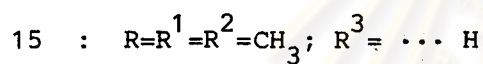
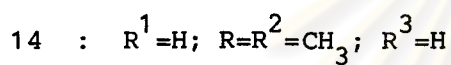
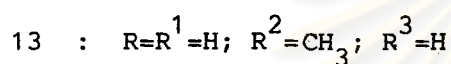
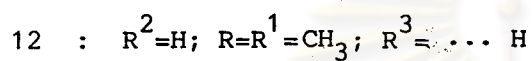
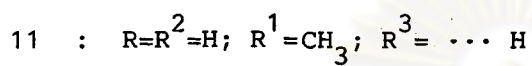
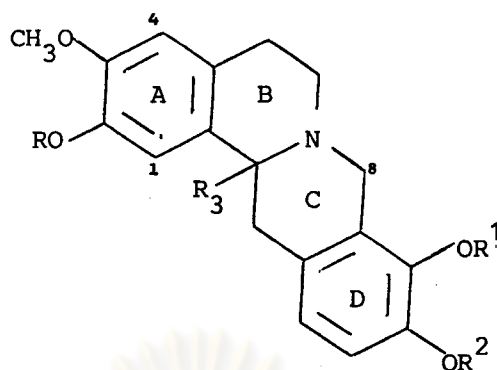


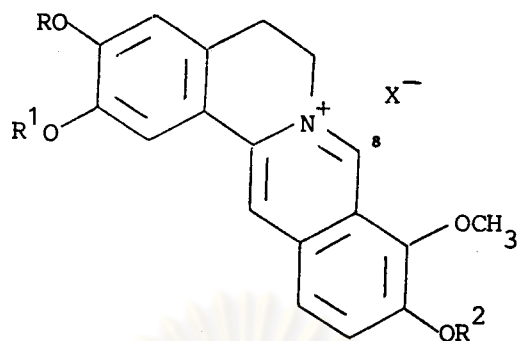
- 1 :  $R=R^1=R^2=R^3=R^4=H$   
 2 :  $R^1=R^3=H; R=R^2=R^4=CH_3$   
 3 :  $R^1=R^2=H; R=R^3=R^4=CH_3$   
 4 :  $R=R^3=H; R^1=R^2=R^4=CH_3$   
 5 :  $R^3=H; R=R^1=R^2=R^4=CH_3$



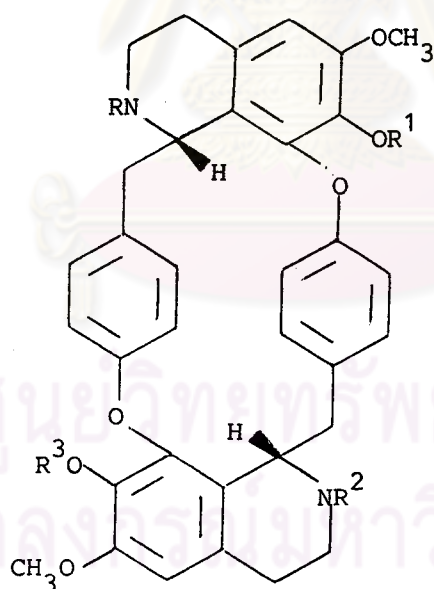
- 6 :  $R=CH_3; R^1=H$   
 7 :  $R^1=CH_3; R=H$   
 8 :  $R=R^1=CH_3$







- 22 :  $R=R^2=CH_3$ ;  $X=NO_3$   
 23 :  $R=R^1=CH_3$ ;  $R^2=H$ ;  $X=Cl$   
 24 :  $R^1=R^2=CH_3$ ;  $R=H$ ;  $X=Cl$   
 25 :  $R=CH_3$ ;  $R^1-R^2=H$ ;  $X=Cl$   
 26 :  $R=R^1=-CH_2-$ ;  $R^2=CH_3$ ;  $X=Cl$



- 27 :  $R=R^1=R^2=R^3=H$   
 28 :  $R^1=R^3=CH_3$ ;  $R=R^2=H$   
 29 :  $R=H$ ;  $R^1=R^2=R^3=CH_3$   
 30 :  $R=R^1=R^2=R^3=CH_3$   
 31 :  $R^1=R^3=H$ ;  $R=R^2=CH_3$