CHAPTER II

HISTORICAL

1 Distribution

1.1 Chemical and botanical aspects of isoquinoline alkaloids

A precise definition of the term "alkaloid" (alkali-like) is some what difficult because there is no clear-cut boundary between alkaloids and naturally occuring complex amines. Typical alkaloids are derived from plant sources, they are basic, they contain one or more nitrogen atoms (usually in a heterocyclic ring) and they usually have a marked physiological action on man or other animals. The nitrogen of alkaloids, taken in their broadest sense, may have a nitrogen atom which is primary (mescaline), secondary (ephedrine), tertiary (atropine) or quaternary (one of the N-atoms of tubocuraline), and this factor affects the derivatives of the alkaloid which can be prepared and the isolation proceduces. In the plant alkaloids may exist in the free state, as salts or as amine or alkaloid N-oxides. But, for practical considerations it must be more restrictive with some exceptation. There are numerous groups of alkaloids isolated from the lower plants, animals, microorganism, flowering plants and marine natural products.

In the higher plant system of Engler, there are 60 orders, and 34 of these contain alkaloid- bearing species. The most important alkaloid - contaning families are the Liliaceae, Amaryllidaceae, Compositae, Lauraceae, Ranunculaceae, Menispermaceae, Papaveraceae, Leguminosae, Rutaceae, Loganiaceae, Apocynaceae, Solanaceae and Rubiaceae

Among those alkaloids, isoquinoline alkaloids have played an important part in the development of the chemical and biological sciences.

Alkaloids with the isoquinoline ring system or those derived from a phenylalanine unit and therefore related structurally and biogenetically to the isoquinolines comprise at least 25 different types as follow (Govindachari and Viswanathan, 1972)

Type of isoquinoline alkaloids

1 Simple isoquinolines

2 1-phenylisoquinolines

3 1-benzylisoquinolines

4 Cularine group

5 Phthalideisoquinolines

6 Protoberberines

7 Protopine group

8 Benzophenanthridines

9 Aporphines

10 Proaporphines

11 Dibenzo pyrrocolines

12 Morphine group

13 Protostephanine

14 Hasubanans

15 Pavine group

16 Ochotensine group

17 Rhoeadine group

18 Bisbenzyl isoquinolines

19 Emetine group

20 Erythrinans

21 Amaryllidaceae

22 Indoloisoquinolines

23 1-Phenethylisoquinolines

24 Isopavine group

25 Terpene alkaloids

The number of isoquinoline alkaloids of known structure is approximately to 1,200 both in tetrahydroisoquinoline and quaternary isoquinoline salts. The majority of isoquinoline alkaloids have been isolated from the nine plant families such as Anonaceae, Berberidaceae, Fumariaceae, Hernandiaceae, Lauraceae, Menispermaceae, Papaveraceae, Ranunculaceae and Rutaceae. But they are also known to occcur in other plant families, e.g. Alangiaceae, Amaryllidaceae, Cactaceae, Combretaceae, Convolvulaceae, Euphorbiaceae, Leguminoseae, Magnoliaceae, Monimiaceae, Nymphaeaceae and Rubiaceae. With respect to their structural features, the isoquinoline alkaloids can be devided into two main classes. The first class is that of the simple isoquinoline alkaloids. The simple isoquinolines are structurally the simplest of the isoquinoline alkaloids.

They are usually bicyclic, although tricyclic species such as peyoglutan and mescalotam are also included among them. The nitrogen function in ring B is often tertiary and N-methylated, but it may also be secondary, N-formylated, N-acetylated, N-ethylated or oxidized to the imine stage. Quaternary simple isoquinoline, e.g. lophotine and 2-methyl-6,7-dimethoxy isoquinolinium salt, have also been isolated. Of more than passing interest is pilocereine, the only trimeric isoquinoline alkaloid fully characterized. Simple isoquinolines display great variety in their substitution pattern, depending, of course, upon their biogenetic origin. Most simple isoquinolines have been obtained from the Cactaceae, but they also occur among the Alangiaceae, Annonaceae, Berberidaceae, Euphorbiaceae, Leguminosae, Menispermaceae, Papaveraceae and Ranunculaceae (Menacherry *et al*, 1986).

The second class is the benzyl-derived isoquinoline alkaloids. They do not present a structural uniformity having benzylisoquinolines act as precursors to so many other naturally occurring isoquinoline type e.g. isoquinolines, pavines, isopavins, bisbenzylisoquinoline, cularines, protoberberines, erythrina base and others. Because relatively a large number of isoquinoline alkaloids in this class are known, their occurrence are distributed in many plant families.

1.2 Botanical aspects of the Menispermaceae

The Menispermaceae is one of a large family containing approximately 73 genera and about 350 species, wihch are almost entirely tropical. The exceptions being *Menisperum*, a northern temperate genus with 2 disjunct species in North America and Northern Asia, and a few species of *Cocculus* which extend into North America and temperate Asia.

There are 30 genera of this family occur in Asia, 30 in Africa, 22 in America and 10 in Australia to the Pacific. Of the 25 Malesian genera 20 occur in continental Asia, and 6 occur in Africa of which 2 (*Cissampelos* and *Cocculus*) are also in America. Of the Malesian genera 9 are shared with Australia and of these 6 extend into Asia, *Legnephora* is limited to central and East Malesia, *Corrania* and *Sarcopetalum* occur in New Guinea. Only 2 of the Malesian genera are endermic, *Chaenandra* and *Macrococculus*, both in New-Guinea. The Menispermaceae is characterized by dioecious woody or sometimes herbaceous climbers, rarely erect shrubs or trees (*Cocculus* sp.); tubers sometimes present (*Stephania* spp.); sometimes producing exudate or rarely latex (*Fibraurea* ; *Tinomiscium*). Wood often with concentric rings or arcs of vascular bundles separated radially by interfascicular rays, or vascular bundles in one ring, wood sometimes yellow. Young shoots often tendrilliform. Young stems usually drying longitudinally striate. Stipules absent. Leave spiral, simple, often palmatinerved at base and sometime peltate, or pinninerved,margin

usually entire, sometimes boardly crenate, sometimes deeply 3-5 lobed, petiole often swollen at base, sometimes also at apex, sometimes leaving a raised discoid scar on the stem.

Inflorescences axillary or on defoliate branches or cauliflorous, solitary or fasciculate, various in form, often cymes, thyrses or pseudoracemes, branching of cymes rarely umbelliform (*Stephania* spp.), flowers rarely in a disciform capitulum (*Stephania* spp.); female usually fewer flowered than male, female rarely with accrescent bracts (*Cissampelos* spp.). Flowers small, usually green, yellow or white, actinomorphic or female sometimes zygomorphic. Sepals usually in 1-2 (-4) whorls of 3, or 1 whorl of 4, the outer whorl(s) smallest, imbricate but the innermost whorl sometimes valvate and sometimes connate, sepals rarely spirally arranged (*Hypserpa*); in female sometimes reduced to 1 or 2. Petals mostly 3-6 in 1 or 2 whorls or 0, free or sometimes ± connate, usually smaller than the sepals, rarely larger (*Sarcopetalum*), the lateral edges or lobes often inflexed and sometimes clasping the opposite stamen, often glandular within, in female sometimes reduced to 1 or 2.

Stamens mostly 3 or 6 , sometimes 9 or up to about 40, often free and opposite a petal, or variously connate, sometimes forming a peltate synandrium, connective sometimes adaxially or abaxially thickened, rarely terminally prolonged (*Macrococculus*) ; anthers introrse to extrorse with dehiscence longitudinal to transverse. Staminodes sometimes present in female, usually subulate, carpels free,

usually 3 or 6, sometimes 1 or to 12, sometimes borne an a short gynophore ; style terminal when present; stigma often sessile, reflexed and lobed or divided. Pistillodes 0 in male.

Ovules 2 reducing to 1 in development, attached ventrally. Fruits of 1-6 (-10) drupes sometimes borne on an enlarged globose, discoid or columnar carpophore which is rarely shortly branched (*Anamirta*, *Tiliacora*).

Drupes sometimes narrowed at base into a stipe, style-scar terminal, ventral or close to base ; exocarp membranous to coriaceous, mesocarp fleshy; endocarp usually bony, rarely papyraceous to crustaceous (*Pycnarrhena* spp.) rugose, tuberculate, spiny, ridged or variously ornamented on at least the dorsal surface, sometimes smooth or surface fibrous, usually with a condyle ; i.e. a ventral sometimes hollow intrusion into the seed cavity around which the seed is curved, or a ventral groove, cavity or chamber ; the condyle when hollow often 2-chambered and with 2 lateral or ventral apertures or condyle septiform or lamelliform, then sometimes centrally perforate.

Seed often horseshoe-shaped; endosperm present or absent, sometimes ruminate. Embryo usually either elongate and with semiterete or flattened contiguous cotyledons or flat and very thin with divaricate foliaceous cotyledons, sometimes broadly ellipsoidal with thick contiguous cotyledons, rarely cotyledons much folded (*Arcangelisia*); radicle vary small. (Forman, 1986)

According to Forman the members of Menispermaceae were divided into 5 tribes, there are *Coscinieae*, *Menispermeae*, *Tiliacoreae*, *Tinosporeae* and *Fibraureeae*. But two of these, *Fibraureeae* and *Tinosporeae* should probably be combined. The tribes in Asia are characterized by the following combinations of characters.

Coscinieae : sepals imbricates. Petals 0, stamens either all or only the inner 3 connate. Carpels 3-6. Drupe with style-scar sublateral towards base on lateral. Endocarp smooth or fibrillo-pilose, subglobose with condyle obsolete, or subhemispherical with condyle deeply intrusive and 2-chambered. Endosperm present, sometimes ruminate. Seed broadly ellipsoidal or cup-shaped. Embryo with thin foliaceous divaricate cotyledons which are sometimes much folded.

Menispermeae : sepals usually free in 1-few whorls or sometimes connate when in 1 whorl, the innermost whorl sometimes valvate, or sepals spiral. Petals (0-) 3-6 (-9) sometimes connate. Female flowers with perianth sometimes reduced to 1-2 parts. Stamens free or partly connate or united into a peltate synandrium. Carpels 1-6. Drupe strongly curved with style near base. Endocarp with ± horseshoe-shaped dorsal region usually ornamented with projections or transverse ridges ; condyle deeply intrusive, either lamelliform and ± obovate with the seed-cavity curved around its margin or hollow with 1-2 chambers, sometimes perforate. Endosperm usually present, but absent in *Pachygone*. Seed elongate, strongly curved. Embryo elongate

and curved with narrow contiguous cotyledons.

Tiliacoreae: sepals imbricate or inner whorl valvate and sometimes connate. Petals rarely absent. Stamens free or connate. Carpels 3-10. Drupe with style-scar near base or lateral. Endocarp smooth, wrinkled, rugose or coarsely reticulate ; straight and condyle absent or curved with condyle intrusive and septiform. Endosperm usually absent, but present and ruminate in *Tiliacora*. Seed ellipsoidal, straight. Embryo with thick accumbent cotyledons or elongate and strongly curved with elongate contiguous cotyledons.

Tinosporeae (include *Fibraureeae*): sepals imbricate, rarely connate at the base. Petals 6 or O. Stamens free or united into a peltate synandrium. Carpels 3 (-4). Drupe with style-scar terminal. Endocarp spiny, verrucose, rugose or smoth, condyle a ventral hollow or longitudinal groove or deeply intrusive and clavate endosperm present, sometimes ventrally ruminate. Seed usually straight and ventrally hollowed or grooved, sometimes cup-shaped. Embryo with foliaceous divericate or imbricate cotyledons.

There are 22 genera, and 51 species in Thailand, of with 9 species are endermic (Shown by asterich). All of them are as follows :

1 *Albertisia papuana* Becc.

Albertisia puberula Forman.*

2 *Anamirta cocculus* (Linn.) Wight & Arn

[Waidin (หวายดิน), kho khlan (โคคลาน) (Central) ; thao kha nom (เถาขะโนม), lumpri (ลุมพรี) (South-Eastern) ; mae nam nong (แม่น้ำนอง) (Northern) ; thao wan thong

(เถาวัลย์ทอง) (South-Western)]

3 *Arcangelisia flava* (Linn.) Merr.

[Khamin khruea (ขมิ้นเครือ) (South-Eastern) ; khamin ruesi (ขมิ้นฤาษี), hap (ฮับ) (Peninsular)]

4 *Aspidocarya uvifera* Hook.J.& Thoms.

5 *Cissampelos hispida* Forman*

Cissampelos pareira Linn. var. *hirsuta* Forman.

[Khong khamao (ขงเขมา) (Northern) ; khruea manoi (เครือหมาน้อย) (Eastern) ; kon pit (ก้นปิด) (South-Western) ; krung khamao (กรุงเขมา), sifan (สีฟัน) (Peninsular)]

6 *Cocculus hirsuta* (Linn.). Theob.

Cocculus laurifolius DC.

[Yan nanton (ย่านน่านต้น) (North-Eastern, Central); sakae dong (สะแกดง) (North-Eastern) ; suramarit (สุรามฤต) (Eastern)]

Cocculus orbiculatus (Linn.) DC.

7 *Coscinium blumeanum* Miers

Coscinium fenestratum (Gaertn.) Colebr.

[Khruea hen (เครือเห็น) (North-Eastern) ; khamin khruea (ขมิ้นเครือ) (South-Eastern)]

8 *Cyclea atjehensis* Forman

Cyclea barbata Miers

[Krung badan (กรุงบาดาล) (South-Eastern) ; krung khamao (กรุงเขมา) (Peninsular).]

Cyclea laxiflora Miers

Cyclea polypetala Dunn.

Cyclea varians Craib*

9 *Diploclisia glaucescens* (Bl.) Diels

[Ma nim dam (มะหนิมดำ), duk khruea (ดูกเครือ) (Northern) ; khruea sai kai (เครือไส้ไก่) (Shan/Northern) ; tap tao (ตับเต่า) (Peninsular)]

10 *Fibraurea tinctoria* Lour.

[Khamin ruesi (ขมิ้นฤาษี) ; khamin khruea (ขมิ้นเครือ) ; man miat (มันเมียด) (Peninsular) ; thaowan thong (เถาวัลย์ทอง) (South-Western); kamphaeng chet chan (กำแพงเจ็ดชั้น) (Central)]

11 *Haematocarpus validus* (Miers) Bakh.f.ex. Forman

12 *Hyperpa nitida* Miers

[Haen kuem (แฮนกึม) (North-Eastern)]

13 *Limacia blumei* (Boerl.) Diels

Limacia oblonga Hook.f. & Thoms.

Limacia scandens Lour.

14 *Pachygone dasycarpa* Kurz.

[Nam phrom (น้ำพรม) (Northern) ; ya nang chang (หญ้านางช้าง) (Eastern)]

Pachygone odorifera Miers

15 *Parabaena sagittata* Miers

[Phak nang (ผักหนัง) (Northern)]

16 *Pericampylus glaucus* (Lamk.) Merr.

[Salit hom kha (สลิดหอมคา) (Northern) ; yan tap tao (ย่างตับเต่า) (Peninsular)]

17 *Pycnarrhena lucida* (Teijsm. & Binn.) Miq.

[Ya nang ton (ย่านางต้น) (South-Western)]

Pycnarrhena poilanei (Gagnep.) Forman

18 *Sinomenium acutum* (Thunb.) Rehder & Wilson

19 *Stephania brevipes* Craib*

[Bua khruea (บัวเครือ) (Northern)]

Stephania capitata (Bl.) Spreng.

Stephania crebra Forman*

Stephania elegans Hook.f. & Thoms.

[Se-khi-pho (เส่มิพอ) (Karen/Northern)]

Stephania glabra (Roxb.) Miers

[Phanang nang (ผนังนั่ง) (Northern)]

Stephania glandulifera Miers

Stephania japonica (Thunb.) Miers

[Kon pit (ก้นปิด), bai kon pit (ใบก้นปิด), (Central) ; pang pon (บังปอน) (Northern) ; tap tao (ตับเต่า), yan pot (ย่านปด) (Peninsular)]

Stephania oblata Craib

Stephania papillosa Craib*

Stephania pierrei Diels

[Bua khruea (บัวเครือ) (North-Eastern) ; bua bok (บัวบก) (South-Western, Eastern and Central) ; kot hua bua (โกฐหัวบัว), sabu lueat (สบู่เลือด) (Central)]

Stephania reticulata Forman

[Tap tao (ตับเต่า) (Peninsular)]

Stephania rotundra Lour.

Stephania suberosa Forman*

[Bua bok (บัวบก) (Central) ; boraphet phung chang (บอระเพ็ดพุงช้าง) (South-Western)]

Stephania subpeltata H.S. Lo.

Stephania tomentella Forman*

Stephania venosa (Bl.) Spreng

[Plao lueat khruea (เปล้าเลือดเครือ) (Northern) ;

cho koe tho (ชอเกอะทอ) (Karen/Northern) ; krathom lueat (กระท่อมเลือด) (North-Eastern); kling klang dong (กลิ้งกลางดง) (South-Western) ; boraphet yang daeng (บอระเพ็ดยางแดง) (Peninsular).]

20 *Tiliacora triandra* (Colebr.) Diels

[Choi nang (จ๊อยนาง) (Northern) ; thao ya nang (เถาย่านาง) (Eastern, Central) ; thaowan khieo (เถาวัลย์แก้ว) (South-Eastern)]

21 *Tinomiscium petiolare* Hook.f. & Thoms.

[Pharai ho thong (ผ้าร้ายห่อทอง) (Peninsular)]

22 *Tinospora baenzigeri* Forman

[Chung cha ling (จุงจาลิง) , ching cha chali (ชิงช้าชาลี) (Central).]

Tinospora crispa (Linn.) Hook.f. & Thoms.

[Boraphet (บอระเพ็ด) (Central)]

Tinospora siamensis Forman*

Tinospora sinensis (Lour.) Merr.

[Ping kaling (ปิงกะลิง) (Northern) ; sali thao chali (สลี เถาชาลี) (Central) ;] (Forman, 1991)

All members of this family seem to produce phenylalanine and tyrosine-derived isoquinoline alkaloids. Aporphines, bisbenzyl-isoquinolines, and quaternary and intensely coloured protoberberines such as berberine and its allies are most typical of the family. In some genera these more usual types of isoquinoline alkaloids are accompanied by less common or even rare types of benzylisoquinoline-related alkaloids. Such types of Menispermaceous alkaloids are the hasubanans, the azafluoranthenes and

related tropolo-isoquinolines, and the dibenzazonines and related *Erythrina* alkaloids. Moreover, in recent time, pavine-type and aristolactam-type alkaloids were detected in the family. Alkaloid chemistry clearly allocates *Menispermaceae* to *Polycarpicae* with the position of one of its more specialized members. Other groups of constituents which seem to be rather characteristic of the family are the bitter and more or less toxic principles, which are sesquiterpenoids like picrotoxin or diterpenoids such as columbin and tinophyllone (Hegnauer, 1969, 1973). It is perhaps not solely accidental that quaternary protoberberine alkaloids like berberine, columbamine, jatrorrhizine and palmatine and diterpinoid bitter principles such as tinophyllone also occur in some genera of Rutaceae. A third group of phytoconstituents, the cyclitols, is known to be accumulated by members of several genera of Menispermaceous plants ; it is represented by the deastereoisomeric cyclo-hexanepentols (+) quercitol and (-) quercitol (viburnitol) ; they are presently known to occur in the genera *Cissampelos*, *Cocculus* , *Cyclea*, *Legnephora*, *Menispermum* , *Pachygone* , *Stephania*, *Tiliacora* and *Triclisia*.The phenolic constituents were studied only superficially hitherto. Leaves contain flavonols or flavones, or both, but seem to lack representatives with trihydroxylated B-ring and true tannins. All other classes of phyto-constituents were neglected by phytochemist. Nevertheless, some incidental observations might prove in future to be taxonomically relevant.

1.3 Botanical aspects of the Coscinieae tribe

The tribe *Coscinieae* is one of the smallest in the Menispermaceae, consisting of only three small genera: *Anamirta, Arcangelisia* and *Coscinium.* The five species which make up the tribe all occur within the Indo-Melesian region, these are :

1) *Anamirta cocculus* (L.) Wight & Arn.

2) *Arcangelisia flava* (L.) Merr.

3) *Arcangelisia tympanopoda* (Lauterb& K.Schum.)Diels

4) *Coscinium blumeanum* Miers

5) *Coscinium fenestratum* (Gaertn.) Colebr.

In spite of the small size of the tribe, some important morphological feature vary considerably between genera. The leaves are often peltate in *Coscinium* but not peltate in the other two genera. The inflorescence in *Coscinium* are composed of peduncled capitula, but they are paniculate in the other genera. In the fruits of *Arcangelisia*, the condyle is absent or inconspicuous and consequently the seed is broadly ellipsoidal in shape. In *Anamirta* and *Coscinium*, however, the condyle is deeply intrusive into the seed-cavity with the seed formed around it, resulting in a deeply concave, subhemispherical seed. In *Arcangelisia* the seeds are distinctive in having deeply ruminate endosperm. Taking together, the gross morphological characters within the *Coscinieae* indicate that *Anamirta* and *Arcangelisia* are more closely related to each other than either are to *Coscinium.* (Forman, 1978).

2. Chemistry of the Alkaloids

2.1 Alkaloids isolated from the Menispermaceae

The alkaloids of the Menispermaceae have received considerable attention for a long time. The Menispermaceae are widely distributed in the tropical countries and have been studied throughout the world. The vast majority of alkaloids found in the Menispermaceae are of the benzylisoquinoline type. The alkaloids and their structures which have been reported in 68 species of Menispermaceae are shown in talble 1 & 2.

The structure of alkaloids found to date in the Menispermaceae classified under general structural type and made a precise of type are shown as follows:

Alkaloid type	Precise
Aporphine alkaloids	A
1-Benzyl-tetrahydroisoquinolines alkaloids	Benz
Bisbenzylisoquinoline alkaloids	Bis
Hasubanan alkaloids	H
Proaporphine alkaloids	Pa
Protoberberine alkaloids	P
Morphine alkaloids	M
Miscellaneous Base	Misc

Table 1 Alkaloids isolated from the Menispermaceae (Thonber, 1972)

Plant species	Alkaloids present	Formulae
Albertisia papuana	Aromoline	Bis 62
	Cocsoline	Bis 35
	Daphnoline	Bis 67
	Dehydrotelobine	Bis 40
	Homoaromoline	Bis 68
	Isotrilobine	Bis 36
	Lindoldhamine	Bis 29
	Obaberine	Bis 70
	O-methylcocsoline	Bis 37
	Oxyacanthrine	Bis 71
Anamirta cocculus	Berberine	P2
	Columbamine	P4
	L-8-oxotetrahydropalmatine	P
	Magnoflorine	A7
	Menispermine	-
	Palmatine	P2
	Paramenispermine	-
Arcangelisia flava	Berberine	P1
	Columbamine	P4
	Dehydrocorydalmine	P7
	Homoaromoline	Bis68

Table 1 (continue)

	Hydroxyberberine	P
	Jatrorrhizine	P6
	Pycnarrhine	Misc.7
	Shobakunine	-
	Thalifendine	P15
Burasaia madagascariensis	Columbamine	P4
	Jatrorrhizine	P6
	Palmatine	P2
Chasmanthera dependens (Ohiri, 1983)	Bisnorargemonine	Misc.6
	Columbamine	P4
	Coreximine	P19
	Govanine	P18
	Jatrorrhizine	P6
	Magnoflorine	A7
	Pallidine	M9
	Palmatine	P2
	Pseudocolumbamine	P20
Chondodendron candicans	d-Bebeerine	Bis 19
	Isochondodendrine	Bis 49
Chondodendron limaciifolium	Isochondodendrine	Bis 49

Table 1 (continue)

Chondodendron microphyllum	d-Bebeerine	Bis 19
	Isochondodendrine	Bis 49
	L-Isococlaurine	(Benz.2)
Chondodendron platyphyllum	L-Berberine	Bis 18
	Isochondodendrine	Bis 49
	L-Isococlaurine	(Benz.2)
Chondodendron tomentosum	Cycleanine	Bis 48
	d-Chondocuranine	Bis 16
	d-Chondocurine	Bis 17
	Isochondodendrine	Bis 49
	d,l-Tubocurarine	Bis 25
	L-Curine	Bis 18
	Norcycleanine	Bis 50
Cissampelos insularis	Cycleanine	Bis 48
= *Cyclea insularis*	Cycleanoline	P13
= *Paracyclea insularis*	Insulanoline	Bis 51
	Insularine	Bis 52
	Isochondodendrine	Bis 49
	Magnoflorine	A 7
	Norcycleanine	Bis 50

Table 1 (continue)

Cissampelos pareira	Cissampareine	Bis 53
	Cyclanoline	P 13
	Isocondodendrine	Bis 49
	Hayatidine	Bis 21
	Hayatine	bis 22
	Hayatinine	Bis 23
	L-Curine	Bis 18
	4"-Omethylcurine	Bis 24
Cissampelos ochiaiana	Cyleanine	Bis 48
	Insularine	Bis 52
	Isochondodendrine	Bis 49
	L-Curine	Bis 18
Cissampelos mucronata	Isocondodendrine	Bis 49
Cocculus hirsutus	d,l-Coclaurine	Benz 1
	d-Trilobine	Bis 36
Cocculus laurifolius	Cocculidine	Misc.1
	Cocculine	Misc.2
	Dihydroerysodine	Misc.3
	Coclaurine	Benz.1
	Laurifoline	A 6

Table 1 (continue)

	Magnoflorine	A 7
	Trilobine	Bis 38
Cocculus leaeba	Palmatine	P 2
	Oxycanthine	Bis 71
Cocculus pendulus (Guinaudeau, 1987)	1,2 -Dehydrokohatamine	Bis 58
	1,2 -Dehydrokohatine	Bis 57
	1,2 -Dehydronortelobine	Bis 59
	5 -Hydroxyapateline	Bis 55
	5 -Hydroxytelobine	Bis 56
	Kohatamine	Bis 54
	Siddiquamine	Bis 61
	Siddiquiene	Bis 60
Cocculus sarmentosus	Cocsarmine	A1
	Isotriboline (homotriboline)	Bis 36
	Menisarine	Bis 42
	Trilobine	Bis 38
Cocculus trilobus	Cocculolidine	Misc.1
	Isotrilobine	Bis 36
	Magnoflorine	A7
	Normenisarine	Bis 43

Table 1 (continue)

	Trilobamine (daphnoline)	Bis 67
	Trilobine	Bis 32
Cyclea atjehensis	Cycleatjehenine	
	Cycleatjehine	
Cyclea barbata	Homoaromoline	Bis 68
	Isotetrandrine	Bis 8
Cyclea peltata (Kupchan, 1973)	Berbamine	Bis 2
	Cycleacurine	Bis 20
	Cycleadrine	Bis 3
	Cycleahomine chloride	Bis 4
	Cycleanorine	Bis 5
	Cycleapeltine	Bis 65
	Fangchinoline	Bis 6
	Isochondodendrine	Bis 49
Coscinium blumeanum	Berberine	P 1
	Jatrorrhizine	P 6
	Palmatine	P 2

Table 1 (continue)

Coscinium fenestratum	Berberine	P1
	Berberubine	P
	12,13-Dihydro-8-oxoberberine	P
	Jatrorrhizine	P 6
	N,N-Dimethyllindcarpine	A 10
	Oxyberberine	P
	Palmatine	P 2
	Tetrahydroberberine	P
	Thalifendine	P 15
Epinetrum cardifolium	Cycleanine	Bis 48
	Isochondodendrine	Bis 49
	Norcycleanine	Bis 50
Epinetrum mangenati	Cycleanine	Bis 48
	Isochondodendrine	Bis 49
	Norcycleanine	Bis 50
Fibraurea chloroleuca (=*F. tinctoria*) (Siwon, 1981)	Berberine	P 1
	Berberrubine	P
	Dehydrocorydalmine	P 7
	Jatrorrhizine	P 6
	Magnoflorine	A 7
	Palmatrubine	P
	Pseudocolumbamine	P 20

Table 1 (continue)

Heptacyclum zenkeri	Dehydrodiscretine	P 17
Jatrorhiza palmata	Columbamine Jatrorrhizine Palmatine	P 4 P 6 P 2
Legnephora moorei (=*Pericampylus incanus*)	Dehydrocorydalmine Menisperine (N-methylisocorydinium)	P 7
Limacia cuspidata	Cuspidaline Limacine Limacusine	Bis 26 Bis 12 Bis 69
Limacia oblongata	Cuspidaline Limacine Limacusine	Bis 26 Bis 12 Bis 69
Limaciopsis loangensis (Cave , 1978)	Isotetrandrine Nor-2 isotetrandrine N-Oxy-2 -isotetrandrine 8-Oxopalmatine	Bis 8 Bis 9 Bis 10 P

Table 1 (continue)

Menispermum canadense	Dauricine	Bis 27
	Dehydrocheilanthifoline	-
Menispermum dauricum (Takani, 1983)	Acutumidine	-
	Acutumine	-
	Dauricine	Bis 27
	Daurinoline	Bis 28
	Dauriporphine	A 17
	Menisporphine	A 18
	Sinomenine	M 1
Pachygone loyaltiensis	Apateline	Bis 34
	Bisnoraromoline	-
	Daphnandrine	Bis 65
	Daphnoline	Bis 67
	1, 2 -Dehydroapateline	Bis 39
	1, 2 -Dehydrotelobine	Bis 40
	Isotrilobine	Bis 36
	O-Methylcocsoline	Bis 37

Table 1 (continue)

Pachygone ovata (Abdel-kawi, 1984)	Coclaurine	Benz.1
	Liriodenine	A 22
	Magnoflorine	A 7
	Nortrilobine	-
	Trilobine	Bis 38
Parabaena hirsuta	Palmatine	P 2
Pericampylus formosanus	(+) Stepharine	Pa3
Pleogyne australis (=*P. cuminghamii* L.)	-Isochondodendrine	Bis 49
	Curine	Bis 18
Pycnarrhena longifolia	Aromoline	Bis 62
	Berbacolorflammine	Bis 1
	Colorflammine	Bis 64
	Daphnoline	Bis 67
	Homoaromoline	Bis 68
	Krukovine	Bis 11
	Limacine	Bis 12
	Magnoflorine	A 7
	Obaberine	Bis 13
	Pycnarrhine	Misc. 7

Table 1 (continue)

Pycnarrhena manillensis	Berbamine	Bis 2
	Isotetrandrine	Bis 8
	Phaeanthine	bis 14
	Pycnamine	Bis 15
Pycnarrhena novoguinensis (Verpoorte, 1978)	Berbamine	Bis 2
	Isofangchinoline	Bis 7
	Limacine	Bis 12
	Phaeantine	Bis 14
	Pycnamine	Bis 15
Sinomenium acutum	Disinomenine	M 2
	Magnoflorine	A 7
	Michelalbine	A 9
	Norsinoacutine	M 3
	Sinactine	P 11
	Sinoacutine	M 4
	Sinomenine	M 1
	Stepharine	Pa 3
	Tuduranine	A 16

Table 1 (continue)

Stephania capitata	Crebanine	A 3
	Cycleanine	Bis 48
	d-Dicentrine	A 4
	Epistephanine	Bis 72
	Phanostenine	A 11
	Stephanine	A 14
Stephania cepharantha	Berbamine	Bis 2
	Cepharamine	H 1
	Cepharanthine	Bis 63
	Cycleanine	Bis 48
	Homoaromoline	Bis 68
	Isotetrandrine	Bis 8
Stephania drinklagei	(+) Corydine	A 2
	Dicentrine	A 4
	(+) Isocorydine	A 5
	(-) Roemerine	A 12
Stephania elegans	Aknadinine	M 5
	Cyclanoline	P 13
	Cycleanine	Bis 48
	Epihernandolinol	M 6
	Hasubanonine	H 4

Table 1 (continue)

	Isochondodendrine	Bis 49
	Isotetrandrine	Bis 8
	Magnoflorine	A 7
	N-Methylcorydalmine	P 16
Stephania glabra	Columbamine	P 4
	(-) Corydalmine	P 8
	Cycleanine	Bis 48
	Dehydrocorydalmine	P 7
	Gindarine = Tetrahydropalmatine	P 3
	Gindarinine = Palmatine	P 2
	Jatrorrhizine	P 6
	Palmatine	P 2
	Stepharanine	P 9
	Stepharatine	P 14
	(-) Stepholidine	P 10
	Tetrahydropalmatine	P 3
Stephania hernandifolia	4-Demethylhasubanonine	H 2
	4-Demethylnorhasubanonine	H 3
	Isochondodendrine	Bis 49
	Fangchinoline	Bis 6
	Isotrilobine	Bis 36

Table 1 (continue)

Stephania japonica (Matsui, 1978,1982,1984. Yamamura, 1985)	Cyclanoline	P 13
	Epistephamiersine	H 12
	Epistephanine	-
	Hasubanonine	H 4
	Homostephanoline	H 5
	Hypoepistephanine	Bis 73
	Insularine	Bis 52
	Lanuginosine	A 23
	Magnoflorine	A 7
	Metaphanine	H 6
	Miersine	H 18
	Oxo-epistephamiersine	H 14
	16-Oxoprometaphanine	H 8
	Oxostephabinine	H 10
	Oxostephamiersine	H 13
	Oxostephanine	A 10
	Oxostephasunoline	H 15
	Protostephanine	Misc 4
	Prometaphanine	H 7
	Stebisimine	Bis 74
	Stephamiersine	H 11
	Stephanine	A 14
	Stephasunoline	H 15

Table 1 (continue)

	Stepinonine	Misc 5
	Steponine	P 12
	Thalrugosine	-
Stephania kwansiensis	Tetrahydropalmatine	P 3
Stephania longa	Longanone	H 17
Stephania sasakii (Kumitomo, 1981)	Berbamine	Bis 2
	Bisakanadinine	M 7
	Cepharanthine	Bis 63
	Crebanine	A 3
	Dehydrocrebanine	A 19
	Dehydrostesakine	A 20
	4,5 - Dioxydehydrocrebanine	A 21
	4-Hydroxycrebanine	A 31
	d-Isocorydine	A 5
	Lanuginosine	A 23
	Liorodenine	A 22
	L-Tetrahydropalmatine	P 3
	N-Methylpapaveralinium	Benz.6
	Phanostenine	A 11
	(R) -Roemeroline	A 12

Table 1 (continue)

	Steponine	P 12
	Stesakine	A 15
Stephania suberosa (Patra, 1986)	Cepharanthrine 2'- -N-oxide	
	2-norcepharanthine	
	Norstephasubine	Bis 76
	Stephasubinine	Bis 77
	Stephasubine	Bis 75
Stephania tetrandra	Cyclanoline	P 13
	Fanchinoline	Bis 6
Stephania venosa	Anonaine	A
	Apoglazionine	A
	Asimilobine	A
	Ayuthianine	A 28
	Corydine	A 2
	Crebanine	A 3
	Kikumamanin	P
	Mecambroline	A
	N-Carboxamidostepharine	Pa 1
	Nuciferline	A
	O-Methylstepharinosine	Pa 4
	Oxostephanosine	A 25

Table 1 (continue)

	Reticuline	Benz.5
	Stephadiolamine- -N-oxide	-
	Stepharine	Pa3
	Stepharinosine	Pa5
	Sukhodianine	A 29
	Tetrahydropalmatine	P 3
	Thailandine	A 26
	Thalrugosamine	-
	Tuduranine	A 16
	Ushinsunine	A 30
	Uthongine	A 27
Synclisia scabrida (Ohiri, 1983)	Cocsuline	Bis 35
	Cycleanine	Bis 48
	Norcycleanine	Bis 50
Tiliacora acuminata (=*T. racemosa*)	Tiliacorine	Bis 31
	Tiliarine	Bis 30
	Tiliacorenine	Bis 32
Tiliacora dinklagei	Nortiliacorinine A	Bis 33
	Tiliacorine	Bis 31
	Tiliacorinine	Bis 32

Table 1 (continue)

Tiliacora triandra	Nortiliacorinine A	Bis 33
	Tiliacorine	Bis 31
	Tiliacorinine	Bis 32
	Tilianangine	Bis 47
	Yanangine	Bis 46
Tinomiscium petiolare	L-Isocorypalmine	P 5
Tinospora bakis (=*Coculus bakis*)	Berberine	P 1
	Palmatine	P 2
Tinospora capillipes (Chang, 1984)	Columbamine	P 4
	Dehydrodiscretamine	P 17
	Jatrorrhizine	P 6
	Palmatine	P 2
	Stepharamine	P 9
Tinospora crispa (=*Cocculus crispa*)	Berberine	P 1
	Palmatine	P 2
Tinospora rumphii	Berberine	P 1

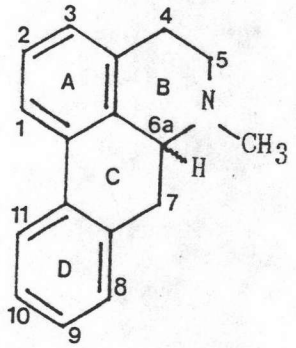
Table 1 (continue)

Trilisia dictyophyllia (Spiff, 1981)	Cocsuline	Bis 35
	Tridictophylline	M 8
	Trigilletimine	Bis 41
Trilisia gilletti	Gilletine	Bis 44
	Isogelletine-N-oxide	Bis 45
	Obamegine	Bis 13
	Stebisimine	Bis 74

Note : P = Protoberberine alkaloids, which can find their structures in table 3 (page 71-113).

Table 2 The structure of formulae in table 1

Aporphine alkaloids (A)

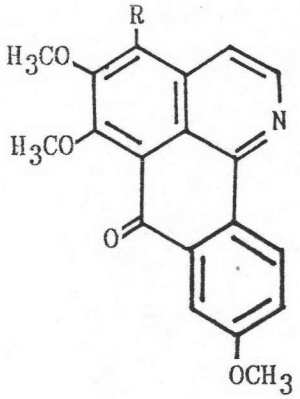


Alkaloid	1	2	6	8	9	10	11
Cocsarmine (A1)	OMe	OMe	$(Me)_2$	-	OMe	OMe	-
Corydine (A2)	OH	OMe	Me	-	-	OMe	OMe
Crebanine (A3)	-O-CH_2-O-		Me	OMe	OMe	-	-
Dicentrine (A4)	-O-CH_2-O-		Me	-	OMe	OMe	-
Isocorydine (A5)	OMe	OMe	Me	-	-	OMe	OH
Laurifoline (A6)	OH	OMe	$(Me)_2$	-	OH	OMe	-
Magnoflorine (A7)	OH	OMe	$(Me)_2$	-	-	OMe	OH
Menisperine (A8)	OMe	OMe	$(Me)_2$	-	-	OMe	OH
Michelalbine (A9)	-O-CH_2-O-		Me	-	-	-	-
N,N-dimethyllindcarpine (A10)	OMe	OH	$(Me)_2$	-	-	OMe	OH
Phanostenine (A11)	-O-CH_2-O-		Me	-	OMe	OH	-
Roemerine (A12)	-O-CH_2-O-		Me	-	-	-	-
Roemeroline (A13)	-O-CH_2-O-		Me	-	OH	-	-
Stephanine (A14)	-O-CH_2-O-		Me	OMe	-	-	-
Stesakine (A15)	-O-CH_2-O-		Me	OMe	OH	-	-
Tuduranine (A16)	OMe	OMe	H	-	-	OH	-

Table 2 (continue)

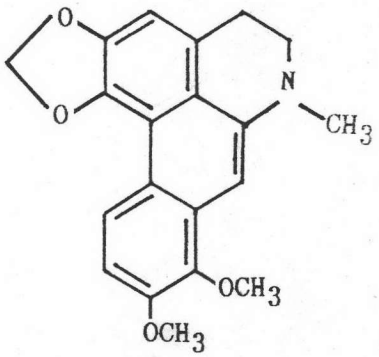
Dauriporphine (A17) R=OMe

Menisporphine (A18) R=H



Dehydrocrebanine (A19) R=Me

Dehydrostesakine (A20) R=H



4,5-Dioxydehydrocrebanine (A21)

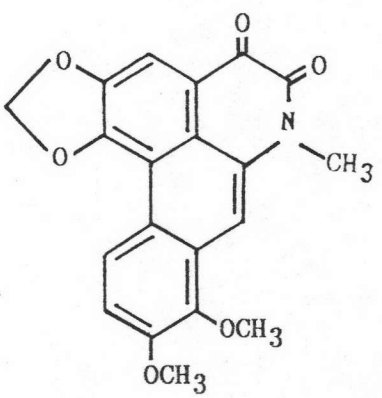


Table 2 (continue)

Lioriodenine (A22) R_1=H R_2=H

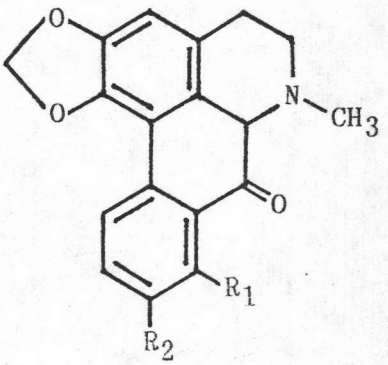
Lanuginosine (A23) R_1=H R_2=OMe

Oxostephanine (A24) R_1=OMe R_2=H

Oxostaphanosine (A25) R_1=OH R_2=H

Thailandine (A26) R_1=OMe R_2=H N-Me

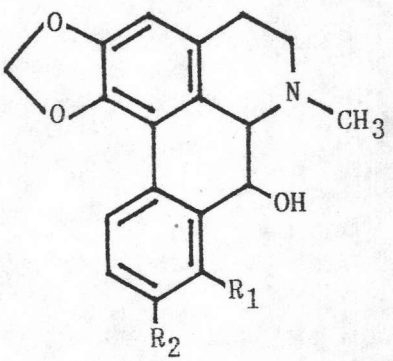
Uthongine (A27) R_1=OMe R_2=OMe N-Me



Ayuthianine (A28) R_1=OMe R_2=H

Sukhodianine (A29) R_1=OMe R_2=OMe

Ushinsunine (A30) R_1=H R_2=H



4-Hydroxycrebanine (A31)

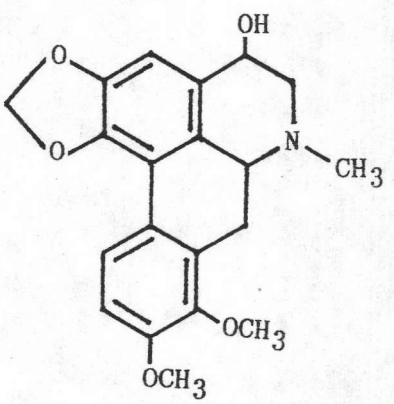
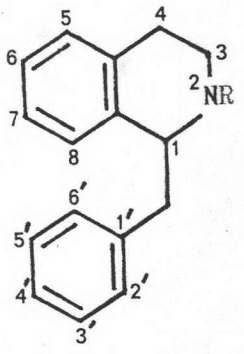


Table 2 (continue)

1-Benzyl-tetrahydroisoquinoline (Benz)



Alkaloid	R	3'	4'	6	7
Coclaurine (Benz 1)	H	-	OH	OMe	OH
Isococlaurine (Benz 2)	H	-	OH	OH	OMe
Laudanine (Benz 3)	Me	OH	OMe	OMe	OMe
N-methylcoclaurine (Benz 4)	Me	-	OH	OMe	OH
Reticuline (Benz 5)	Me	OH	OMe	OMe	OH

N-Methylpapaveraldinium chloride

(Benz 6)

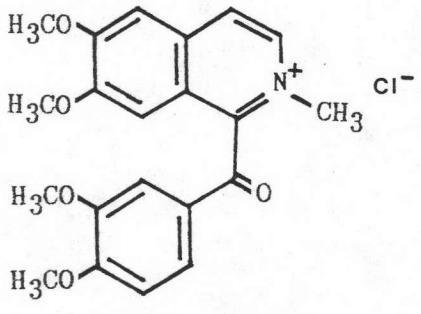
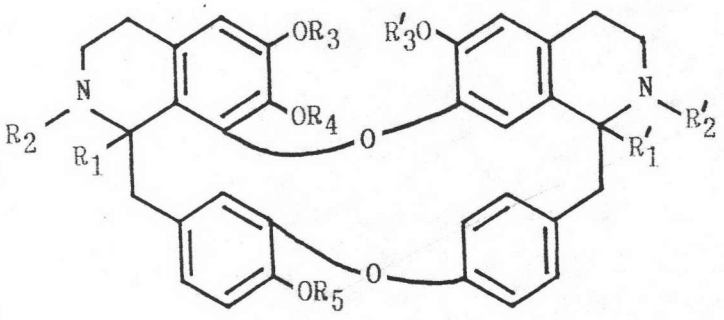


Table 2 (continue)

Bisbenzylisoquinoline alkaloids (Berbamine type)

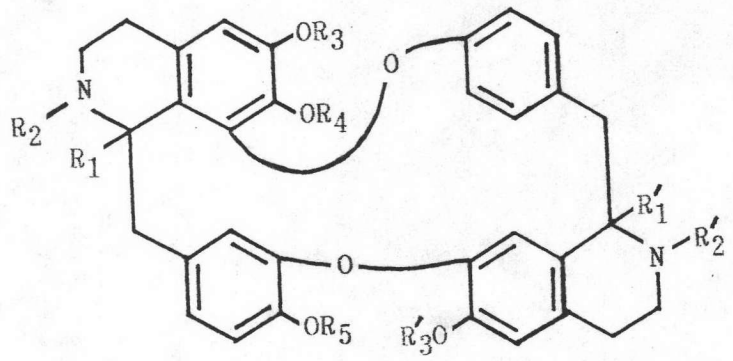


Alkaloids	R_2	R_3	R_4	R_5	R'_2	R'_3	Configuration
Berbacolorflammine (Bis 1)	Me	Me	H	Me	Me	Me	- -
Berbamine (Bis 2)	Me	Me	Me	H	Me	Me	1-R, 1'-S
Cycleadrine (Bis 3)	Me	Me	H	Me	Me	Me	- -
Cycleahomine Cl^- (Bis 4)	$(Me)_2$	Me	Me	Me	Me	Me	1-S, 1'-S
Cycleanorine (Bis 5)	Me	Me	Me	Me	H	Me	1-S, 1'-S
Fanchinoline (Bis 6)	Me	Me	H	Me	Me	Me	1-S, 1'-S
Isofanchinoline (Bis 7)	Me	Me	H	Me	Me	Me	1-S, 1'-S
Isotetrandrine (Bis 8)	Me	Me	Me	Me	Me	Me	1-R, 1'-S
Nor-2-Isotetrandrine (Bis 9)	Me	Me	Me	Me	H	Me	1-R, 1'-S
N-Oxy-2'-isotetrandrine (Bis 10)	Me	Me	Me	Me	O,Me	Me	1-R, 1'-S
Krukovine (Bis 11)	Me	Me	H	H	Me	Me	1-R, 1'-R

Table 2 (continue)

Limacine (Bis 12)	Me	Me	H	Me	Me	Me	1-R, 1'-R
Obamegine (Bis 13)	Me	Me	H	H	Me	Me	1-R, 1'-S
Phaeanthine (Bis 14)	Me	Me	Me	Me	Me	Me	1-R, 1'-R
Pycnamine (Bis 15)	Me	Me	Me	H	Me	Me	1-R, 1'-R

Bisbenzylisoquinoline alkaloids (Curine type)



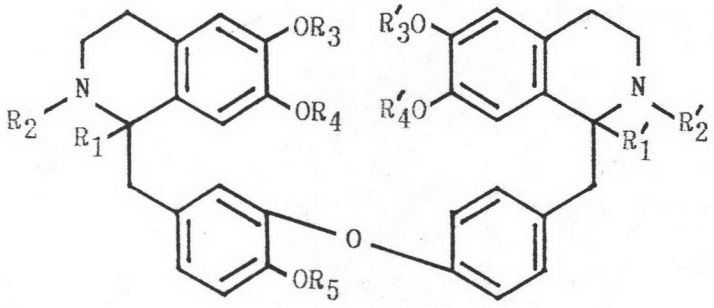
Alkaloid	R_2	R_3	R_4	R_5	R'_2	R'_3	Configuration
d-Chondocurarine (Bis 16)	$(Me)_2$	Me	H	H	$(Me)_2$	Me	- -
d-Chondocurine (Bis 17)	Me	Me	H	H	Me	Me	- -
l -Curine (Bis 18)	Me	Me	H	H	Me	Me	1-S, 1'-S
d-Curine (Bis 19)	Me	Me	H	H	Me	Me	1-R, 1'-R
Cycleacurine (Bis 20)	Me	Me	H	H	Me	H	1-R, 1'-R
Hayatidine (Bis 21)	Me	Me	H	Me	Me	Me	1-S, 1'-R
Hayatine (Bis 22)	Me	Me	H	H	Me	Me	- -
Hayatinine (Bis 23)	Me	Me	H	Me	Me	Me	- -

Table 2 (continue)

4"-O-Methylcurine (Bis 24)	Me	Me	H	Me	Me	Me	1-S, 1'-S
d-Tubocurarine (Bis 25)	$(Me)_2$	Me	H	H	$(Me)_2$	Me	- -

Note : Curine = Bebeerine = Chondodendrine

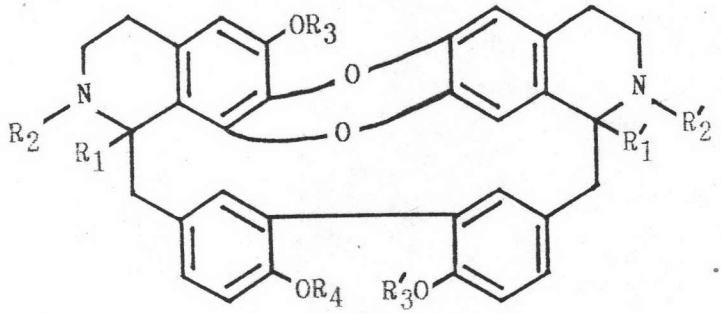
Bisbenzylisoquinoline alkaloids (Dauricine type)



Alkaloid	R_2	R_3	R_4	R_5	R'_2	R'_3	R'_4	Configuration
Cuspidaline (Bis 26)	Me	Me	H	Me	Me	Me	H	1-R, 1'-R
Dauricine (Bis 27)	Me	Me	Me	H	Me	Me	Me	1-R, 1'-R
Daurinoline (Bis 28)	Me	Me	Me	H	Me	H	Me	1-R, 1'-R
Lindoldhamine (Bis 29)	H	Me	H	H	H	Me	H	1-R, 1'-R

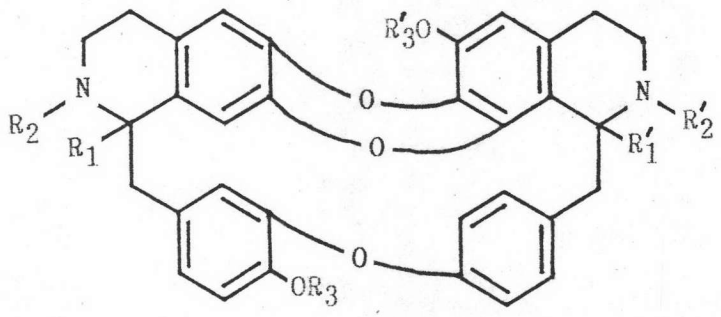
Table 2 (continue)

Bisbenzylisoquinoline alkaloids (Dibenzo-p-dioxin type)

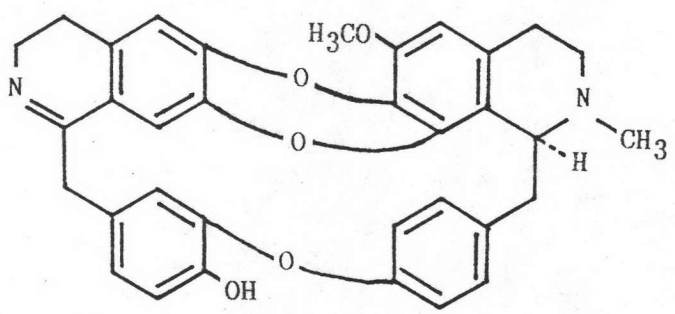


Alkaloid	R_2	R_3	R_4	R'_2	R'_3	Configuration
Tiliarine (Bis 30)	Me	Me	H	H	Me	1-S, 1'-S
Tiliacorine (Bis 31)	Me	Me	Me	Me	H	1-R, 1'-S
Tiliacorinine (Bis 32)	Me	Me	Me	Me	H	1-S, 1'-S
Nortiliacorinine A (Bis 33)	H	Me	Me	Me	H	1-S, 1'-S

Table 2 (continue)

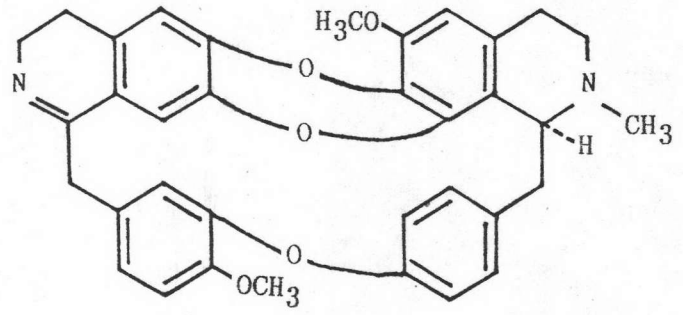


Alkaloid	R_2	R_3	R'_2	R'_3	Configuration
Apateline (Bis 34)	H	H	Me	Me	1-R, 1'-S
Cocsuline (Bis 35)	Me	H	Me	Me	1-S, 1'-S
Isotrilobine (Bis 36)	Me	Me	Me	Me	1-S, 1'-S
O-Methyl cocsoline (Bis 37)	H	Me	Me	Me	1-S, 1'-S
Trilobine (Bis 38)	Me	Me	H	Me	1-S, 1'-S

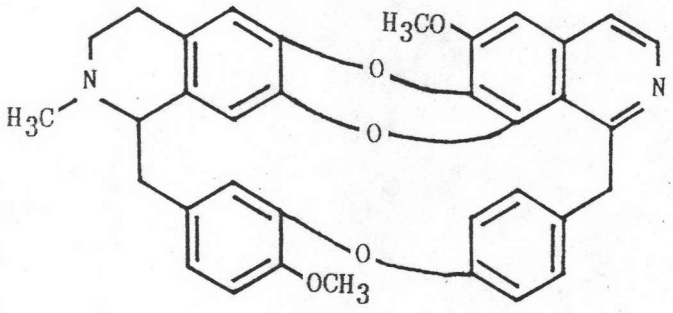


1,2-Dehydroapateline (Bis 39)

Table 2 (continue)

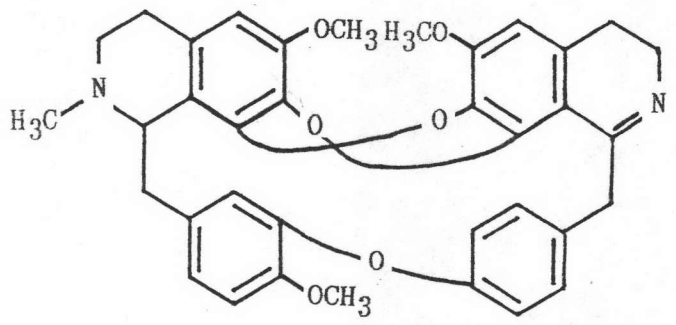


1,2 -Dehydrotelobine (Bis 40)



Trigilletimine (Bis 41)

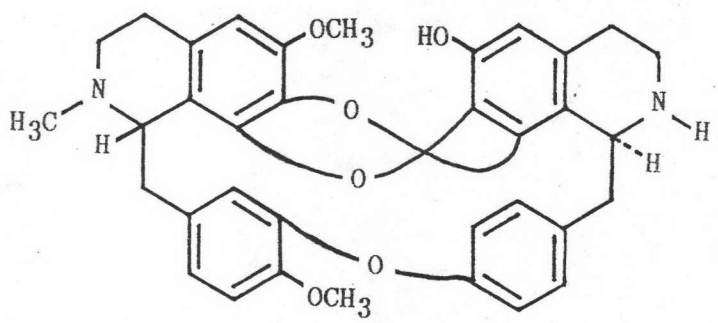
Table 2 (continue)



Menisarine (Bis 42)

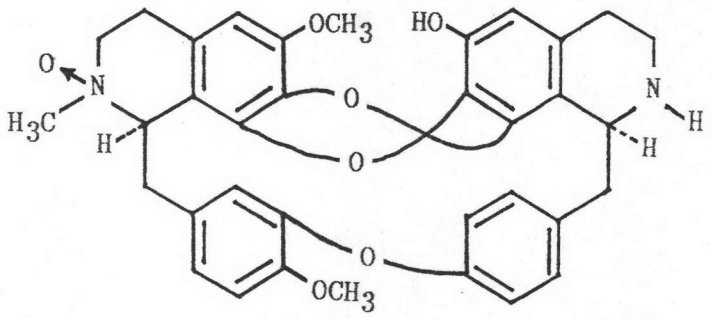
Normenisarine (Bis 43)

(=O-demethylmenisarine, exact location of OH is not determind)

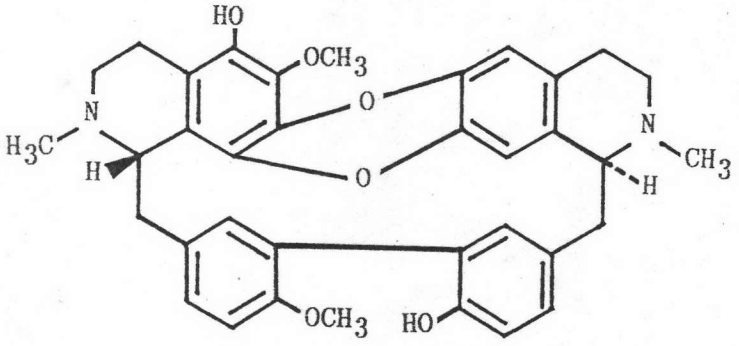


Gilletine (Bis 44)

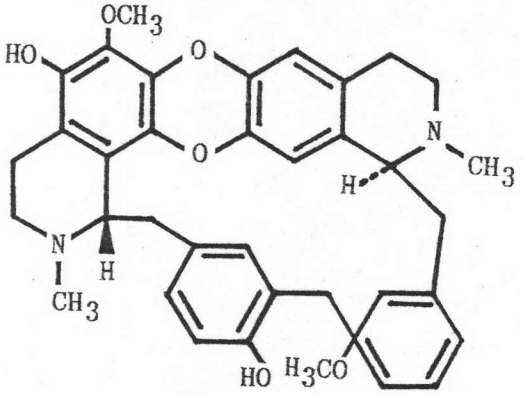
Table 2 (continue)



Isogilletine-N-Oxide (Bis 45)



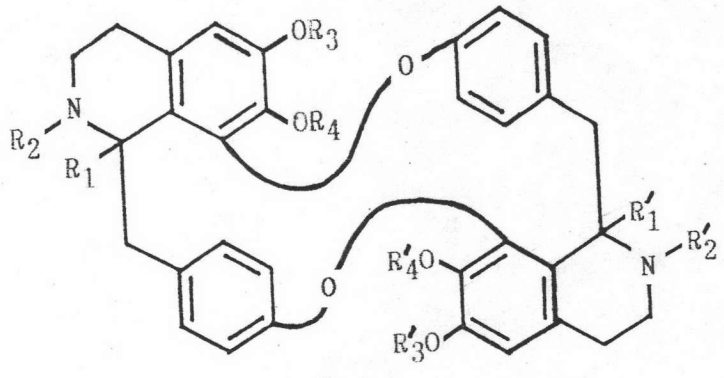
Yanangine (Bis 46)



Tilianangine (Bis 47)

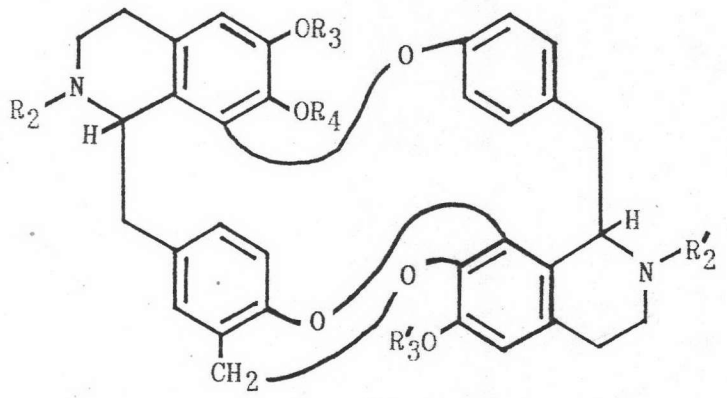
Table 2 (continue)

Bisbenzylisoquinoline alkaloids (Isochondodendrine type)

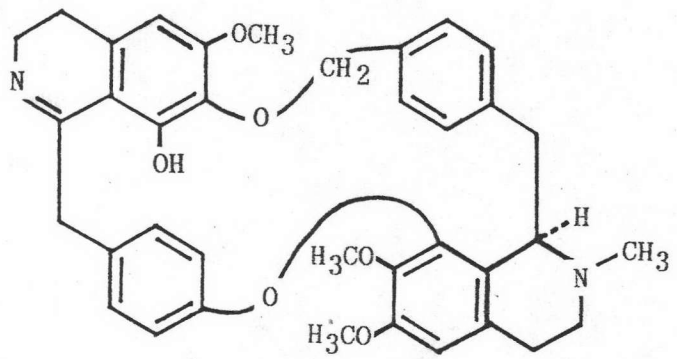


Alkaloid	R_2	R_3	R_4	R'_2	R'_3	R'4	Configuration
Cycleanine (Bis 48)	Me	Me	Me	Me	Me	Me	1-R, 1'-R
Isochondodendrine (Bis 49)	Me	Me	H	Me	Me	H	1-R, 1'-R
Norcycleanine (Bis 50)	Me	Me	Me	Me	Me	H	- -

Table 2 (continue)



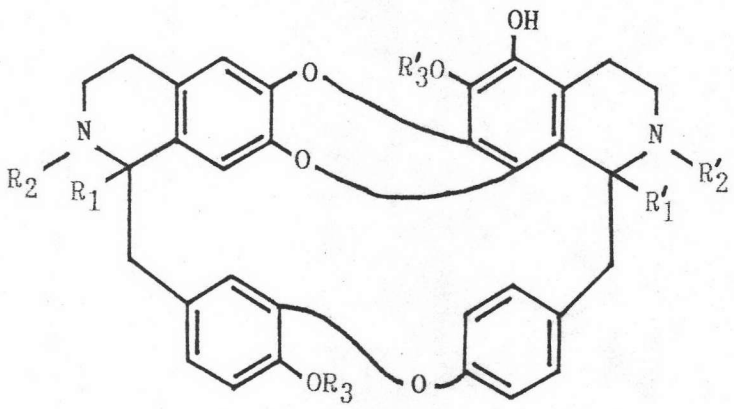
Alkaloid	R_2	R_3	R_4	R'_2	R'_3	Configuration
Insulanoline (Bis 51)	Me	Me	H	Me	Me	1-R, 1'-R
Insularine (Bis 52)	Me	Me	Me	Me	Me	1-R, 1'-R



Cissampareine (Bis 53)

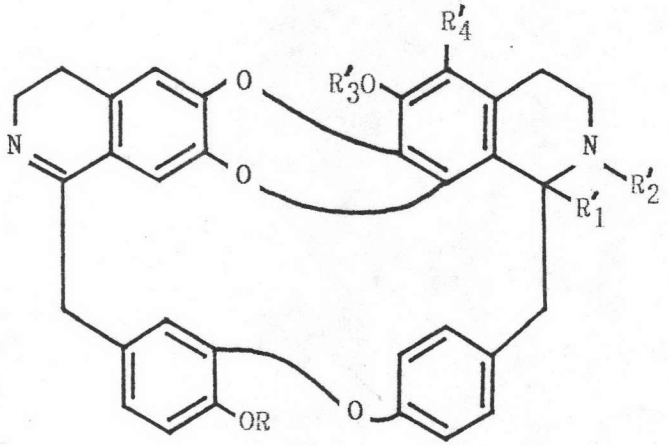
Table 2 (continue)

Bisbenzylisoquinoline alkaloids (Micranthine type)

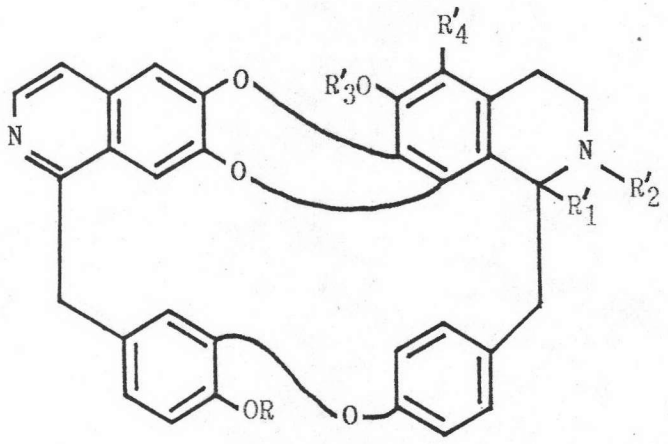


Alkaloid	R_2	R_3	R'_2	R'_3	Configuration
Kohatamine (Bis 54)	H	Me	Me	Me	1-S, 1'-S
5'-Hydroxyapateline (Bis 55)	H	H	Me	Me	1-R, 1'-S
5'-Hydroxytelobine (Bis 56)	H	Me	Me	Me	1-R, 1'-S

Table 2 (continue)



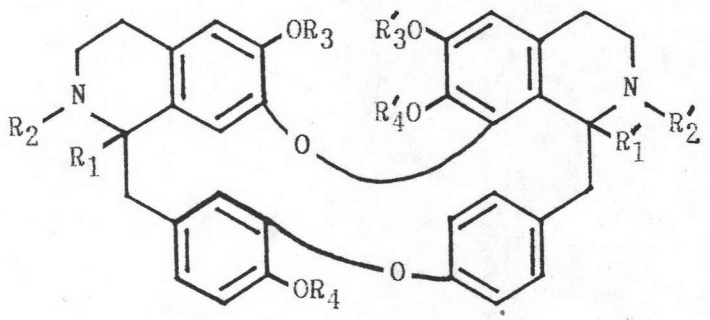
Alkaloid	R_1	R'2	R'3	R'4	Configuration
1,2-Dehydrokohatine (Bis 57)	H	Me	Me	OH	- 1'-S
1,2-Dehydrokohatamine (Bis58)	Me	Me	Me	OH	- 1'-S
1,2-Dehydro-2'-nortelobine (Bis 59)	Me	H	Me	H	- 1'-S



Alkaloid	R	R'2	R'3	R'4	Configuration
Siddiquine (Bis 60)	H	Me	Me	OH	- 1'-S
Siddiquamine (Bis 61)	Me	Me	Me	OH	- 1'-S

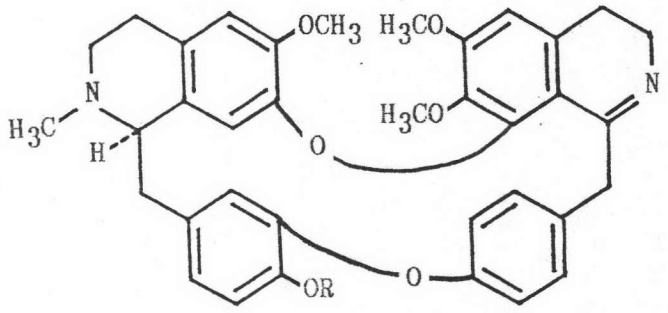
Table 2 (continue)

Bisbenzylisoquinoline alkaloids (Oxyacanthin type)



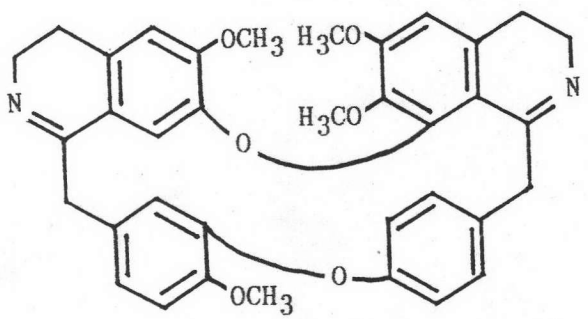
Alkaloid	R_2	R_3	R_4	R'_2	R'_3	R'_4	Configuration
Aromoline (Bis 62)	Me	Me	H	Me	Me	H	1-R, 1'-S
Cepharanthine (Bis 63)	Me	Me	Me	Me	- CH_2-		1-R, 1'-S
Colorflamming (Bis 64)	Me	Me	Me	Me	Me	H	- -
Cycleapeltine (Bis 65)	Me	Me	Me	Me	Me	H	1-S, 1'-S
Dapnandrine (Bis 66)	H	Me	Me	Me	Me	H	1-R, 1'-R
Dapnoline (Bis 67)	H	Me	H	Me	Me	H	1-R, 1'-S
Homoaromoline (Bis 68)	Me	Me	Me	Me	Me	H	1-R, 1'-S
Limacusine (bis 69)	Me	Me	Me	Me	Me	H	1-R, 1'-R
Obaberine (Bis 70)	Me	Me	Me	Me	Me	Me	1-R, 1'-S
Oxyacanthine (Bis 71)	Me	Me	H	Me	Me	Me	1-R, 1'-S

Table 2 (continue)



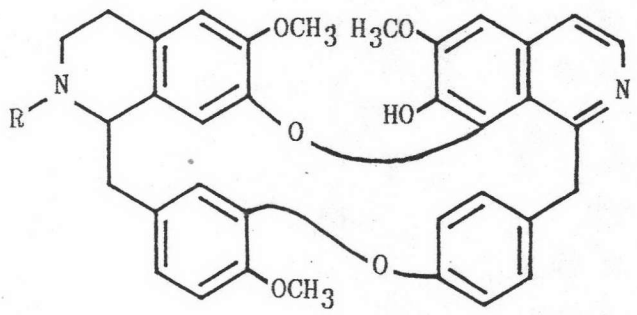
R=Me Epistephanine (Bis 72)

R=H Hypoepistephanine (Bis73)



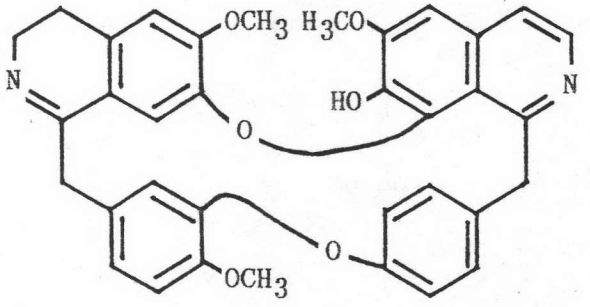
Stebisimine (Bis 74)

Table 2 (continue)



R=Me, Stephasubine (Bis 75)

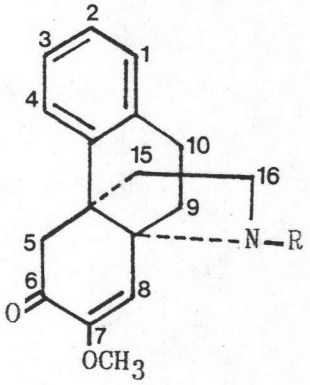
R=H, 2-Norstephasubine (Bis 76)



Stephasubinine (Bis 77)

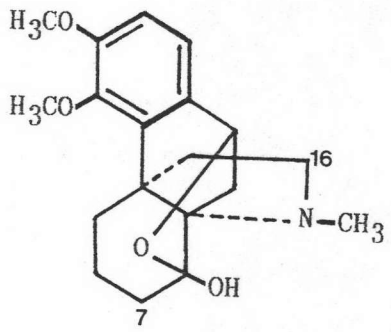
Table 2 (continue)

Hasubanan alkaloids (H)

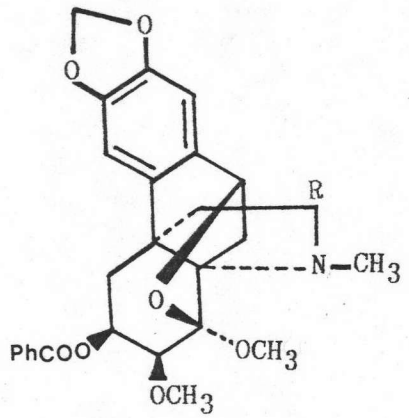


Alkaloid	3	4	8	R
Cepharamine (H1)	OMe	OH	H	Me
4-Demethylhasubanonine (H2)	OMe	OH	OMe	Me
4-Demethylnorhasubanoline (H3)	OMe	OH	OMe	H
Hasubanonine (H4)	OMe	OMe	OMe	Me
Homostephanoline (H5)	OH	OMe	OMe	Me

Table 2 (continue)



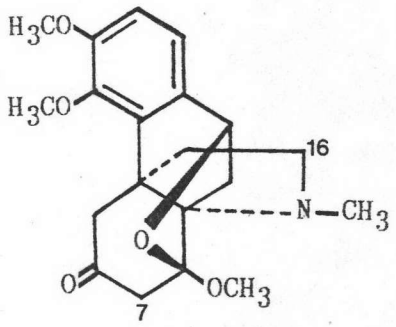
Alkaloids	7	16
Metaphanine (H6)	O	H_2
Prometaphanine (H7)	OMe	H_2
16-Oxoprometaphanine (H8)	OMe	O



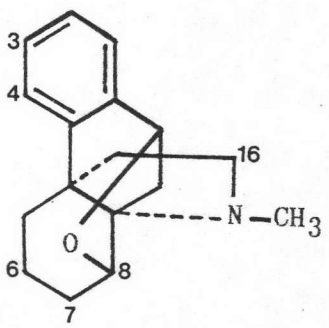
Stephabenine (H9) R = H_2

Oxostephabenine (H10) R = O

Table 2 (continue)



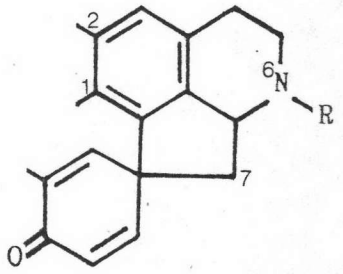
Alkaloids	7	16
Stephamiersine (H11)	OMe	H_2
Epistephamiersine (H12)	OMe	H_2
Oxostephamiersine (H13)	OMe	O
Oxoepistephamiersine (H14)	OMe	O



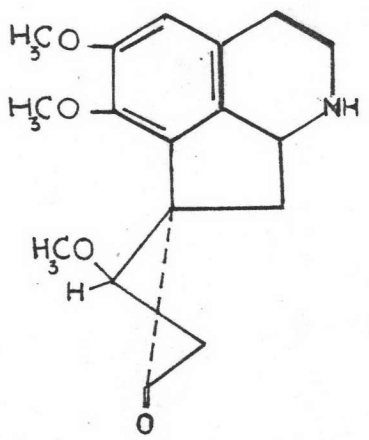
Alkaloids	3	4	6	7	8	16
Stephasunoline (H15)	OMe	OMe	OH	OMe	OH	H_2
Longanone (H16)	OMe	OH	O	OMe	OMe	H_2
Oxostephasunoline (H17)	OMe	OMe	OH	OMe	OH	O
Miersine (H18)	OMe	OMe	OH	OMe	OH	H_2

Table 2 (continue)

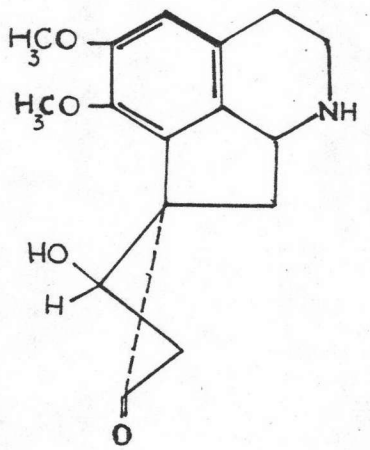
Proaporphine alkaloids (Pa)



Alkaloid	1	2	6(R)
N-Carboxamidostepharine (Pa1)	OMe	OMe	$-CONH_2$
Pronuciferine (Pa2)	OMe	OMe	Me
Stepharine (Pa3)	OMe	OMe	H



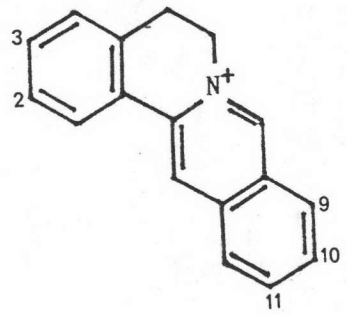
O-methylstapharinosine (Pa4)



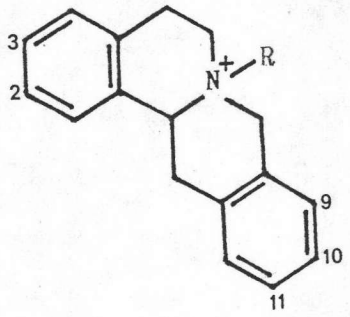
Stepharinosine (Pa5)

Table 2 (continue)

Protoberberine alkaloids (P)



Formula A

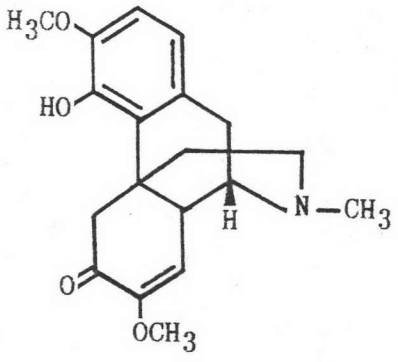


Formula B

Formula A	Formula B	2	3	9	10	11/R
Berberine (P1)		-O-CH_2-O-		OMe	OMe	-
Palmatine (P2)	Tetrahydropalmatine(P3)	OMe	OMe	OMe	OMe	-
Columbamine (P4)	Isocorypalmine (P5)	OH	OMe	OMe	OMe	-
Jatrorrhizine (P6)		OMe	OH	OMe	OMe	-
Dehydrocorydalmine(P7)	Corydalmine (P8)	OMe	OMe	OMe	OH	-
Stepharamine (P9)	Stepholidine (P10)	OH	OMe	OMe	OH	-
	Sinactine (P11)	OMe	OMe	-O-CH_2-O-		-
	Steponine (P12)	OMe	OH	OH	OMe	R=Me
	Cyclanoline (P13)	OH	OMe	OH	OMe	R=Me
	Stepharoline (P14)	OMe	OMe	OMe	OMe	11=OH
Thalifendine (P15)		-O-CH_2-O-		OMe	OH	-
	N-Methylcorydalmine(P16)	OMe	OMe	OMe	OH	R=Me
Dehydrodiscretamine(P17)		OMe	OH	OMe	OH	-
	Govanine (P18)	OH	OMe	-	OMe	11=OMe
Coreximine (P19)		OH	OMe	-	OMe	11=OH
Pseudocolumbamine(P20)		OH	OMe	-	OMe	11=OMe

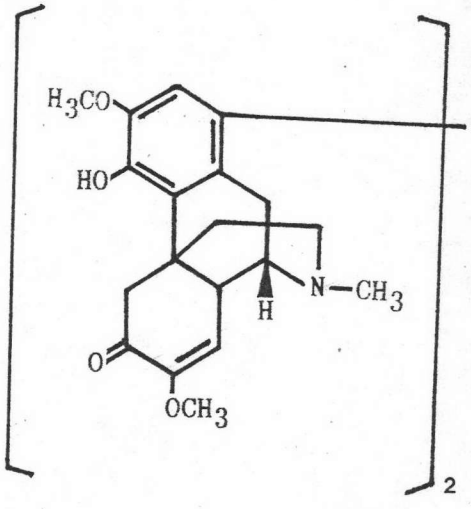
Table 2 (continue)

Morphinondienone alkaloids (M)



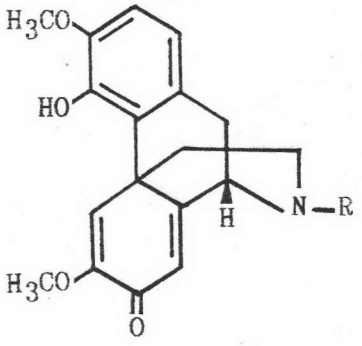
Sinomenine (M1)

(Coculine)



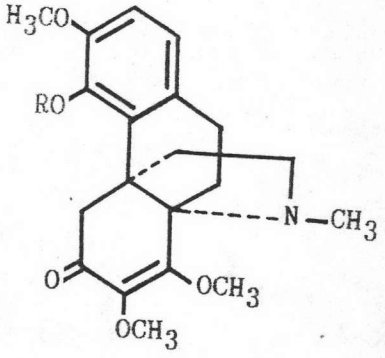
Disinomenine (M2)

(Dehydrosinomenine)



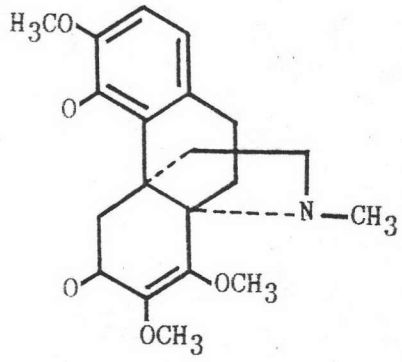
Norsinoacutine R=H (M3)

Sinoacutine R=Me (M4)

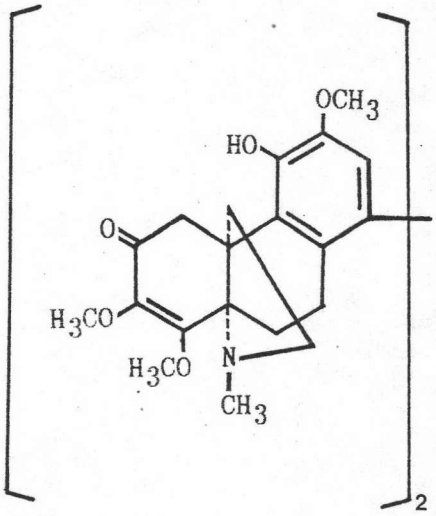


Aknadinine (M5)

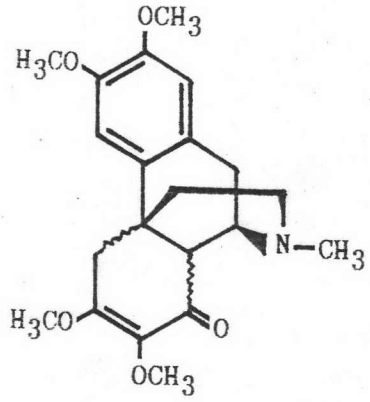
Table 2 (continue)



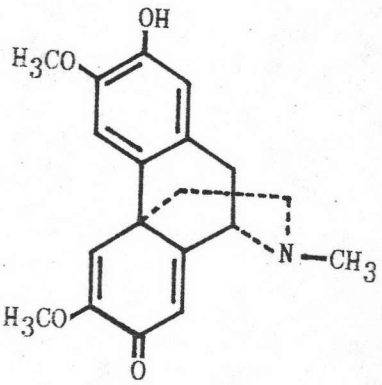
Epihernandolinol (M6)



Bisakanadinine (M7)



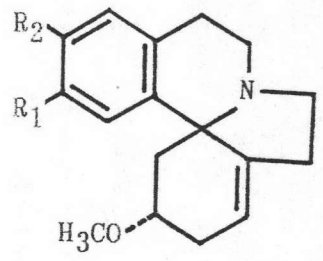
Tridictophylline (M8)



Pallidine (M9)

Table 2 (continue)

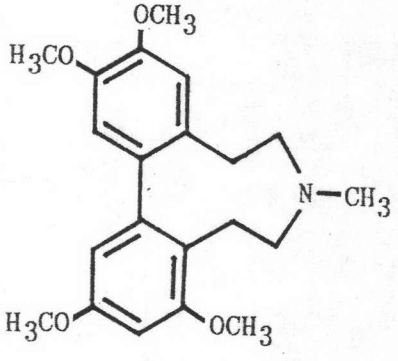
Miscellaneous base (Misc.)



Cocculidine (Misc 1) R_1=OMe, R_2=OMe

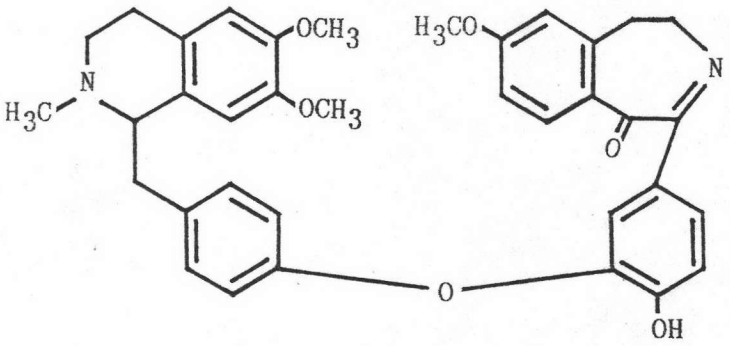
Cocculine (Misc 2) R_1=OH , R_2=OH

Dihydrocrysodine (Misc 3) R_1=OMe, R_2=OH

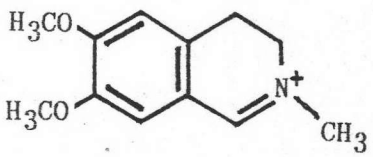


Protostephanine (Misc 4)

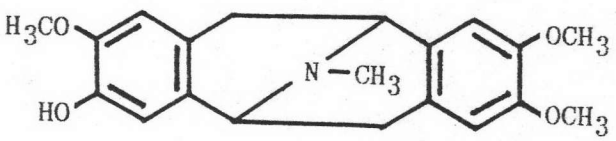
Table 2 (continue)



Stepinonine (Misc 5)



Pycnarrhina (Misc 7)

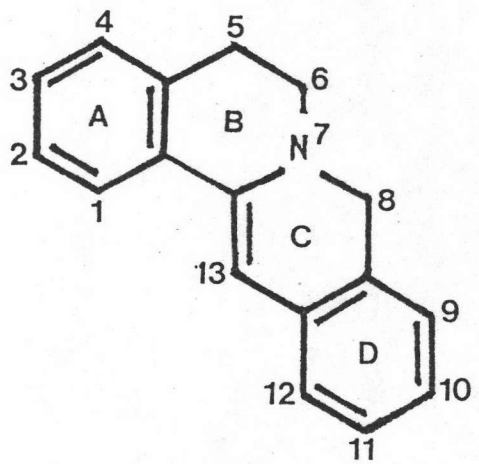


Bisnorargemonine (Misc 6)

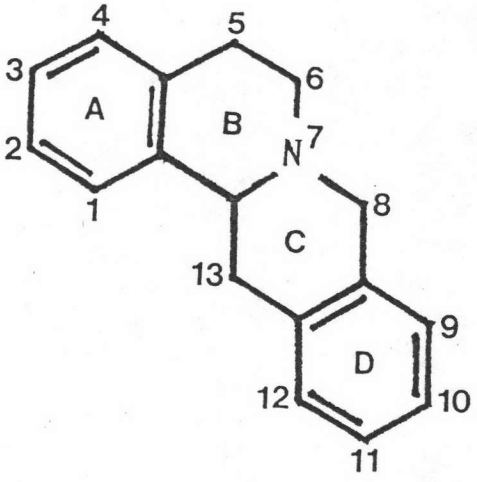
2.2 Distribution of protoberberine alkaloids in plants

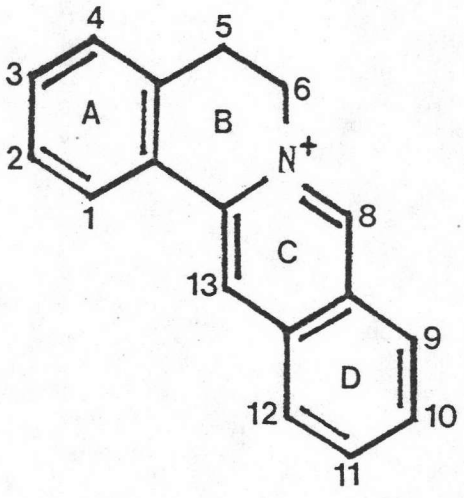
The protoberberines are one of the most widely distributed of the isoquinoline alkaloid groups, being present in at least nine plant families particularly the Annonaceae, Berberidaceae, Lauraceae, Menispermaceae, Papaveraceae and Rutaceae. Most protoberberine alkaloids exist in nature either as tetrahydroprotoberberines or quaternary protoberberine salts, but some dihydroprotoberberines are also known.

The basic structures of these three subgroups are mentioned below.



Dihydroprotoberberines





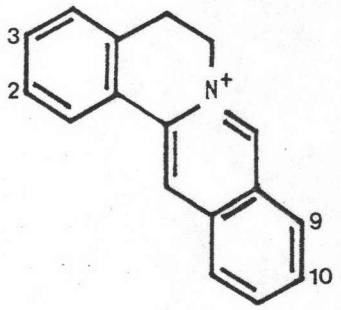
Tetrahydroprotoberberines Quaternary protoberberine salt

Substituents are usually present at C-2 and C-3 and either at C-9 and C-10 or at C-10 and C-11. In the case of C-10 and C-11 are substituted it is called "pseudo" variety. In some instances a hydroxyl or methoxyl substituent may present at C-1. A methyl group is sometimes found at C-8 or C-13, while in a few cases an alcoholic hydroxyl is located at C-13 or C-5.Some retroprotoberberines are known which are characterized by the presence of one extra carbon atom as a side chain bonded to ring D. (Shamma, 1972)

The distribution of protoberberine alkaloids in plants are summarized as table 3.

Table 3 Distribution of protoberberine alkaloids in plants

3.1 Quaternary protoberberine



Name	Structure				Plants
	2	3	9	10	
Berberine (Umbellatine)	-O-CH_2-O-		OMe	OMe	*Anamirta cocculus* *Aquilegia olympica* *Arcangelisia flava* *A. lemniscata* *A. lourerie* *Argemone mexicana* *Berberis asiatica* *B. buxifolia* *B. darwinii* *B. empetrifolia* *B. glauca* *B. julianae*

Table 3 (continue)

Berberine				*B. lycium*
				B. oblonga
				B. nervosa
				B. petiolaris
				B. vulgaris
				Chelidonium majus
				Coelocline polycarpa
				Coptis groenlandica
				C. japonica
				C. occidentalis
				C. quinavefolia
				C. teeta
				C. trifolia
				Corydalis cheilantheifolia
				C. ophicarpa
				Coscinium blumeanum
				C. fenestratum
				C. wallichianum
				Dicranostigma lactucoides
				D. leptopodum
				Evodia meliifolia
				Fibraurea chloroleuca
				F. tinctoria

Table 3 (continue)

				Fumaria kraliki
				Glaucium corniculatum
				G. grandiflorum
				Hunnemannia fumariaefolia
				Hydrastis canadensis
				Mahonia aquifolium
				M. repens
				Nandina domestica
				Papaver albiflorum
				P. lecoquii
				P. rhoeas
				Phellodendron amurense
				P. wilsonii
				Thalictrum alpinum
				T. baicalense
				T. foliosum
				T. javanicum
				T. longistylum
				T. lucidum
				T. minus
				T. polyganum
				T. revolutum
				Tinospora baenzigeri
				T. crispa
				T. glabra

Table 3 (continue)

					T. merrilliana *T. rhumphii* *T. smilacina* *Toddalia aculeata* *Xylopia polycarpa* *Zanthoxylum caribaeum* *Z. monophyllum*
Berberubine	-O-CH_2-O-		OH	OMe	*Coscinium fenestratum* *Fibraurea chloroleuca* *Thalictrum polygranum*
Columbamine	OH	OMe	OMe	OMe	*Anamirta cocculus* *Arcangelisia flava* *Berberis oblonga* *B. vulgaris* *Burasaia madagascariensis* *Chasmanthera dependens* *Coptis quinavefolia* *Enantia chlorantha* *E. polycarpa* *Fibraurea chloroleuca* *Jatrorrhiza palmata* *Mahonia repens* *Stephania glabra*

Table 3 (continue)

					Thalictrum alpinum *T. folialosum* *T. japonicum* *T. longistylum* *T. minus* *T. polycarpum* *T. revolutum* *T. rugosum*
Coptisine	-O-CH_2-O-		-O-CH_2-O-		*Chelidonium majus* *Coptis groenlandica* *C. japonica* *C. quinavefolia* *Corydalis cava* *C. ophiocarpa* *Dicranostigma lactucoides* *D. leptopodum* *Fumaria densiflora* *F. judaica* *F. kraliki* *F. parviflora* *Hunnemannia fumariaefolia* *Papaver albiflorum* *P. conifine* *P. lecoquii*

Table 3 (continue)

					P. rupifragum *P. pseudo-orientale*
Dehydro- cheilanthifoline	OH	OMe	$-O-CH_2-O-$		*Bocconia cordata* *Corydalis ophiocarpa* *Fumari parviflora* *Menispermum cannadense*
Dehydrocorydalmine	OMe	OMe	OMe	OH	*Arcangelisia flava* *Berberis floribunda* *Corydalis ambigna* *Legnephora moorii* *Stephania glabra*
Dehydrodiscretamine	OMe	OH	OMe	OH	*Corydalis tashiroi* *Thalictrum foliolosum*
Demethylleneberberine	OH	OH	OMe	OMe	*Thalictrum javanicum*
Groenlandicine	OMe	OH	$-O-CH_2-O-$		*Bocconia cordata* *Coptis groenlandica* *Coptis spp.* *Nandina domestica*

Table 3 (continue)

Jatrorrhizine (Jateorhizine, Neprotine)	OMe	OH	OMe	OMe	*Arcangelisia flava* *A. lourerii* *Berberis julianae* *B. heteropoda* *B. oblonga* *B. vulgaris* *Burasaia madagascariensis* *Chasmanthera dependens* *Coptis japonica* *C. quinavefolia* *Coscinium blumeanum* *C. fenestratum* *C. wallichianum* *Enantia chlorantha* *E. polycarpa* *Fibraurea chloroleuca* *Jatrorrhiza palmata* *Mahonia philippinensis* *M. repens* *Stephania glabra* *Thalictrum foliolosum* *T. lucidum* *T. revolutum* *Tinospora baenzigeri* *T. crispa*

Table 3 (continue)

Palmatine	OMe	OMe	OMe	OMe	*Anamirta cocculus*
					Arcangelisis flava
					A. lourerii
					Berberis jaeschkeana
					B. julianae
					B. oblonga
					B. petiolaris
					B. vulgaris
					Chasmanthera dependens
					Cocculus carolinus
					C. leaeba
					Coscinium blumeanum
					C. fenestratum
					C. wallichianum
					Enantia chlorantha
					E. pilosa
					E. polycarpa
					Fibraurea chloroleuca
					Fumaria densiflora
					Jatrorrhiza palmata
					Leontice leontopatalum
					Mahonia repens
					Papaver pseudo-orientale
					Stephania glabra
					S. kwansiensis

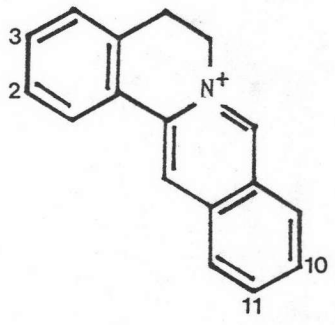
Table 3 (continue)

					Tinospora cordifolia *T. crispa* *T. glabra* *T. merrilliana* *T. sagittata* *T. sinensis* *Thalictrum alpinum* *T. foliolosum* *T. javanicum* *T. longistylum* *T. minus* *T. podocarpum* *T. revolutum*
Palmatrubine	OMe	OMe	OH	OMe	*Fibraurea chloroleuca* *Stephania glabra* *Thalictrum polygamum*
Stepharanine	OH	OMe	OMe	OH	*Stephania glabra* *S. intermedia* *Tinospora capillipes*
Thalifendine	-O-CH_2-O-		OMe	OH	*Arcangelisia flava* *Thalictrum alpinum* *T. fendleri*

Table 3 (continue)

				T. foliolosum *T. minus* *T. podocarpum* *T. polygamum* *T. revolutum* *T. rugosum*

3.2 Quaternary pseudoprotoberberines



Name	Structure				Plants
	2	3	10	11	
Dehydrodiscretine (Pseudojatrorrhizine)	OMe	OH	OMe	OMe	*Fibraurea chloroleuca* *Heptacyclum zenkeri* *Thalictrum fauriei*

Table 3 (continue)

Dehydropseudo cheilanthifoline	OH	OMe	-O-CH_2-O-		*Corydalis ophiocarpa* *Fumaria parviflora* *Isopyrum thalictroides*
Pseudoberberine	-O-CH_2-O-		OMe	OMe	*Isopyrum thalictroides*
Pseudocolumbamine	OH	OMe	OMe	OMe	*Isopyrum Thalictroides* *Fibraurea chloroleuca*
Pseudocoptisine	-O-CH_2-O-		-O-CH_2-O-		*Coptis groelandica* *Isopyrum thalictroides*
Pseudopalmatine	OMe	OMe	OMe	OMe	*Enantia polycarpa*
Thalifaurine	OMe	OH	-O-CH_2-O-		*Thalictrum fauriei*

3.3 Quaternary protoberberines methylated at C-13

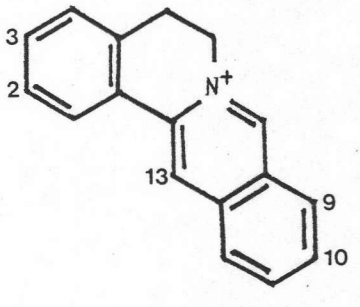
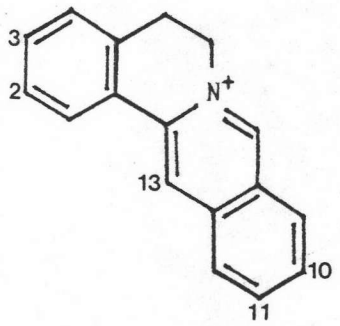


Table 3 (continue)

Name	Structure					Plants
	2	3	9	10	13	
Corysamine	-O-CH_2-O-		-O-CH_2-O-		Me	*Chelidonium majus* *Corydalis incisa* *C. cava* *C. lutea* *Dicranostigma lactucoides* *D. leptopodum* *Hunnemannia fumariaefolia* *Papaver albiflorum* *P. rupifragum*
Dehydroapocavidine	OH	OMe	-O-CH_2-O-		Me	*Corydalis cava*
Dehydrocavidine	OMe	OMe	-O-CH_2-O-		Me	*Corydalis cava* *Corydalis meifolia*
Dehydrocorydaline	OMe	OMe	OMe	OMe	Me	*Corydalis ambigua* *C. decumbens* *C. tuberosa* *Berberis floribunda*

Table 3 (continue)

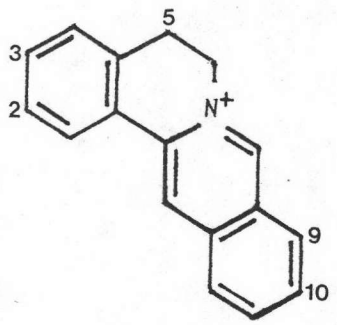
3.4 Quaternary pseudoprotoberberines methylated at C-13



Name	Structure					Plants
	2	3	10	11	13	
Worenine	-O-CH_2-O-		-O-CH_2-O-		Me	*Coptis chinensis* *C. japonica*

Table 3 (continue)

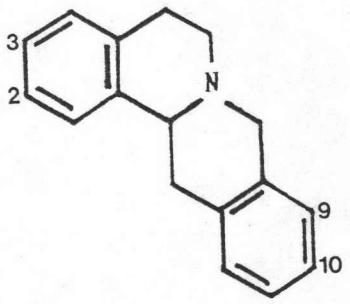
3.5 Quaternary protoberberine hydroxylated at C-5



Name	Structure					Plants
	2	3	5	9	10	
Berberastine	-O-CH_2-O-		OH	OMe	OMe	*Coptis spp.* *Hydrastis canadensis*
Thalidastine	-O-CH_2-O-		OH	OMe	OH	*Thalictrum fendleri* *T. foliolosum* *T. minus* *T. rugosum*

Table 3 (continue)

3.6 Tetrahydroprotoberberines



Name	Structure				Plants
	2	3	9	10	
(-) Aequaline ((-) Discretamine)	OMe	OH	OMe	OH	*Desmos tiebaghiensis* *Duguetia calycina* *Mitrella kentii* *Schefferomitra subaequalis* *Xylopia buxifolia* *X. discreta*
Bharatamine	OH	OMe	-	-	*Alangium lamarckii*
Canadine	$-O-CH_2-O-$		OMe	OMe	*Corydalis cava* *C. cheilantheifoline*

Table 3 (continue)

					Corydalis ophiocarpa *C. ternata* *C. tuberosa* *Fagara rhoifolia* *Hydrastis canadensis* *Mahonia aquifolium* *Papaver albiflorum* *P. lecoquii* *Xanthoxylum brachyacanthum* *X. veneficum*
Cheilanthifoline	OH	OMe	$-O-CH_2-O-$		*Argemone spp.* *Cheilidonium meifolia* *Corydalis cheilanthifolia* *C. ophiocarpa* *C. scouteri* *C. sibirica* *Fumaria judaica* *F. officinalis* *F. parviflora* *F. vaillantii* *Papaver macrostomum* *P. trinifolium*

Table 3 (continue)

Corydalmine (Kikemanine, Schefferine, Cycemanine)	OMe	OMe	OMe	OH	*Corydalis pallida* *Papaver oligosperma* *Polyalthia oligosperma* *Schefferomitra subaequalis* *Stephania glabra* *S. Suberosa*
Corypalmine (discretinine, Tetrahydroja-trorrhizine)	OMe	OH	OMe	OMe	*Berberis floribunda* *B. hemaloica* *Coptis teeta* *Corydalis caseana* *C. cava* *C. chelianthefolia* *C. incisa* *C. ochroleuca* *C. ophiocarpa* *C. thalictrifolia* *C. tuberosa* *Dicentra oregana* *Guatteria discolor* *Hydrastis canadensis* *Mahonia aquifolium* *Pachypodanthium confine* *P. staudtii* *Xylopia discreta*

Table 3 (continue)

Isocorypalmine (Tetrahydro-columbamine)	OH	OMe	OMe	OMe	*Bocconia frutescens* *Corydalis cava* *C. lutea* *C. ophiocarpa* *Glaucium fimbrilligerum* *Hydrastis canadensis* *Pachypodanthium confine* *P. staudtii* *Tinomiscium petiolare*
Nandinine	$-O-CH_2-O-$		OH	OMe	*Nandina domestica*
Sinactin	OMe	OMe	$-O-CH_2-O-$		*Corydalis meifolia* *Fumaria officinalis* *Sinomenium acutum*
Scoulerine	OH	OMe	OH	OMe	*Bocconia frutescens* *Corydalis cava* *C. caseana* *C. micrantha* *C. montana* *C. sibirica* *C. tuberosa* *Cryptocarya longifolia*

Table 3 (continue)

					Erythrina orientalis *Eshcholtzia lobbii* *Fumaria officinalis* *Hunnemannia fumariaefolia* *Hypecoum procumbens* *Papaver albiflorum* *P. lecoquii* *P. tauricola* *P. trinifolium*
Stepholidine	OH	OMe	OMe	OH	*Desmos tiebaghiensis* *Monanthotaxis cauliflora* *Stephania glabra* *S. suberosa*
Stylopine (Tetrahydrocoptisine)	$-O-CH_2-O-$		$-O-CH_2-O-$		*Cheilidonium gortschakovii* *C. majus* *C. meifolia* *Corydalis cava* *C. marschallia* *C. ophiocarpa* *C. solida* *Fumaria judaica* *F. kraliki*

Table 3 (continue)

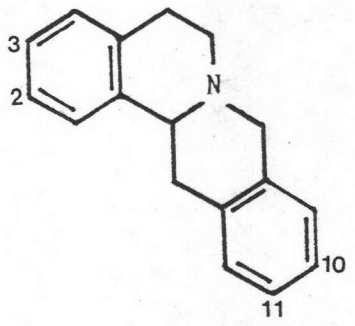
					Fumaria parviflora *F. schleicheri* *F. vaillantii* *Papaver albiflorum* *P. lecoquii* *P. rupifragum*
Tetrahydropalmatine (Gindarine, Caseanine)	OMe	OMe	OMe	OMe	*Chasmanthera dependens* *Corydalis ambigua* *C. aurea* *C. caseana* *C. cava* *C. decumbens* *C. lutea* *C. micrantha* *C. montana* *C. nobilis* *C. ochraleuca* *C. pallida* *C. platycarpa* *C. tuberosa* *Fibraurea chloroleuca* *Glaucium vitellinum* *Hydrastis canadensis*

Table 3 (continue)

					Leontica leontopatalum *Pachypodanthium confine* *Stephania glabra* *S. kwansiensis* *S. sasakii* *S. suberosa*
Tetrahydropalmatrubine	OMe	OMe	OH	OMe	*Stephania suberosa*
Tetrahydrothalifendine	$-O-CH_2-O-$		OMe	OH	*Thalictrum fendleri*

Table 3 (continue)

3.7 Tetrahydropseudoprotoberberines



Name	Structure				Plants
	2	3	9	10	
Artavenustine	OMe	OH	OH	OH	*Annona montana* *A. muricata*
Coreximine (Coramine)	OH	OMe	OMe	OH	*Artabotrys venustus* *Asimina triloba* *Chasnanthera dependens* *Corydalis spp.* *Dicentra eximia* *Erythrina orientalis* *Guatteria ouregou* *Papaver somniferum* *Stephania suberosa*

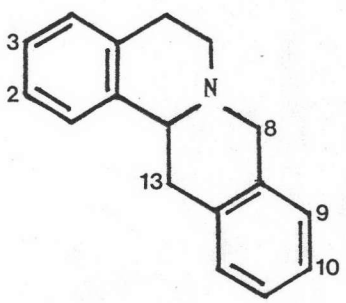
Table 3 (continue)

Coryovanine (Corygoranine)	OH	OMe	-O-CH_2-O-		*Corydalis govaniana* *Stephania suberosa*
Corytenchine	OMe	OMe	OMe	OH	*Corydalis ochotensis*
10-Demethylxylopinine	OMe	OMe	OH	OMe	*Duguetia calycina*
10-Demethyldiscretine	OMe	OH	OH	OMe	*Guatteria discolor*
Discretine	OMe	OH	OMe	OMe	*Duguetia obovata* *Guatteria discolor* *G. scandens* *Pachypodanthium staudtii* *Xylopia discreta*
Govadine	OH	OMe	OH	OMe	*Corydalis govaniana*
Govanine	OH	OMe	OMe	OMe	*Chasmanthera dependens* *Corydalis govaniana*

Table 3 (continue)

Xylopinine	OMe	OMe	OMe	OMe	*Duguetia obovata* *Guatteria scandens* *Polyalthia oligosperma* *Stephania suberosa* *Xylopia buxifolia* *X. discreta*

3.8 Tetrahydroprotoberberines methylated at C-8 or C-13



Name	Structure						Plants
	2	3	8	9	10	13	
Apocavidine	OH	OMe	-	-O-CH_2-O-		Me	*Corydalis tuberosa*
Cavidine	OMe	OMe	-	-O-CH_2-O-		Me	*Corydalis thalictrifolia*

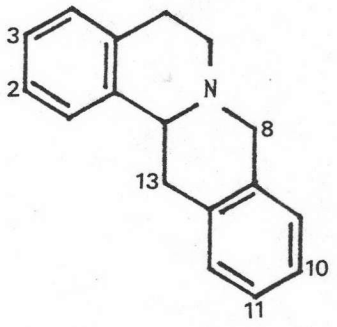
Table 3 (continue)

Corybulbine	OMe	OH	-	OMe	OMe	Me	*Corydalis ambigua* *C. platycarpa* *C. tuberosa*
Corydaline	OMe	OMe	-	OMe	OMe	Me	*Corydalis ambigua* *C. aurea* *C. platycarpa* *C. tuberosa*
Corydalidzine	OMe	OH	-	OMe	OH	Me	*Corydalis koidzumiana*
Epiapocavidine	-O-CH_2-O-		-	OMe	OH	Me	*Corydalis tuberosa*
Isocorybulbine	OH	OMe	-	OMe	OMe	Me	*Corydalis cava* *C. tuberosa*
Lienkonine	OMe	OMe	Me	OH	OMe	-	*Corydalis ochotensis*
Tetrahydro-corysamine	-O-CH_2-O-		-	-O-CH_2-O-		Me	*Corydalis cava* *Corydalis pallida*
Thalictricavine	-O-CH_2-O-		-	OMe	OMe	Me	*Corydalis tuberosa*

Table 3 (continue)

Thalictrifoline (Thalictrofoline)	OMe	OMe	-	$-O-CH_2-O$		Me	*Corydalis thalictrifolia*
Yuanhumine	OMe	OMe	-	OMe	OH	Me	*Corydalis turtschaninovii*

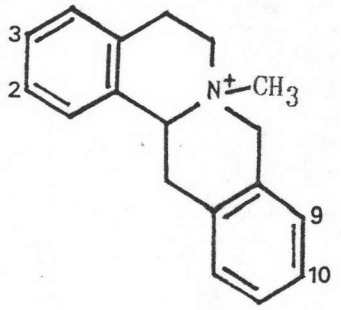
3.9 Tetrahydropseudoprotoberberines methylated at C-8



Name	Structure					Plants
	2	3	8	10	11	
Corytenchirine	OMe	OMe	Me	OMe	OH	*Corydalis ochotensis*

Table 3 (continue)

3.10 Tetrahydroprotoberberine N-methylated

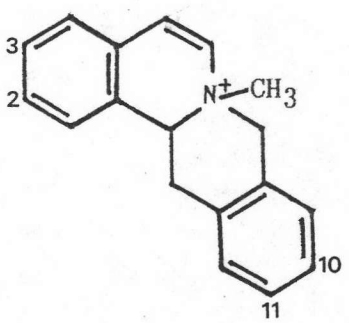


Name	Structure				Plants
	2	3	9	10	
Cyclanoline (Cissamine)	OH	OMe	OH	OMe	*Cissampelos pareira* *Stephania tetrandra*
Escholidine	-O-CH_2-O-		OMe	OH	*Eschscholtzia californica* *E. douglasi* *E. glauca* *Hunnemania fumariaefolia*
N-Methylcorydalmine	OMe	OMe	OMe	OH	*Stephania elegans*

Table 3 (continue)

N-Methyl-isocorypalminium	OH	OMe	OMe	OMe	*Glaucium squamigerum*
N-Methylsinactine	OMe	OMe	-O-CH_2-O-		*Fumaria officinalis*
Steponine	OMe	OH	OH	OMe	*Stephania japonica*

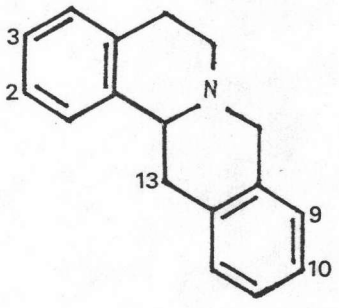
3.11 Tetrahydropseudoprotoberberines N-methylated



Name	Structure				Plants
	2	3	10	11	
Phellodendrine	OH	OMe	OMe	OH	*Phellodendron amurense*

Table 3 (continue)

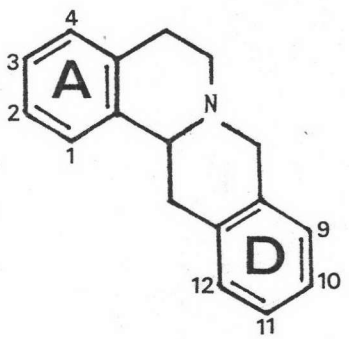
3.12 Tetrahydroprotoberberines hydroxylated at C-13



Name	Structure					Plants
	2	3	9	10	13	
13-Hydroxytetra-hydropalmatine	OMe	OMe	OMe	OMe	OH	*Corydalis ophiocarpa*
13-Hydroxystylopine	-O-CH_2-O-		-O-CH_2-O-		OH	*Corydalis ophiocarpa*
Ophiocarpine	-O-CH_2-O-		OMe	OMe	OH	*Cocculus pendulus* *Corydalis campulicarpa* *C. cheilanthifolia* *C. govaniana* *C. ophiocarpa*

Table 3 (continue)

3.13 Tetrahydroprotoberberines with uncommon oxygenation patterns on ring A and ring D



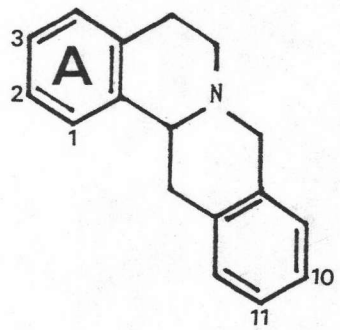
Name	Structure							Plants
	1	2	3	4	9	10	11	
Capauridine (dl-Capaurine)	OH	OMe	OMe	-	OMe	OMe		*Corydalis aurea* *C. cava* *C. micrantha* *C. montana* *C. ophiocarpa* *C. pallida* *Stephania glabra* *S. kwansiensis*

Table 3 (continue)

Capaurimine	OH	OMe	OMe	-	OMe	OH	-	*Corydalis montata* *C. pallida* *Stephania suberosa*
Caseanadine	OH	OMe	-	-	OMe	OMe	-	*Corydalis caseana* *C. clarkei*
Clarkeanidine	OH	OMe	-	-	OH	OMe	-	*Corydalis clarkei*
O-methylthaicanine	-	OMe	OMe	OMe	OMe	OMe	-	*Parabaena sagittata*
Stepharotine	-	OMe	OMe		OMe	OMe	OH	*Stephania rotunda*
Thaicamine	-	OMe	OMe	OH	OMe	OMe	-	*Parabaena sagittata*

Table 3 (continue)

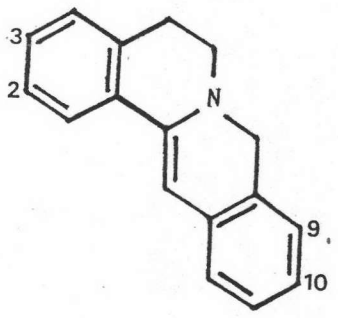
3.14 Tetrahydropseudoprotoberberines with uncommon oxygenation patterns on ring A



Name	Structure					Plants
	1	2	3	10	11	
Caseadine	OMe	OH	-	OMe	OMe	*Corydalis caseana*
Caseamine	OH	OMe	-	OH	OMe	*Corydalis caseana*
Stephabinamine	OH	OMe	OMe	OMe	OH	*Stephania suberosa*
Tetrahydrostephabine	OH	OMe	OMe	OMe	OMe	*Stephania suberosa*

Table 3 (continue)

3.15 Dihydroprotoberberines



Name	Structure				Plants
	2	3	9	10	
Dihydropalmatine	OMe	OMe	OMe	OMe	*Stephania kwansiensis*
Lambertine	-O-CH_2-O-		OMe	OMe	*Berberis lambertii*

Table 3 (continue)

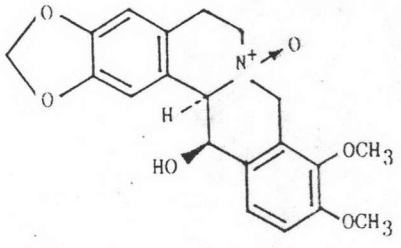
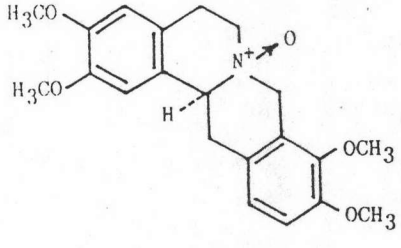
3.16 Protoberberines N-oxides		
Name	Structure	Plants
Carpoxidine (Ophiocarpine N-oxide)		*Corydalis ophiocarpa*
Corynoxidine		*Corydalis koidzumiana*

Table 3 (continue)

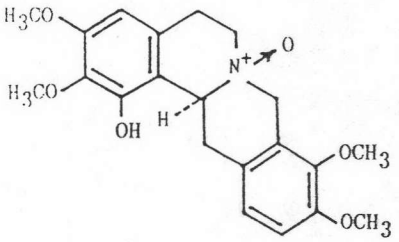
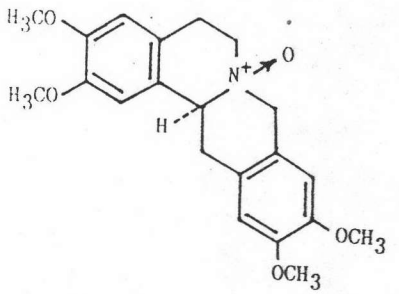
Nokoensine		*Corydalis nokoensis*
Xylopinine N-oxide		*Stephania suberosa*

Table 3 (continue)

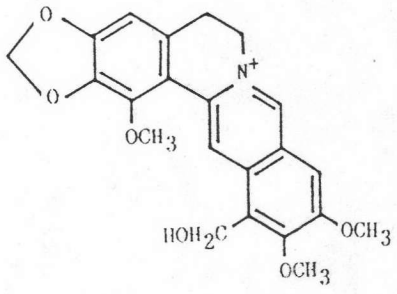
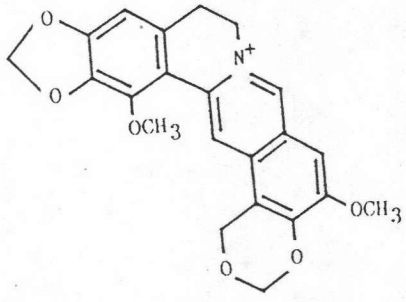
3.17 Retroprotoberberines		
Name	Structure	Plants
Alborine		*Papaver alboroseum* *P. nudicaule* *P. oreophilum* *P. pseudocanescen* *P. pseudo-orientale* *P. pyrenaicum*
Dehydroorientalidine		*Papaver albaroseum* *P. nudicaule* *P. areophilum* *P. orientale* *P. pseudocanescen* *P. Pyrenaicum*

Table 3 (continue)

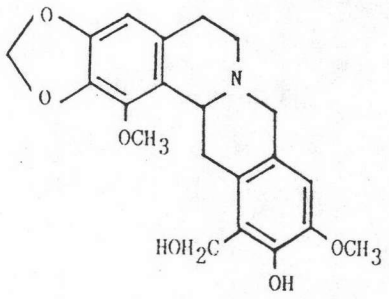
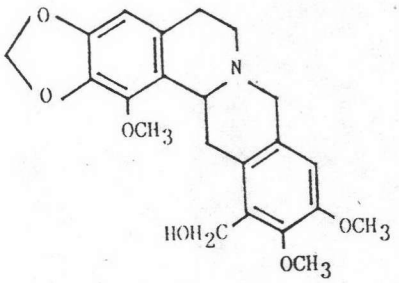
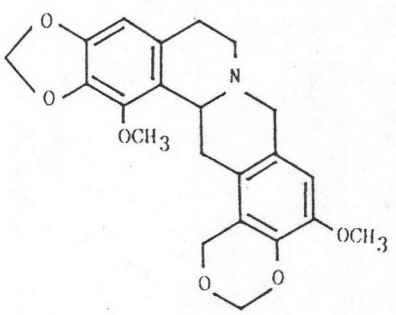
Aryapavine		*Papaver pseudoorientale*
Mecambridine (Oreophiline)		*Meconopsis cambrica* *Papaver spp.*
Orientalidine		*Papaver bracteatum* *P. orientale* *P. pseudo-orientale*

Table 3 (continue)

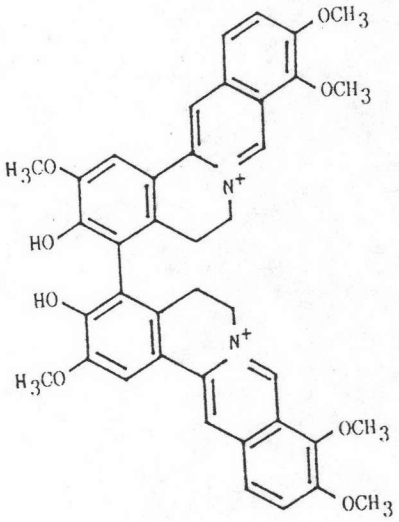
3.18 Miscellaneous protoberberines		
Name	Structure	Plants
Bisjatrorrhizine		*Jatrorhiza palmata*

Table 3 (continue)

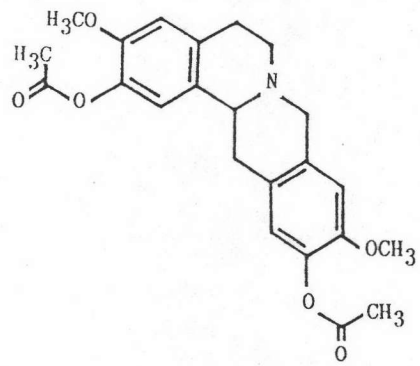
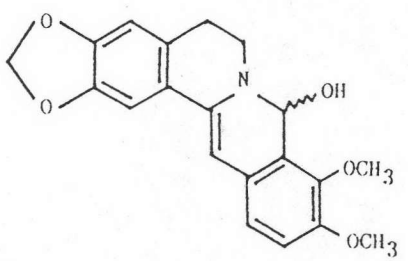
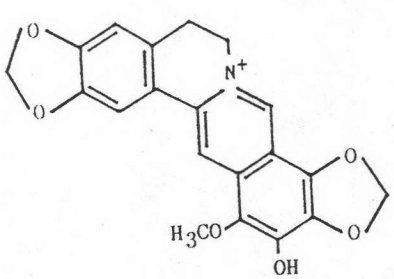
0,0-Diacetylcoreximine		*Guatteria ouregou*
8-Hydroxyberberine (Berberinol)		*Arcangelisia flava*
11-Hydroxy-12-methoxycoptisine		*Coptis groenlandica*

Table 3 (continue)

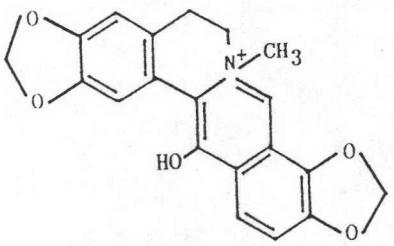
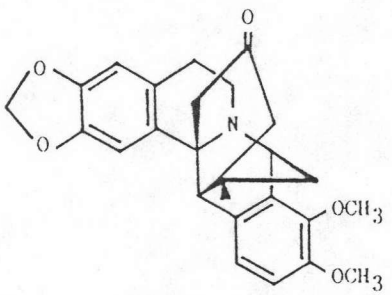
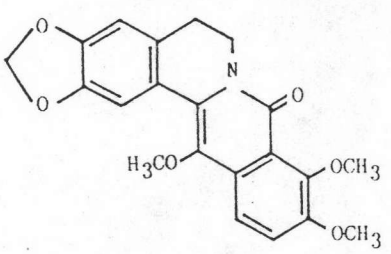
13-β-Hydroxy-N-methylstylopinium		*Papaver atlanticum*
Karachine		*Berberis aristata*
13-Methoxyoxoberberine		*Berberis darwinii*

Table 3 (continue)

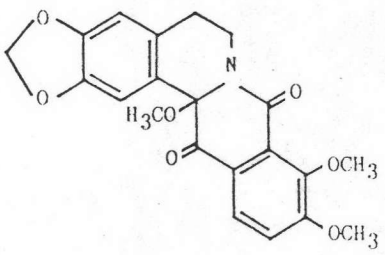
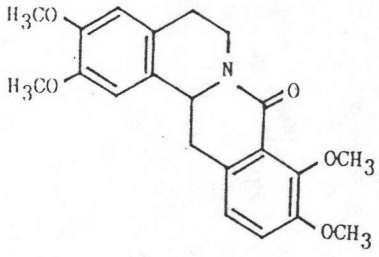
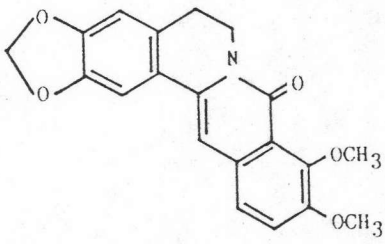
O-Methylprechilenine		*Berberis darwinii*
Oxotetrahydropalmatine		*Anamirta cocculus*
Oxyberberine (Berlambine)		*Berberis empetrifolia* *B. lambertii* *B. oblonga* *Thalictrum foliolosum* *T. longistylum* *T. minus* *T. podocarpum*

Table 3 (continue)

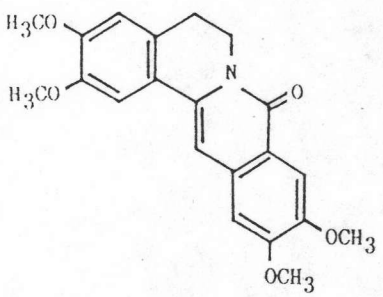
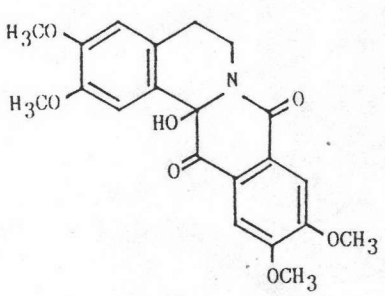
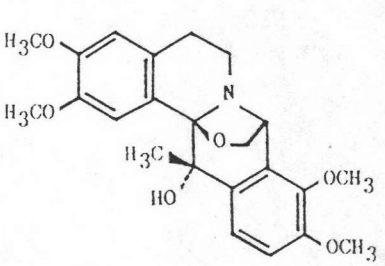
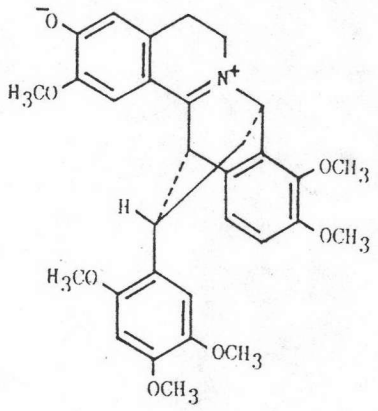
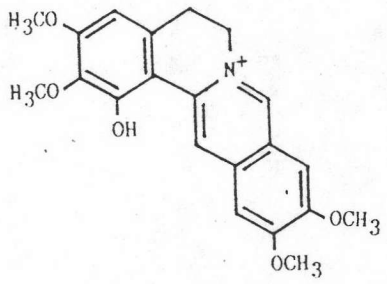
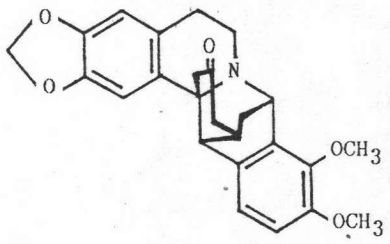
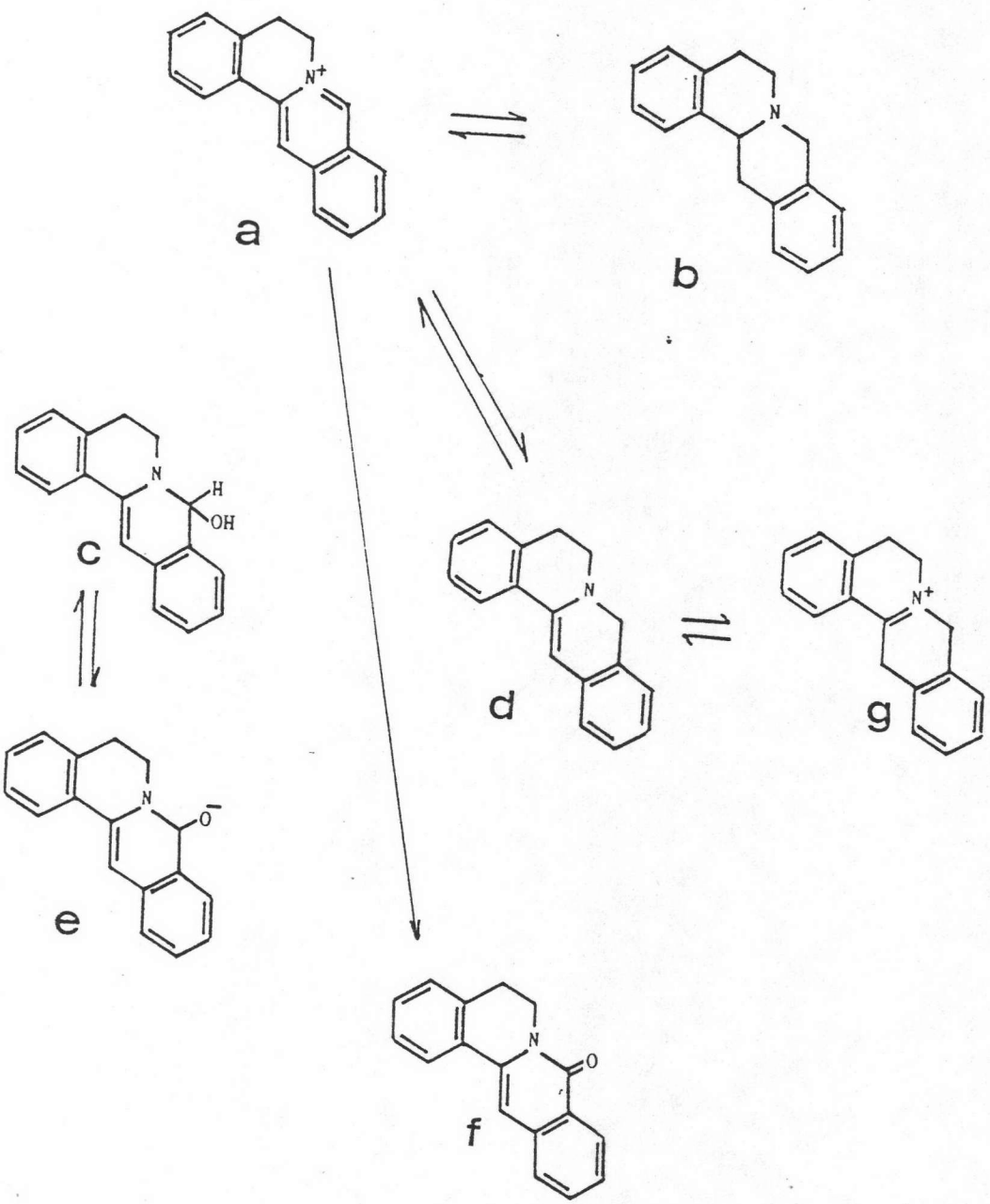
8-Oxypseudopalmatine		*Stephania suberosa*
Prepseudopalmanine		*Berberis darwinii*
Solidaline		*Corydalis solida*

Table 3 (continue)

Staudine		*Pachypodanthium staudtii*
Stephabine		*Stephania suberosa*
Valachine		*Berberis valdiviana*

2.3 Oxidation and reduction of protoberberine alkaloids

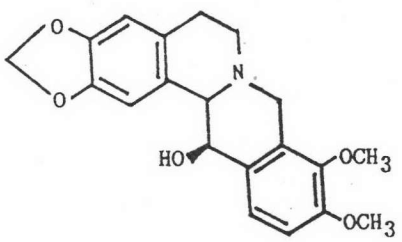
The dihydroprotoberberines (d) and tetrahydroprotoberberines (b) could be oxidized to the corresponding quaternary protoberberines(a) with iodine, mercuric acetate, or simply by standing in air (scheme 1). The quaternary protoberberines (a) could be reduced to the parent tetrahydroprotoberberines (b) with a variety of reducing agents such as mixed metal hydride, zinc/hydrochloric acid, and catalytic reduction in the presence of platinum. If,however, the reduction is carried out with a mixed hydride in a dry aprotic solvent, the reaction stops at the dihydroprotoberberine (d) stage. The quaternary protoberberine salts (a) are unstable in the presence of concentrated alkali. They form the oxo derivatives (f) and the dihydro derivatives (d) by hydrogen transfer. The oxo derivatives(f) are exclusively formed from the quaternary protoberberine salt (a) by oxidation with potassium ferricyanide. The dihydroprotoberberine derivative (d) remains in equilibrium with its immonium form (g) in a protic medium. The immonium form (g) is unstable and undergoes rapid disproportionation to a mixture of the quaternary protoberberine salt (a) and tetrahydroprotoberberine(b). (Bhakuni and Jain, 1989).



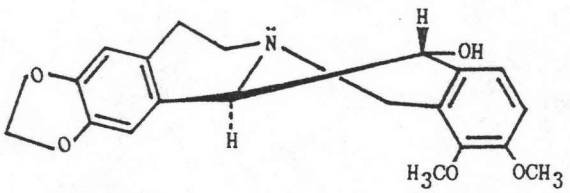
Scheme 1 Oxidation and reduction of protoberberines

2.4 Stereochemistry of protoberberine alkaloids

The stereochemistry of alkaloids such as ophiocarpine and 13-epi-ophiocarpine can be deduced from their IR spectra. Both compounds display Bohlmann bands at about 2800 cm^{-1}, indicating a *trans*-fused B/C ring juncture, but only ophiocarpine has a hydrogen-bonded hydroxyl group. This indicates internal proximity of the hydroxyl proton and the nitrogen lone pair; a situation possible only when the 13-hydroxy group is *beta* and axial as in ophiocarpine.



Ophiocarpine

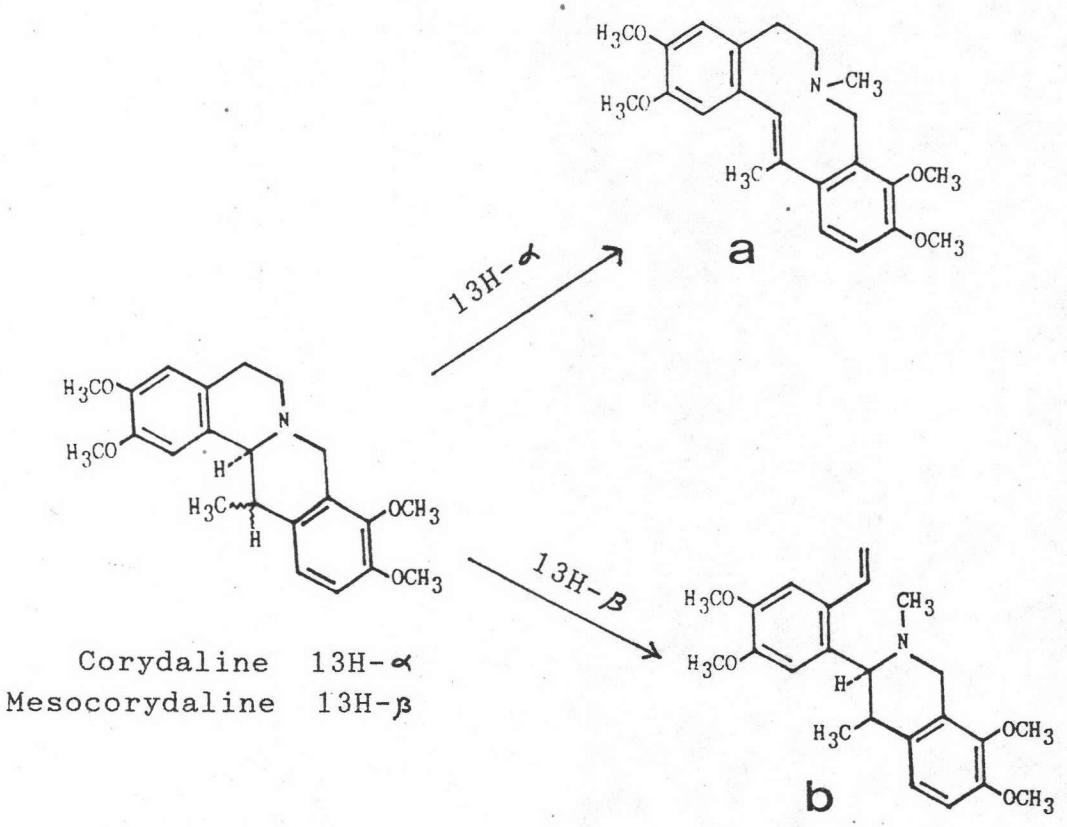


13-Epi-ophiocarpine

These very simple concepts do not hold however when substituents are at position 1, 8 or 13 (other than OH). In particular a compound may show Bohlman bands in a KBr pellet, but not in solution, indicating subtle conformational inversion, *trans* to *cis*, at the nitrogen between crystalline states and liquid. Such a phenomenon is particularly true of 1-substituted protoberberines.

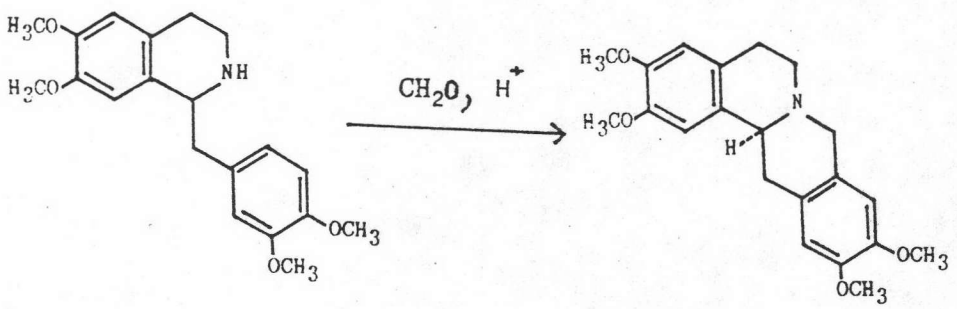
The most reliable way to determine the B/C-ring junction stereochemistry is through kinetic studies of the rates of methylation of the tertiary nitrogen with methyliodide. In general terms the *cis*- quinolizidine compounds react much faster than the corresponding *trans* isomerchanging the substition also changes the basicity of the nitrogen so that 10,11-substituted isomers show faster rates of N-methylation than 9,10-substituted isomers. When substitution is by a phenolic group, the rates of methylation are between those expected for *cis*- and *trans*-quinolizidines and consequently such data must be used with considerable caution.

An interesting demonstration of the differences in stereochemisty of two 13-methyl-substituted tetrahydroprotoberbeines is observed on Hofmann degradation to afford quite different products depending on the availabitity of the β-hydrogen *trans* to the nitrogen lone pair. Corydaline for example afforded (a), but mesocorydaline gave the vinyl derivative (b).



Corydaline 13H-α
Mesocorydaline 13H-β

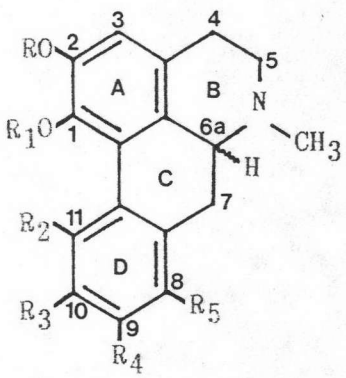
The absolute configuration of the protoberberines was deduced when (-)-N-norlaudanasoline of known absolute configuration afforded (-)norcoralydine. The levorotatory bases have the same absolute configuration as (-) norcoralydine and also exhibit a negative ORD curve in the region of 240 nm. (Cordell, 1981)



(-)N-Norlaudonosoline (-) Norcorylydine

2.5 Aporphine alkaloids

The aporphines are the largest group of isoquinoline alkaloids and are represented by the general structure below.



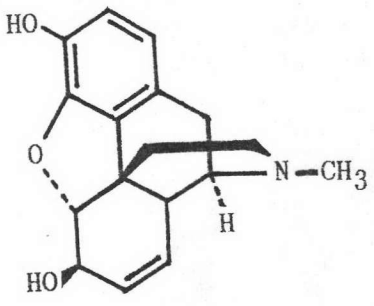
General structure of aporphine alkaloids

These alkaloids are distributed in at least 18 plant families, of which the most important are the Papaveraceae, Anonaceae, Lauraceae, and Monimiaceae. The nitrogen atom is usually methylated, making that nitrogen tertiary. If the nitrogen is secondary, the alkaloid is called a noraporphine, they are not very stable and are often characterized as their N-acetyl derivatives. Several quaternary aporphine salts with two methyl groups attached to the nitrogen are also known. Aporphines are known with the C-6a stereochemistry either or .

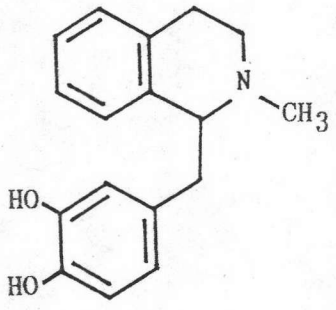
The most diverse structural feature of the aporphines is the oxygenation pattern. Positions 1 and 2 are always oxygenated, either by hydroxy, methoxy or methylene dioxy

groups. It is common to find further oxygen substituents at C-9, C-10 and C-11, and occasionally at C-8. It is rare to find oxygenation at C-7, except in the oxoaporphines, and even rarer to find any oxygenation in ring B.(Cordell, 1981)

The first aporphine alkaloid was obtained not by isolation but as the result of chemical reaction. Thus in 1969 it was found that hot concentrated hydrochloric acid caused rearrangement of morphine (M) to apomorphine (Ma) which is not a natural product. (Cordell, 1981)



Morphine(M)

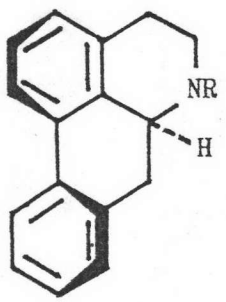


Apomorphine(Ma)

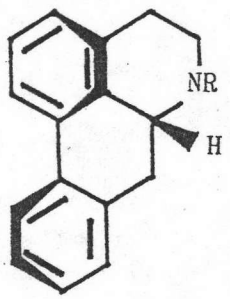
Since that time, nearly 200 natural aporphine alkaloids have been recognized. All of these incorporate in tetracyclic nucleus present in apomorphine. Additionally, they are without exception oxygenated at C-1 and C-2, and very often at other positions as well. The oxygenated substituents are usually hydroxy, methoxy or methylenedioxy groups. (Shamma and Guinaudeau, 1984)

2.6 Stereochemistry and absolute configuration of the apophines

The stereochemistry and absolute configuration of the aporphines have been thoroughly studied. Shamma in 1960 was first to make an interesting observation concerning the lack of planarity of the biphenyl system, and indeed two stereochemical possibilities exist as shown below: (Cordell, 1981)

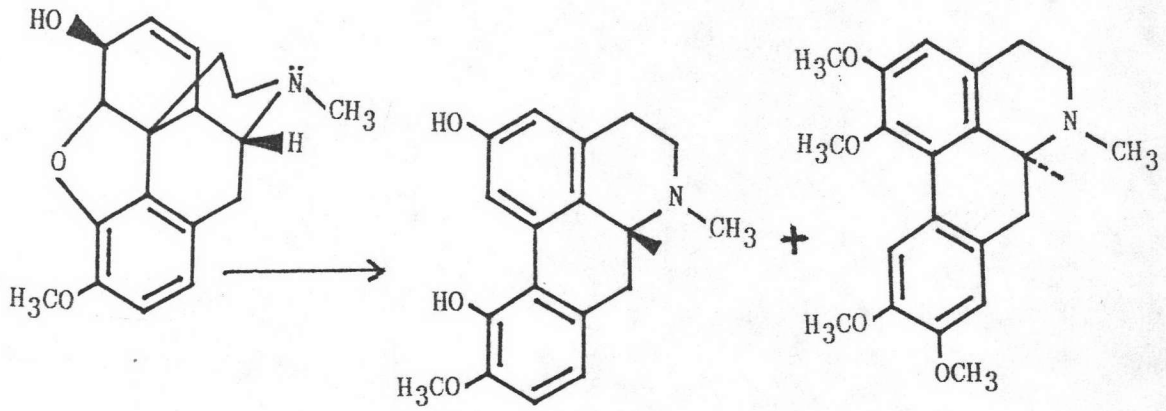


L-S configuration



D-R configuration

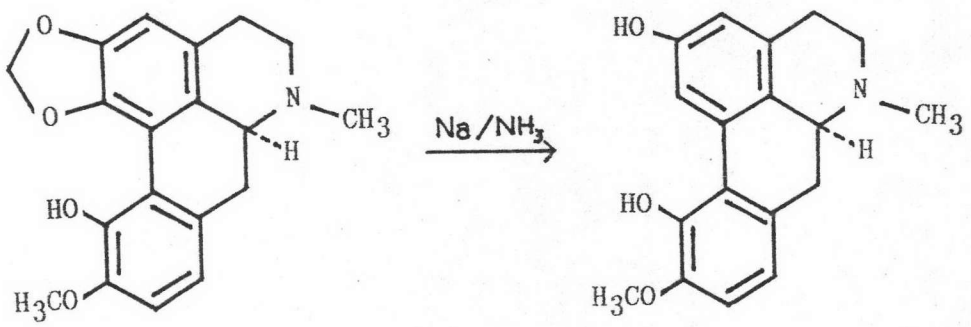
Bentley and Cardwell first observed that since naturally occurring (+) -glaucine, and (-) -morphothebaine, a rearrangement product from codeine are enantiomeric at C-6a and the absolute configuration of (-) -morphothebaine is known to be of the D series, (+) glaucine must belong to the L configuration. They also generalized that all aporphines that are appreciably dextrorotatory at the sodium D line belong to the L series, whereas the levorotatory aporphines are of the D configuration. (Shamma, 1972)



Codeine (-) Morphothebaine (+) Glaucine

(Related to codeine as shown)

The absolute configuration of natural (+)bulbocapnine is also known with certainty and first the above rotation rule since Ayer and Taylor have converted the alkaloid by treatment with sodium in liquid ammonia into (+)morphothebaine of known absolute configuration.(scheme 2) Additionally, a three dimensional x-ray analysis of bulbocapnine methiodide has been carried out. The angle of twist of the biphenyl system is 29.9 . The distance between O-1 and O-11 is 2.74 °A which is just under the sum of the van der Waals radii of the two oxygens, which is 2.80 °A this data is example that the biphenyl system in bulbocapnine methiodide is appreciably strained. (Shamma, 1972).



(+) -Bulbocapine (+) -Morphothebaine

Scheme 2 Absolute configuration of bulbocapnine

The ORD curves of aporphines have been studied. Craig and Roy have noted that aporphines exhibit a cotton effect of high amplitude centered between 235 and 245μm . This curve is independent of the substitution at the 1, 2,3, 9, 10 and 11 positions and is diagnostic of the absolute configuration; if the cotton effect is positive, the alkaloid belongs to the L series, and if the cotton effect is negative, the compound must be of the D series.

Simple specific rotations at the sodium D line, besides being fairly reliable indicators of the absolute configuration, offer a simple way of differentiating between C-1, 2, 9, 10- and C1, 2, 10, 11 -subsituted aporphines. The 1, 2, 9, 10- series exhibits rotations of +119 or less, whereas the 1, 2, 10, 11 -substituted aporphines show values of +139 or more. The occurrence of racemic aporphines in nature is rare. (Shamma 1972)

2.7 Alkaloids isolated from Coscinieae tribe

Over the past 160 years ago alkaloids have these plants recieved considerable attention. The major alkaloids, which have been isolated are protoberberine type, and the main alkaloid is berberine. The more recent work has not resulted in any unexpected novel structure of alkaloids but rather in the isolation of new isomers together with observation of alkaloidal pattern variation. The alkaloids which have been reported in these 5 species of Coscinieae are shown as follows:-

2.7.1 Alkaloids from *Anamirta cocculus* (L.) Wight et Arn.

Anamirta cocculus (L.) Wight et Arn. is a liana which occurs in southeast Asia. Berries of this plant are used as a fish poison. From the berries the sesquiterpene mixture picrotoxin is commercially isolated. The berries have been official in a number of pharmacopaeias The seed shells of this plant were reported to contain alkaloids in 1834 by Pelletier and Couerbe, the two alkaloids isolated, were menispermine ($C_{18}H_{24}O_2N$) and paramenispermine ($C_{18}H_{24}C_2N$). No other reports on alkaloids in *Anamirta cocculus* (L.) Wight et Arn. have been published since the work of Pelletier and Couerbe. Until, in 1980, the studies on Indonesia medicinal plants was reported

(Siwon, Verpoorte, Tieken and Svenden, 1980). In the stems and roots of *Anamirta cocculus* (L.) Wight et Arn., the quaternary protoberberine alkaloids berberine, palmatine, columbamine and L-8-oxotetrahydropalmatine were isolated. There is one of isoquinoline alkaliod was isolated too, magnoflorine.

The occurrence of protoberberine-type alkaliods in *Anamirta cocculus* (L.) Wight et Arn. is not surprising. The genus *Anamirta* belongs to the tribe *Coscinieae* of the Menispermaceae. The other two genera in this tribe. *Arcangelisia* and *Coscinium*, also contain protoberberine alkaloids. Particulary *Arcangelisia* is botanically closely related to *Anamirta*, and *Arcangelisia flava* (L.) Merr. and *Anamirta cocculus* (L.) wight et Arn. have sometimes been confused.

2.7.2 Alkaloids from *Arcangelisia* species

The genus *Arcangelisia* belongs, together with the genera *Coscinium* and *Arcangelisia*, to the tribe Coscinieae of the Menispermaceae. The genus *Arcangelisia* comprises of two species, *A. flava* (L.) Merr. is a liana found in Southeast Asia, *A. tympanopoda*(Lauberb & K. Schum.) Diels. is a liana found so far only in New-Guinea. The two species are differentiated by the size of the fruits, the latter one having larger fruits than the former.

Various medicinal uses of *A. flava* (L.) Merr. have been reported as a febrifuge, tonic, abortive, expectorant and against hepatitis and digestion. Since 1931, Santos repoted the presence of berberine in the stems of *A. flava* (L.) Merr. Santos identified berberine,jatrorrhizine and columbamine and isolated an alkaloid which was called "shobakunine". Thes was later shown to be a mixture of palmatine and berberine.

Following this quite an amount of work was carried out on *A. flava* (L.) Merr. from Philippines by van Steenis Kondo, Estrada *et al*. They reported only berberine, jatrorrhizine and columbamine. In 1988 Garcia *et al* detected berberine, palmatine and jatrorrhizine in the stems and berberine and jatrorrhizine in the roots of *A. laureirii* Diels. (a synomym for *A. flava*) (Garcia, 1881). At that time the studies of Indonesian medicinal plants Vll by Verpoorte, *et al*, isolated and identified six quaternary alkaloids, thalifendine, dehydrocorydalmine,jatrorrhizine, pycnarrhine, berberine and palmatine, and three tertiary alkaloids, hydroxy-berberine, limacine and homoaromoline form stems and roots of *Arcangelisia flava* (L.) Merr. (Siwon *et al*, 1982). For *Arcangelisia tympanopoda* (Lauberb & K. Schum.) Diels, however, it is notable that there has no phytochemical report about it.

2.7.3 The alkaloids of *Coscinium* species

The genus *Coscinium* consists of two species only the widely distributed *C.fenestratum* (Gaetn.) Colebr. (*C. wallichianum* Miers or *C. usitratum* Pierre) and *C. blumeanum* Miers, known only from Peninsular Thailand and the islands off the west coast of Malaya.

Berberine, palmatine and jatrorrhizine have been isolated from roots and stems of *C. wallichianum* (*C. fenestratum*) by Garcia *et al* in 1969 (Garcia, *et al*, 1970). In 1981 Siwon and Verpoorte have collected *Coscinium fenestratum* (Gaertn.) Colebr. on south Kalimantan, Indonesia and major alkaloids berberine and jatrorrhizine have been isolated. Apperciable amounts of berberubine and N,N-dimethyllindcarpine and small amounts of thalifendine and palmatine are also present. Stems and roots contain the same pattern of alkaloids.

For *C. fenestratum* (Gaertn.) Colebr. which collected from India in 1988, apart from berberine, oxyberberine, tetrahydroberberine (canadine), a new minor alkaloid 12,13-dihydro-8-oxo-berberine have been furnished by Malhotra, Taneja and Dhar. (Malhotra *et al*, 1989).

Tomita and Tani isolated palmatine, berberine and jatrorrhizine from *Coscinium blumeanum* Miers collected in Sararvak (North Kalimantan, Malaysia) in 1940.

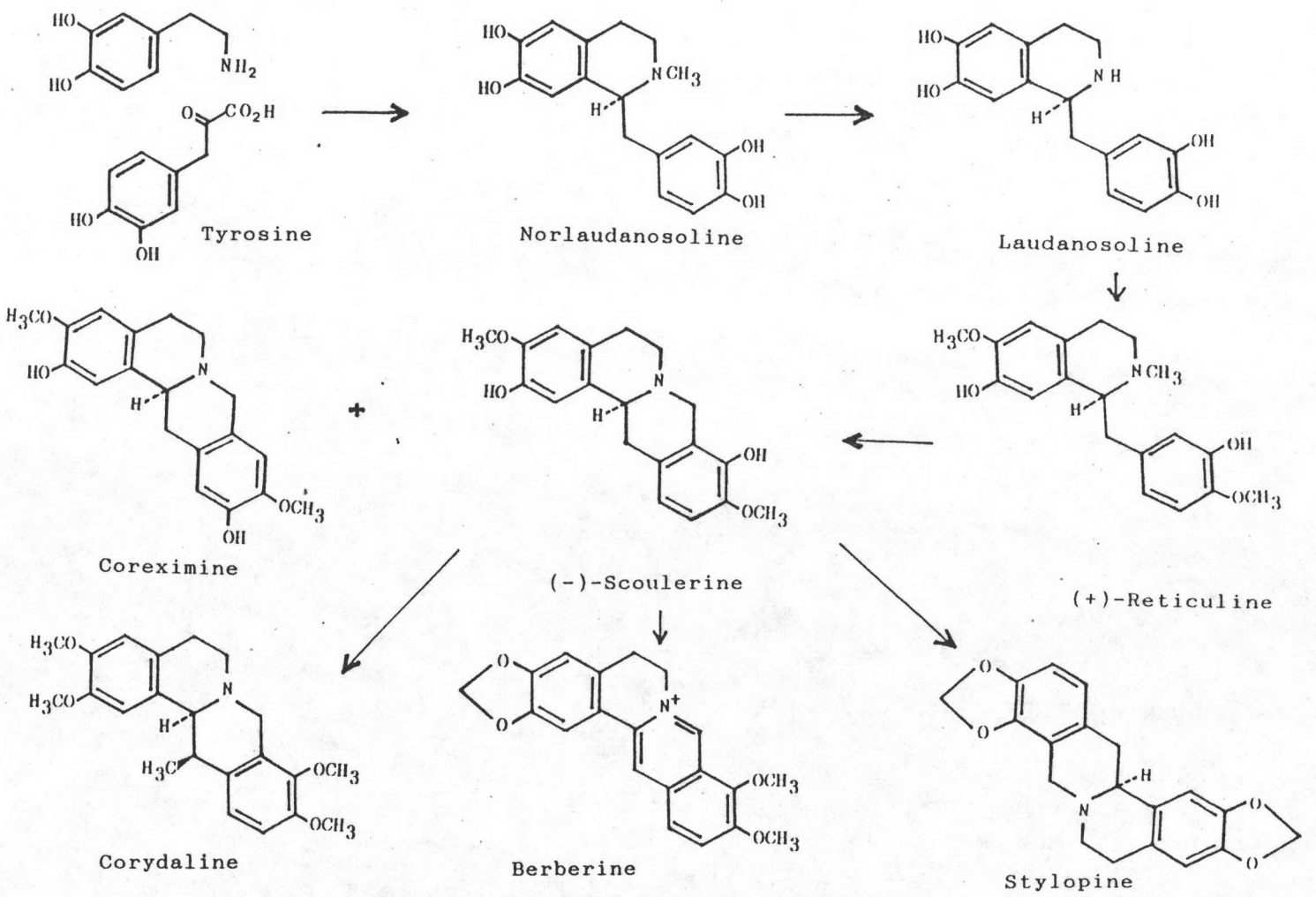
The presence of protoberberine alkaloids in roots and stems of Coscinieae tribe is consistent with their uses in curing microbial infection in folk medicine.

3. Biosynthesis

3.1 Biogenesis of protoberberine alkaloids

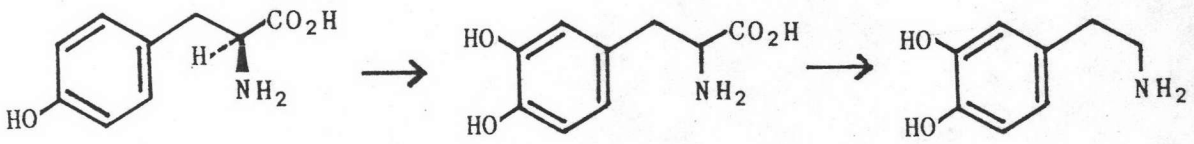
There are two terms, biosynthesis and biogenesis, commonly used in discussing the formation of secondary metabolism products. Biosynthesis is the experimental study of the formation of secondary metabolites. Whereas biogenesis is the hypothetical speculation on the precursor-product relationships in a biosynthetic pathway. By means of this definition biogenesis refers to the manner in which the organic substances are synthesized, altered, or degraded by plant or animal organisms. It is based mainly on the visual dissection of a molecule into recognizable precursor fragments. (Cordell, 1981)

The biogenesis of protoberberine alkaloids was discussed earlier. The relationship of 1-benzyltetrahydro-isoquinolines and protoberberines was recognized quite early. As a result of numerous studies, the biosynthesis of the berberine alkaloids has been well worked out and the currently accepted scheme is shown in scheme 3.

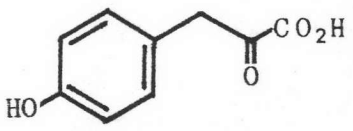


Scheme 3 Biosynthesis of the protoberberine alkaloids

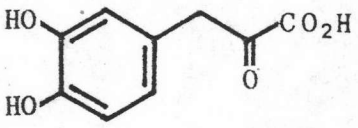
The fundamental units are those for the formation of the benzylisoquinoline alkaloids with the addition of a single carbon atom which becomes C-8 of the skeleton. Thus two molecules of tyrosine are involved, one proceeding to dopamine via dopa, and the second to 3,4-dihydroxyphenyl pyruric acid.



Tyrosine Dopa Dopamine

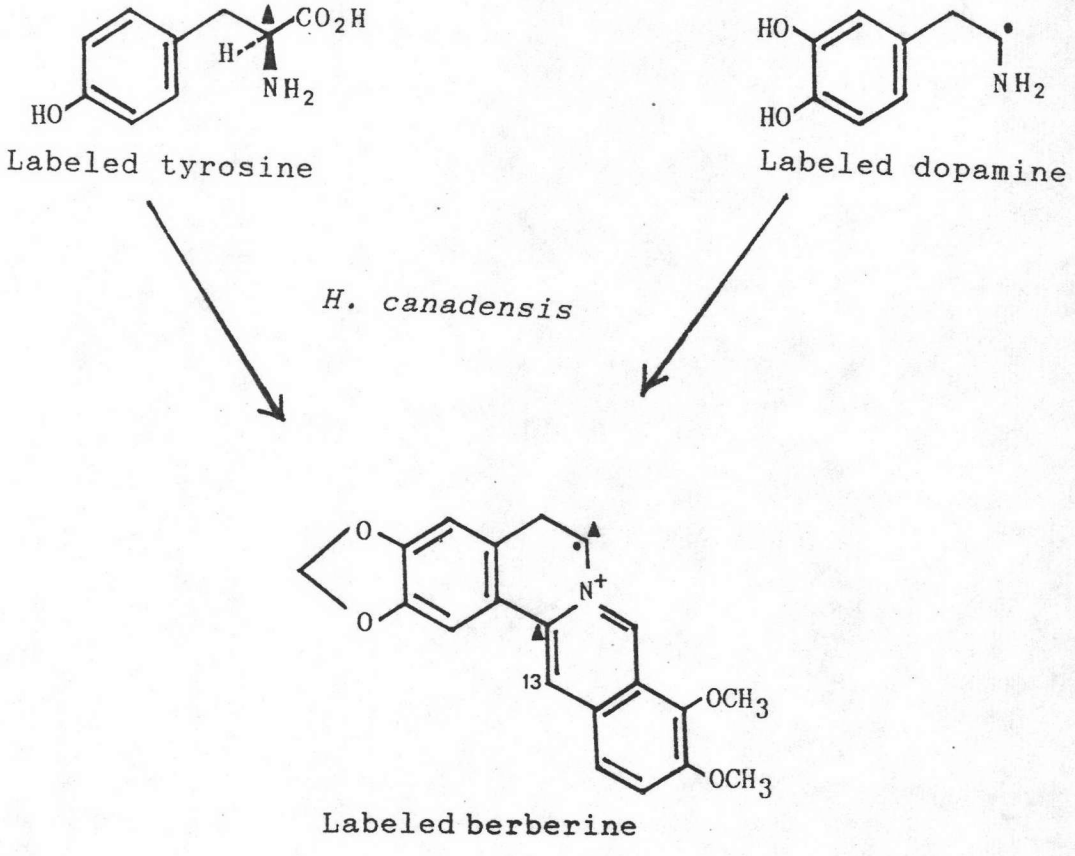


4-Hydroxy phenyl
pyruvic acid



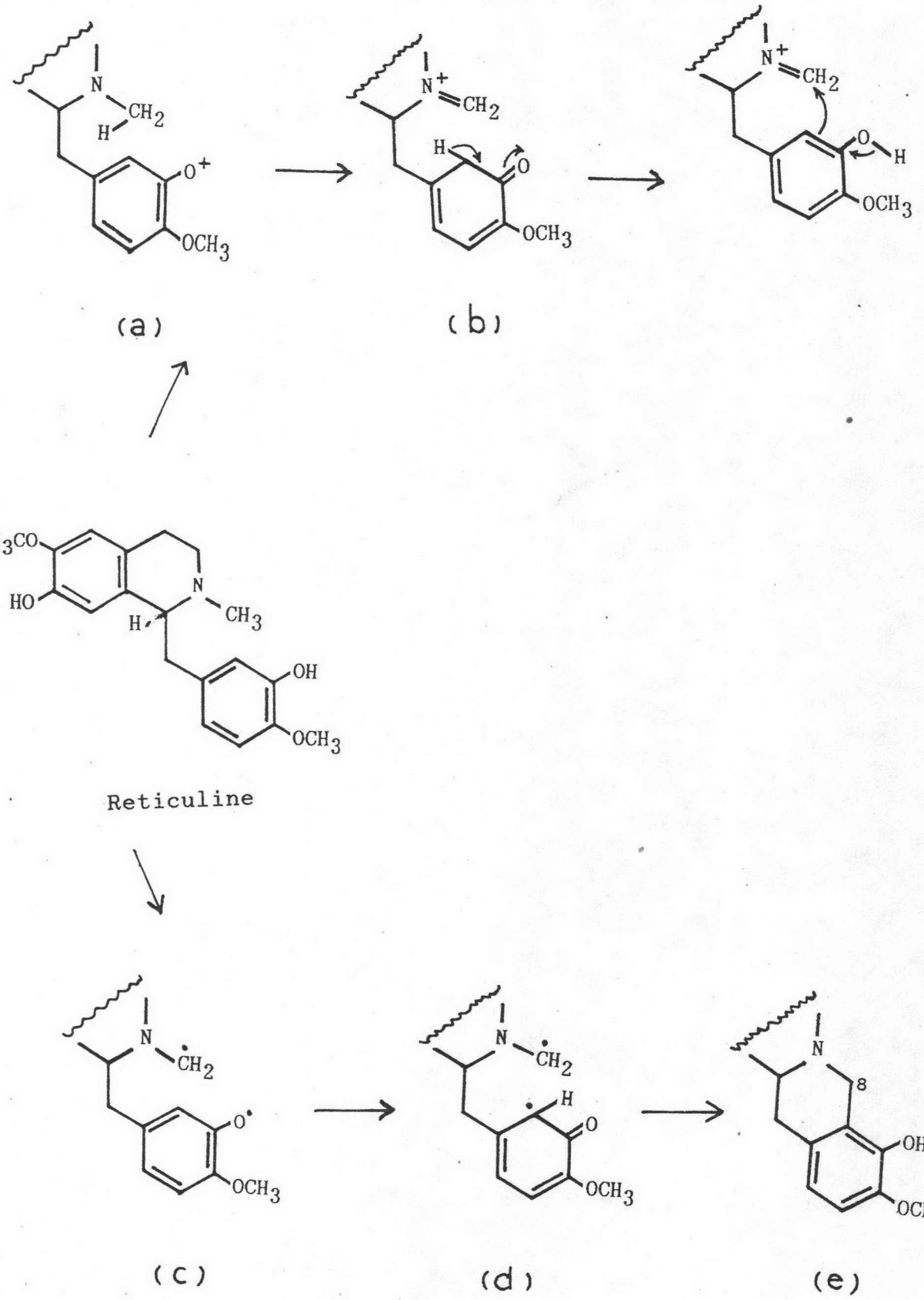
3,4-Dihydroxy
phenyl pyruvic acid

Thus [2-^{14}c] tyrosine labels at C-6 and C-13 of berberine in *Hydrastis canadensis L.* (Ranunculaceae), but [1-^{14}C] dopamine labels only at C-6. Shown below :



However, later observation in several tracer experiments, reticuline was shown to be a biological precursor of protoberberine alkaloids. The early stages of biosynthesis of these alkaloids from reticuline was studied.

The C-8 atom of protoberberine and derivative alkaloids is known as the "Berberine bridge". It has been suggested that the bridge could be formed in nature by oxidative modification of an N-methyl group. Plausible machanisms of the reaction are shown in scheme 4.

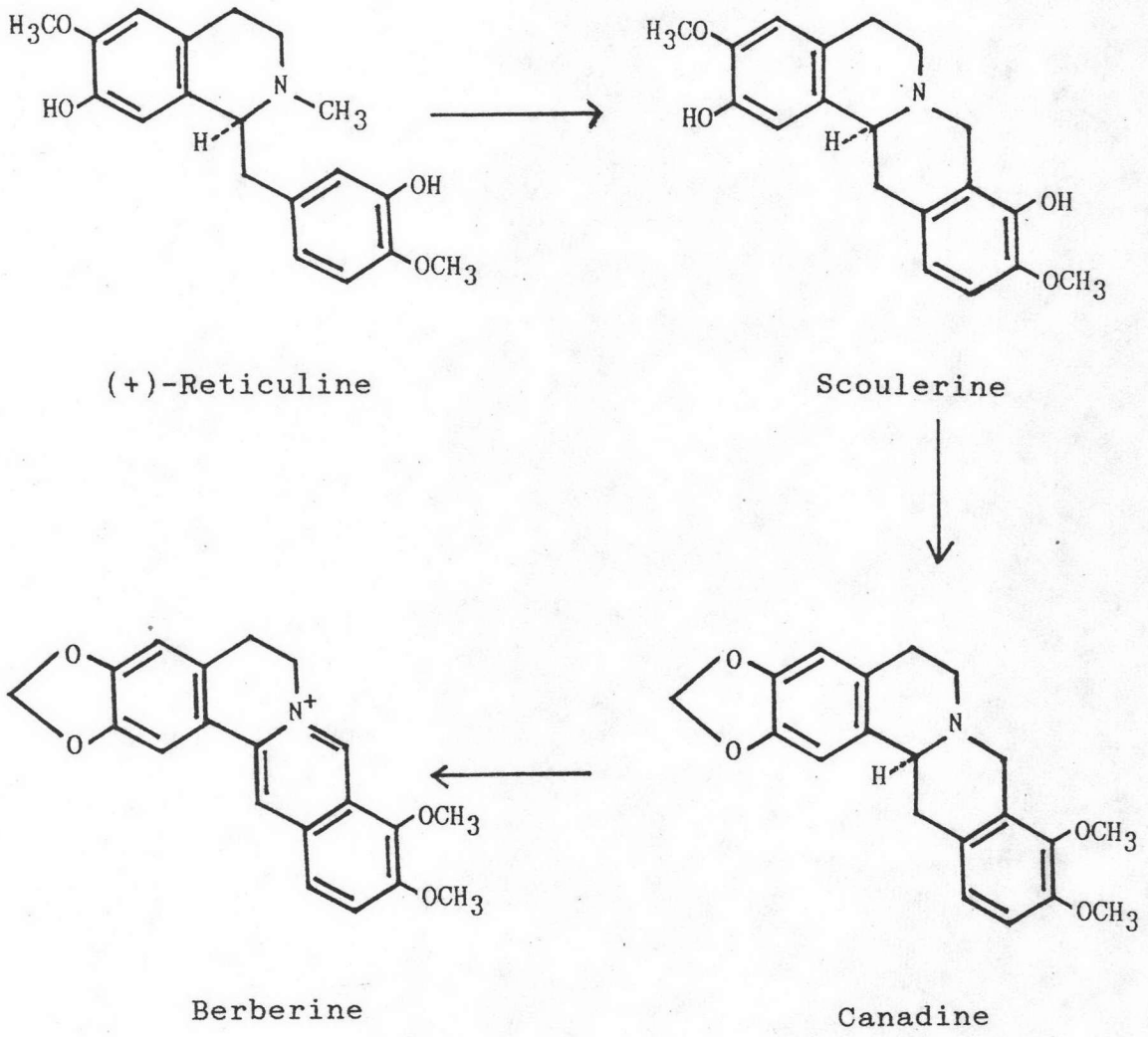


Scheme 4 Mechanism of berberine bridge formation

Two electron oxidation of a suitable precursor such as reticuline could give the phenoxonium ion (a) from which (b) could be derived by intramolecular hydrogen transfer.In an alternative mechanism, one electron oxidation of reticuline could furnish a phenolate radical. A hydrogen atom could then be transferred from the N-methyl group to oxygen, which could be oxidized to the biradical (d). Coupling of radicals could then lead to ring closure to give (e) as in normal c-c bond formation in phenolate oxidaton reactions. Experimental support in favor of the hypothesis was put forward by Barton, Battersby and co-workers directly and by Gupta and Spenser indirectly. Barton *et al* fed reticuline labeled with (^{14}c) in its N-methyl group to *Hydrastis canadensis*. Biosynthetically synthesized berberine was degraded unambiguously and essentially all of the radioactivity was found at C-8 of the alkaloid. Battersby's group by using laudanosoline labeled with [^{14}C] in the methyl group had confirmed the above results. Gupta and Spenser had provided evidence from experiments with methionine -^{14}C.

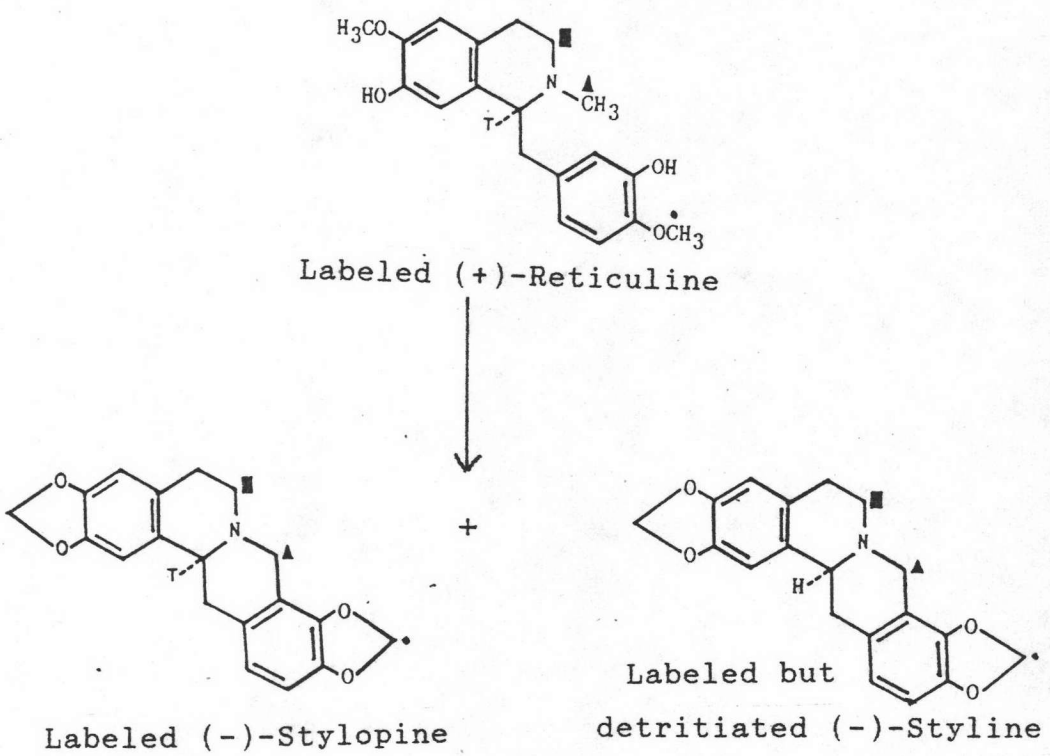
Barton and co-workers have studied biosynthesis of berberine in detail. Feeding doubly labeled reticuline, they confirmed that C-8 of berberine was derived from the N-methyl group of the precursos. Further, it was demonstrated that the methylenedioxy group in berberine was also formed as in other cases by oxidative cyclization of a catechol -*O*- methyl ether. Parallel feeding of both the labeled enantiomers of reticuline showed that (+)

reticuline was converted to berberine 15 times more efficiency than (-) reticuline in *H. canadensis* plants (scheme 5) (-)canadine occurs in *H. canadensis*. Efficient incorporation (8.9%) of (+) canadine into berberine by the plants established its intermediacy, protosinomenine, however, was not incorporated into berberine in the plants. (Bhakuni and Jain, 1989)

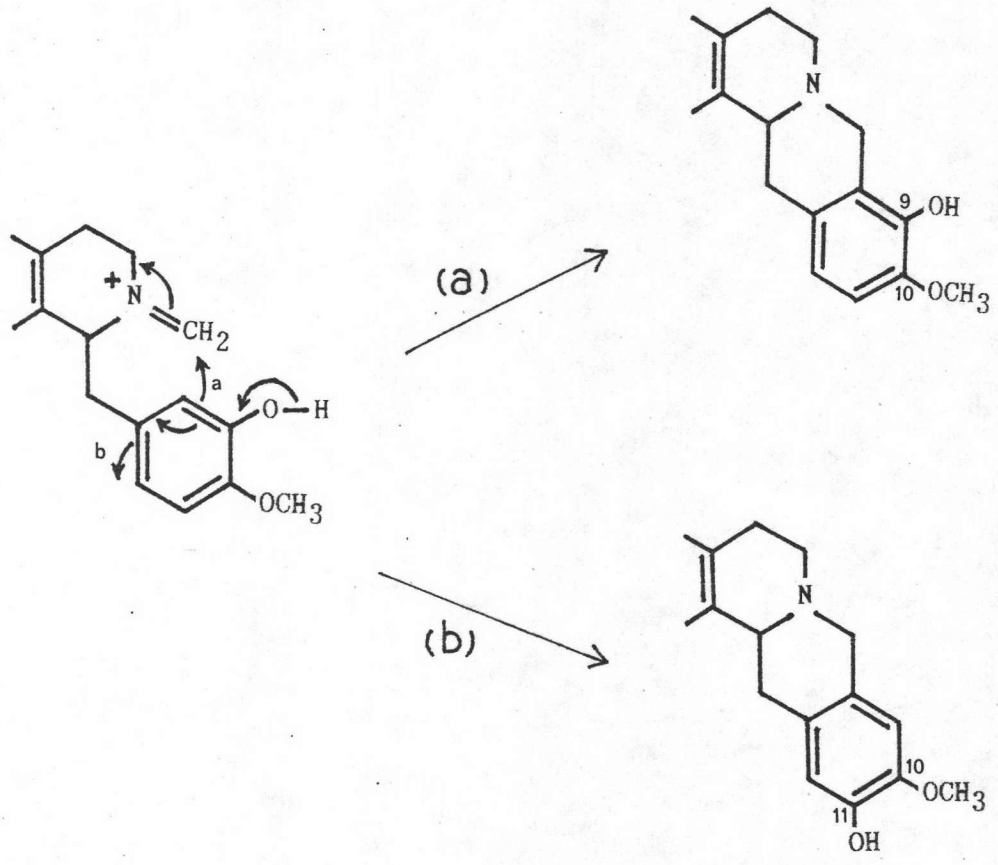


Scheme 5 Biosynthesis of berberine

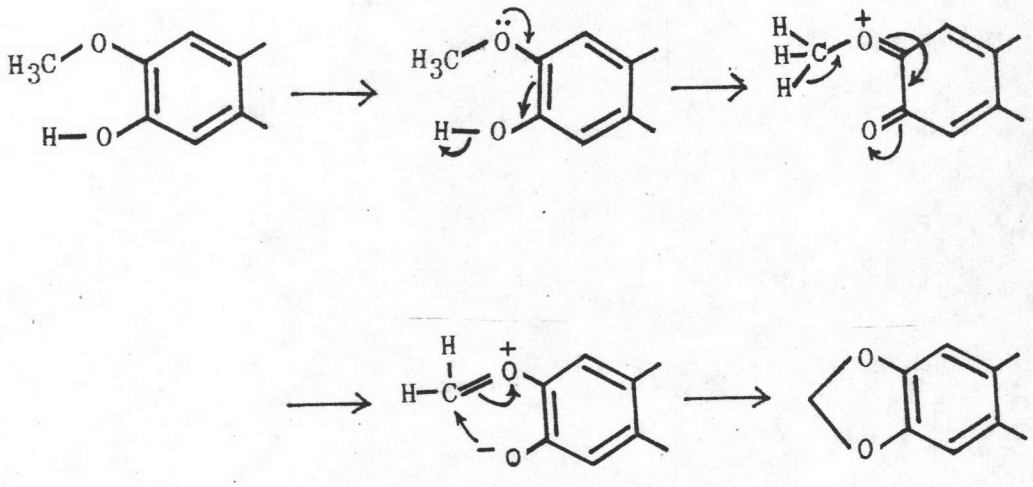
Feeding label (+) laudanosoline to *berberis japonica* Lindl. (Berberidaceae) also gave rise to labeled berberine. Labeled (+) reticuline significantly incorporated into (-) stylopine in *Chelidonium majus* L. (Papaveraceae), while incorporation of (-) reticuline is a much less efficient process. Some of the tritium label at C-14 in (-) stylopine was lost, indicating C-1 oxidation-reduction at the (+) reticuline stage, shown below:



The oxidation of the N-methyl group and subseguent ring closure is thought to proceed *via* the iminium species to give either the 9,10 - (pathway a) or 10,11-disubstituted (pathway b) series of compounds. (Cordell, 1981)



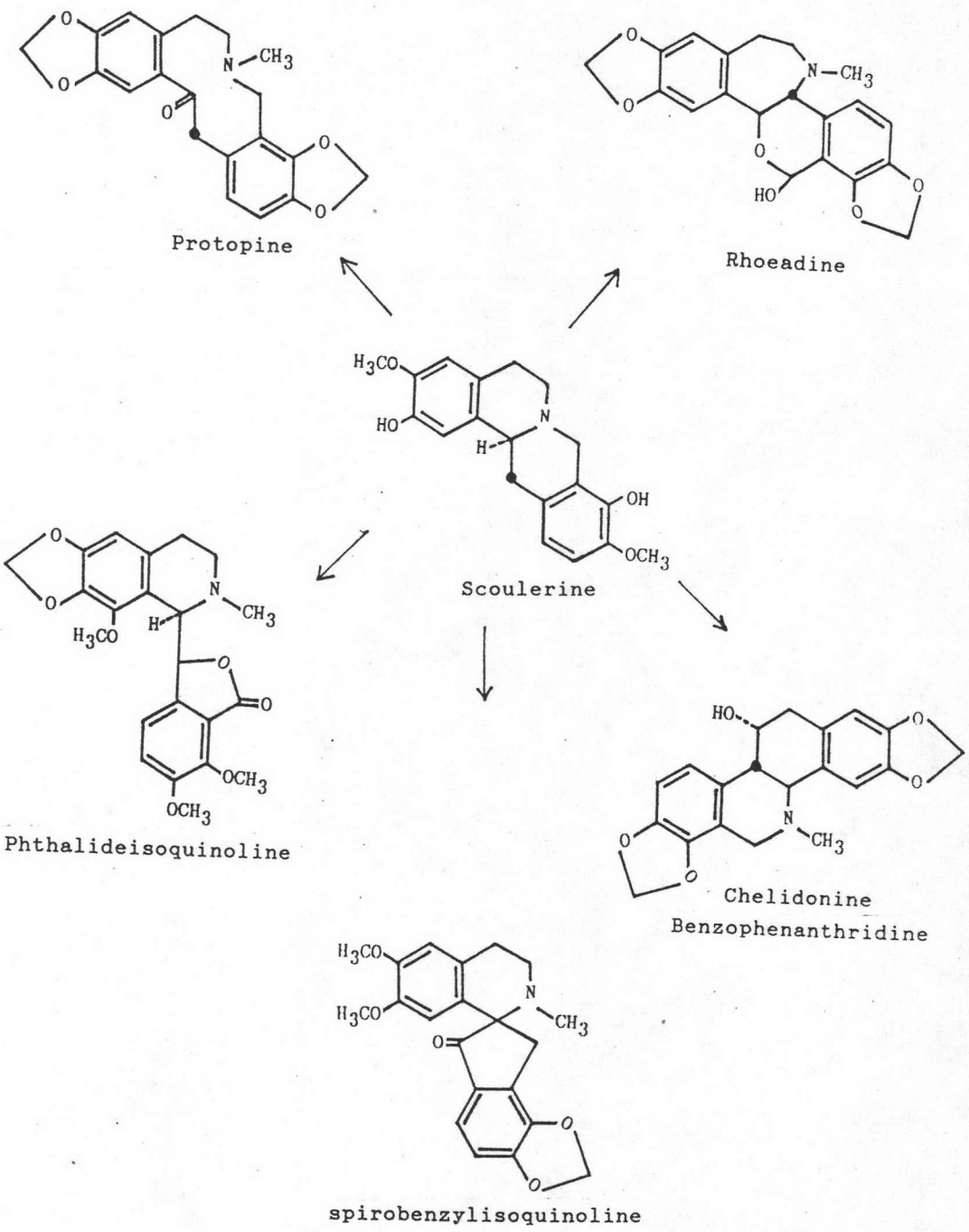
The formation of the methylenedioxy group from an o-methoxyphenol can be visualized either in terms of an ionic or a free-radical machanism, and the former is depicted here. scheme 6.



Scheme 6 The formation of methylenedioxy

Turning to the 5-hydroxylated protoberberine alkaloids, berberastine, thalidastine and tetrahydro-berberastine, it has been shown that dopamine and noradrenaline are incorporated into berberastine much more efficiently than into canadine or berberine. The last two alkaloids, therefore, cannot be precursors for berberastine. Rather, the C-5 hydroxyl must be introduced at some early stage which preceeds the formation of the necessary tetrahydrobenzylisoquinoline intermediate.(Shamma, 1972).

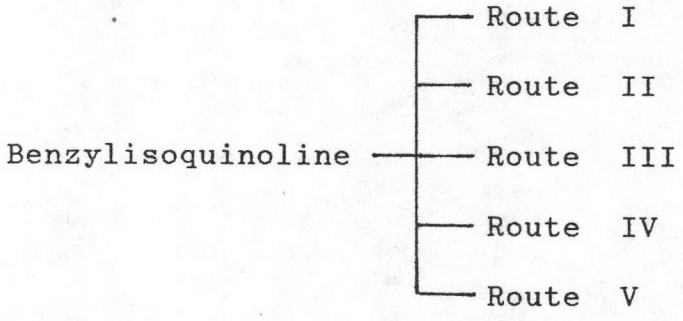
The protoberberines are not only interesting in themselves from a biosynthetic point of view, but are important because they act as precursors to other skeleta. In particular, these alkaloids (e.g. scoulerine) are the precursors of the protopine, rhoeadine, benzophenanthridine (e.g.chelidonine), and phthalideisoquinoline (e.g.narcotine) In addition they are thought to be the precursors of the spirobenzylisoquinoline alkaloids (e.g. ochotensamine) (Cordell, 1981) shown in scheme 7.



Scheme 7 Further elaboration of the protoberberine

3.2 Biosynthesis of aporphine alkaloids

The discussion on the biogenetic synthesis of the aporphine alkaloids has raised a number of points concerning the biosynthesis of this group. In particular and depending on the orientation of phenolic and methoxy groups might envisage any of at least five routes being in operation from a benzylisoquinoline precursor (Figure 1). *In vitro* all these routes appearently can operate.



Route I ⟶ proaporphine ⟶ aporphine

Route II ⟶ neoproaporphine ⟶ aporphine

Route III - morphinandienone ⟶ neoproaporphine aporphine

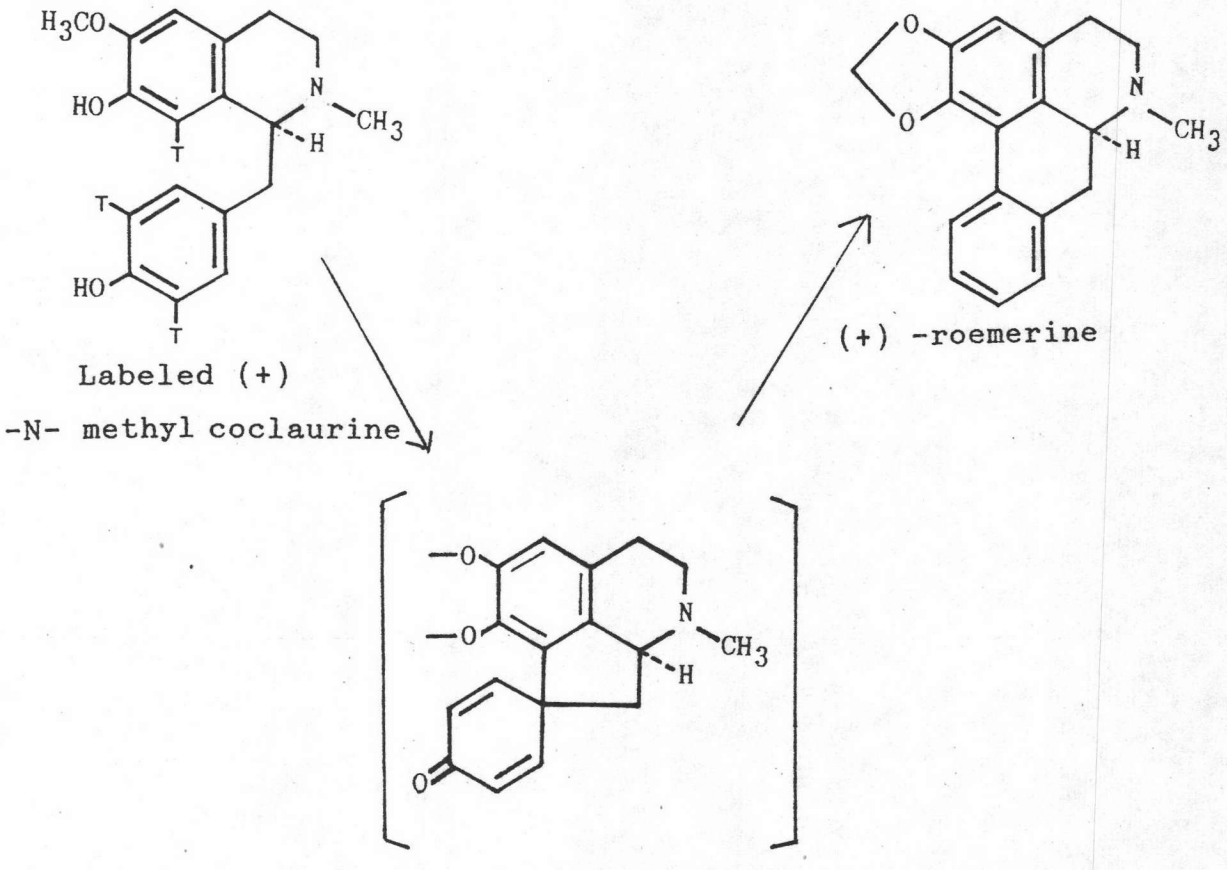
Route IV — directly coupled 3a-substituted quinol ⟶ aporphine

Route V — direct coupling of radicals ⟶ aporphine

Figure 1 Biogenesis of aporphine from benzylisoquinoline

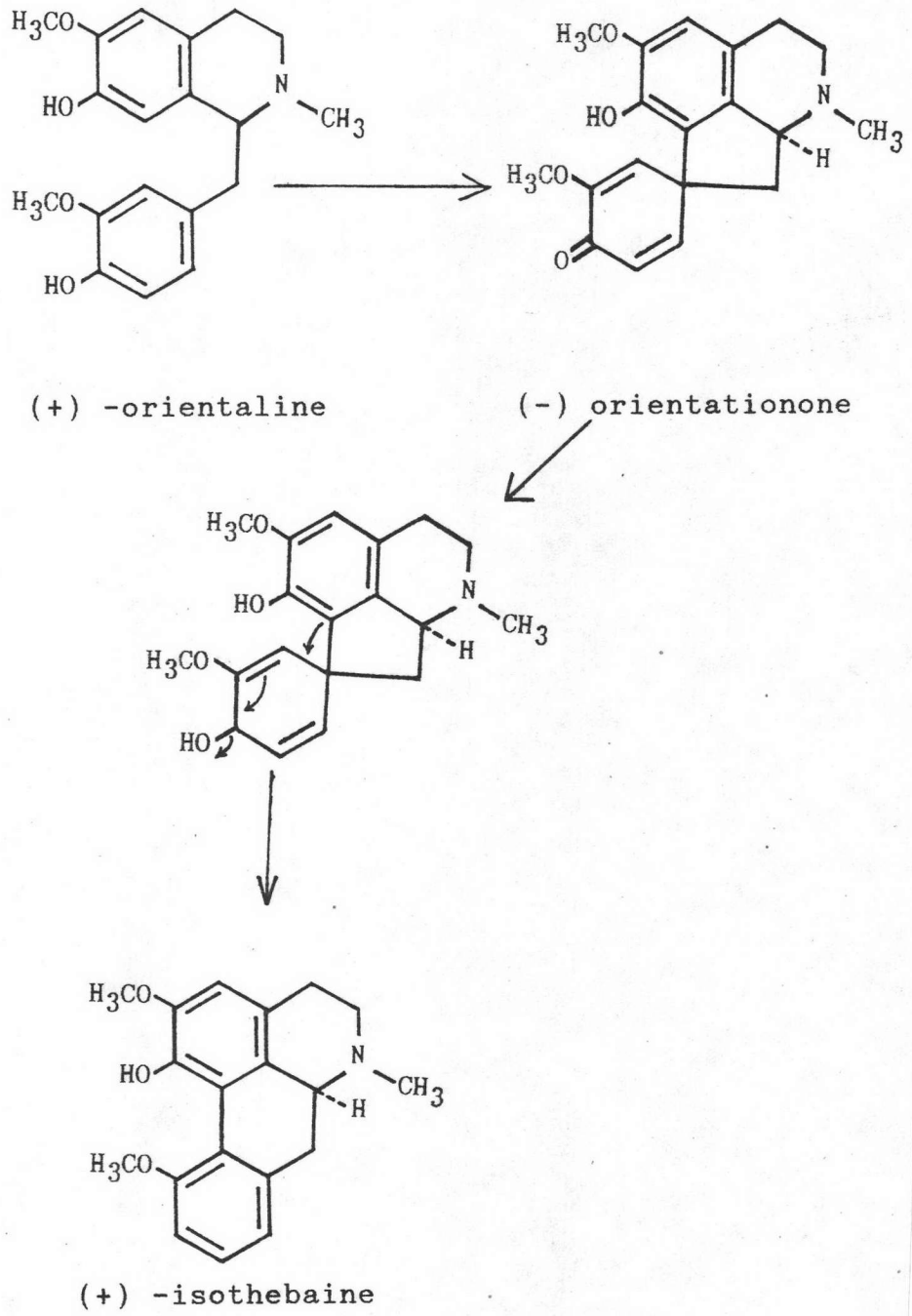
The structure of the aporphine alkaloids (+) - roemerine and (+) -isothebaine indicated that they are probably not derived from a tetrahydrobenzylisoquinoline by direct coupling.

Barton and co-workers investigated the formation of (+)-roemerine in *Papaver dubium* L. and found that tritium labeled (+) -N- methylcoclaurine was well incorporated. The position of the hydroxy group in the precursor suggests that a proaporphine intermediate is involved (scheme 8) similarly.



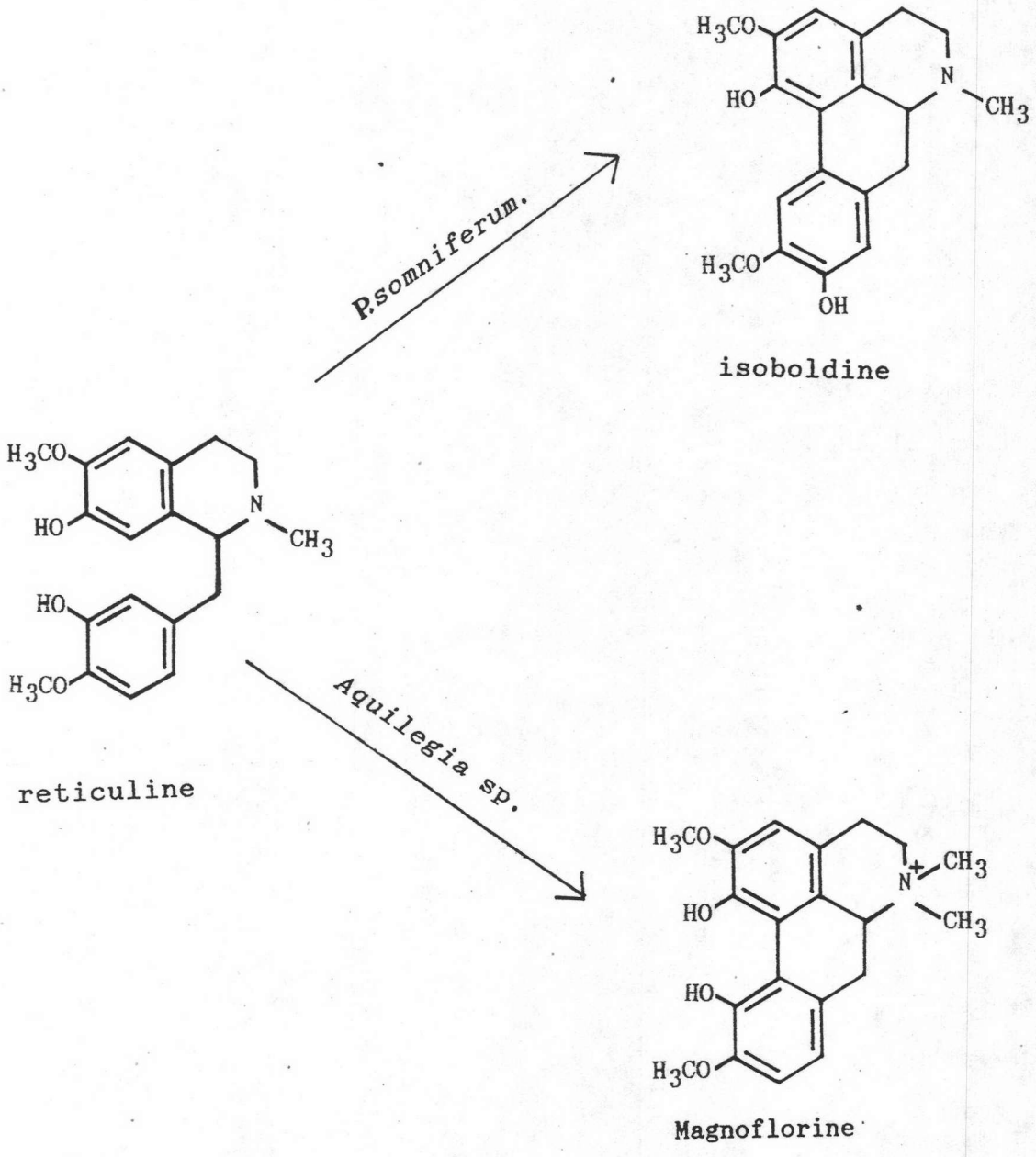
Scheme 8 Proaporphine intermediate is involved

Battersby and co-workers showed that (+)-orientaline was well incorporated into (+) - isothebaine in *Papaver orientalis*. The formation of (+)isothebaine can be envisaged as occurring through (-)-orientalinone , a co-constituent, as shown in scheme 9.



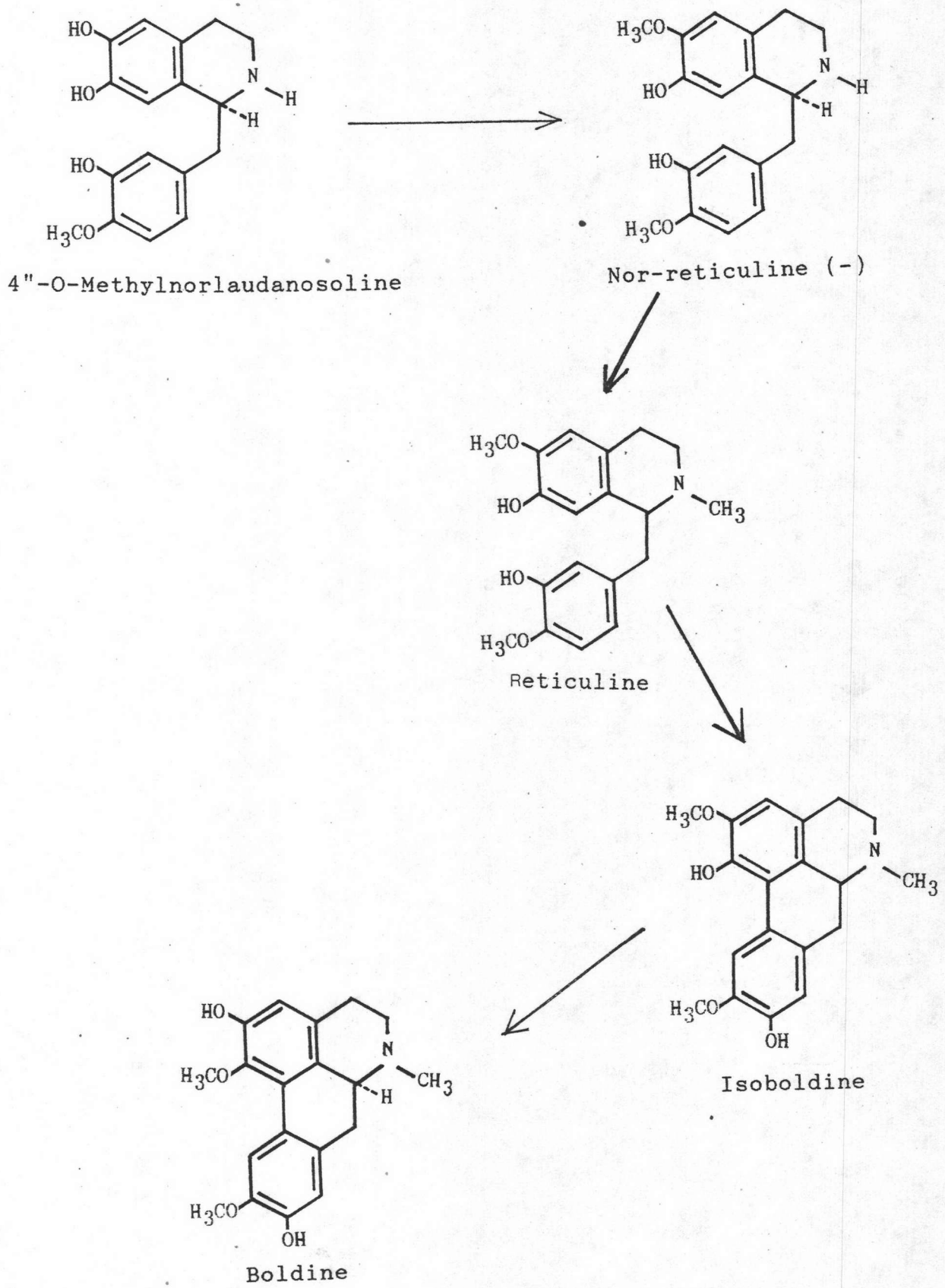
Scheme 9 The incorporated from orientaline to isothebaine

Brachmam & Haussen found that [N-methyl-^{14}C] reticuline was a precursor of isoboldine , but not of magnoflarine in *Papaver somniferum*. Classically, these would be regarded as the products of ortho-para and ortho-ortho coupling of reticuline. Subsequently the same group showed that [N-methyl-^{14}C] reticuline was a precursor of magnoflorine in *Aquilegia* sp. shown below.



The biosynthesis of boldine in *Litsea glutinosa* (Lour.) C.B.Rob.var. *glabraria* Hook. (Lauraceae) has also been studied in detail by Kapil and co-workers, with a quite different result.

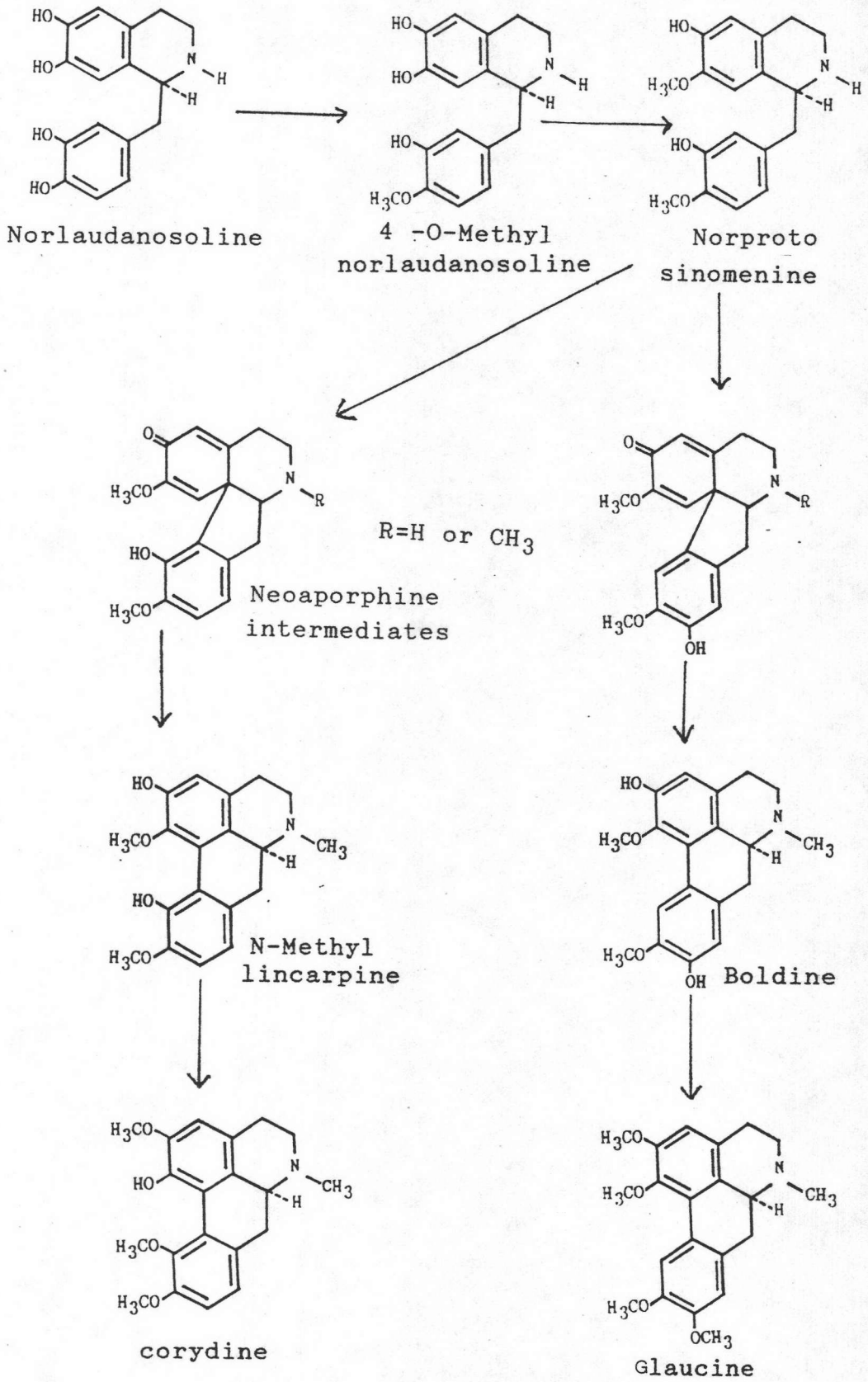
Of several variously methylated benzylisoquinoline precursors only 4 -*O*-methylnorlaudanosaline, nor-reticuline, and reticuline were precursors. In the latter case the (+)isomer reticuline was in corporated with considerable preference into boldine. More surprising however is the high (2%) level of incorporation of [8-^{3}H] isoboldine into boldine, a process that of necessity involves 2-*O*-demethylation followed by 1-*O*-methylation. (scheme 10)



Scheme 10 Biosynthesis of boldine in *Litsea glutinosa* var. *glabaria*

Norprotosinomenine was not a precursor of boldine in this plant, which contrasts with the previously discussed work with boldine in *Dicentra eximia*.

More definitive results have been obtained by Battersby and co-workers concerning the formation of corydine and glaucine in *Dicentra eximia* (Ker.) Torr. (Fumariaceae). Reticuline and orientaline were not precursor, but 4"-*O*-methylnorlaudanosoline and norprotosinomenine were effective precursors. This result clearly rules out direct phenol coupling (for corydine and reticuline) and a proaporphine intermediate. According to Battersby this suggests the pathway shown in scheme 11 involving two alternative neoproaporphine intermediates (A) and (B). Notice that the aporphine (C) has the incorrect o-methylation pattern in comparison with corydine. It would be interesting indeed to know if 1-*O*-demethylation followed by 2-*O*-methylation really occurs at this point in the biosynthesis. Boldine was a poor precursor or glaucine.



Scheme 10 Biosynthesis of boldine in *Litsea glutinosa* var. *glabaria*

These results would suggest that boldine is produced by two different pathways in two different plants. If this is a general trend, the biosynthesis of aporphine alkaloids may never be established. Clearly this is an area in need of considerable further study, and at this time it is not clear which, or how many, of the possible biosynthetic routes may be operating in order to produce the various aporphine alkaloids. (Cordell, 1981)

4 Pharmacology

4.1 Pharmacological activity of protoberberine alkaloids

Protoberberine alkaloids and their derivatives exhibit several types of biolagical activities. However, to date berberine alone was found to be of clinical value and is being used in the treatment of gastrointestinal disorder.

One of the most important actions is the antimicrobial activity of berberine and derivatives, which covers the range of organisms from fungi and protozoa to bacteria. In 1947, Sado has been examined systematically antibacterial activity of berberine chloride, iodide, and palmatine iodide against *Vibrio, Eberthella, Salmonella* and *Escherichia* organisms and observed that the antibacterial action of berberine chloride was virtually invariant between pH 5 and 9. Berberine sulfate inhibited the growth of *Candida tropicalis* and *Xanthomones citri* at a concentration of 3.1 μg/ml and of *Pseudomonas* and *Salmonella* at a concentration > 100 μg/ml. Lahiri and Dutta have recommended the use of berberine as an adjunct to isotonic saline and electrolyte replacement therapy in acute cholera (Lahiri and Dutta,1967). Berberine is reported to depress intestinal peristalsis and to remove inflammatory congestion of the mucosal surface of the intestine. It is also effective in the treatment of diarrhea of infancy and childhood. Berberine has been shown to form a complex with DNA, probably intercalating into supercoiled mitrocondrial DNA

to produce configurational change in DNA (Shamma, 1972)

Better antibacterial activity than berberine has been demonstrated by salts of berberine and sulfanilamide. However, appropriate comparisons with standard antibacterial are lacking. Berberine chloride is found to eliminate *Syphacia obvelata* from the intestine of mice. Berberine is also found effective in the treatment of cutaneous leshmaniasis. Antifungal and antiarrhythmic activities have been shown by a number of 8 ß- substituted berberines. Berberine sulfate and tetrahydropalmatine inhibit the respiratory chain by interfering with the action of NADH oxidase berberubine chloride isolated from *Thalictrum polyganum* is found to prosses antimicrobial activity against *Mycrobacterium smegmatics* at 100 µg/ml. (Bhakuni and Jain,1989)

The anticancer activity of protoberberine have been reviewed by Suffness and Cordell (The alkaloids, 1985). Berberine has been reported to prossess cytotoxic and neoplasm inhibitory activity against KB and Ehrlich ascite tumor cell, but the derivative coralyne chloride displays activity against both the P-388 and L-1210 lymphocytic leukemia systems in mice. A number of coralyne salts and analogs have been synthesized, and structure activity relationship has been studied. Although different salts of coralyne have comparable activity, coralyne acetosulfate is found most active. The planarity and regidity of molecules of these types are found critical activity. Coralyne formed a stable complex with thymus DNA *in vitro* , which is found

responsible for its activity.

Contractive activities of tertiary and quaternary berberine-type alkaloids have been studied on isolated uteri of mice. Quaternary protoberberines including berberine, palmatine, jatrorrhizine, coptisine, and dehydrocorydaline cause marked contraction of uterine muscles, but only a weak spasmolytic activity is exhibited on isolated intestines of mice. On the contrary berberines including canadine, tetrahydropalmatine and tetrahydrojatrorrhizine show strong papaverine-like action, although their contractive activities on uteri are transitory dehydrocorydaline chloride is found to prossess considerable gastric antisecretory activity. When administered orally to rat and guinea pigs, it prevents gastric and duodenal ulcers.

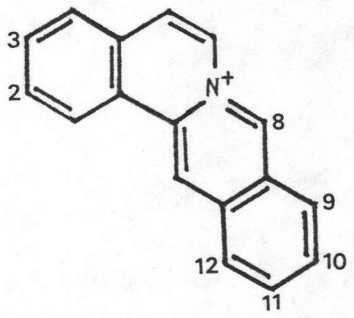
Pavelka and Kovar (Pavelka and Kovar, 1975) have studied the liver alcohol dehydrogenase activity of several protoberberine alkaloids. 13-Ethylberberine has been found to be the most active inhibitor of liver alcohol dehydrogenase the compound is bound more firmly to the enzyme at pH 10 than NAD and NADH.

The quaternary protoberberine alkalaids, berberine, coptisine, and substituted berbine are found to be weak inhibitors of butyrylcholinesterase in human serum, whereas jatrorrhizine and columbamine are found to be more potent.

The pharmacological actions and effects reported in the studies of protoberberine alkaloids, both of the natural (marked with asterisk)and synthetic compounds, are listed in table 4 according to the classification (Simeon *et al*, 1989)

Table 4 Pharmacological activities of protoberberine alkaloids

The simple 5,6-dehydropseudoprotoberberines



	Structure							
Name	2	3	8	9	10	11	12	Activity
Dehydroberberubine	-O-CH_2-O-		-	OH	OMe	-	-	Antitumoral
Isocoralyne	OMe	OMe	Me	-	-	OMe	OMe	Antileukemic

Quaternary protoberberines

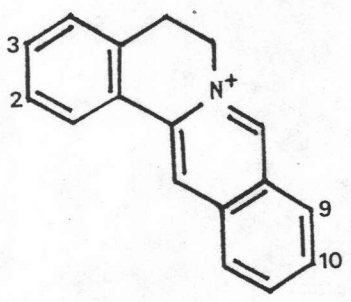


Table 4 (continue)

	Structure				
Name	2	3	9	10	Activity
9-Acetylberberrubine	-O-CH_2-O-		OAc	OMe	Antitumoral Ganglionic stimulant block Parasympathomimetic
9-Benzoylberberubine	-O-CH_2-O-		OBen	OMe	Antitumoral
Berberine*	-O-CH_2-O-		OMe	OMe	α_1-adrenalytic α_2-adrenalytic Antiarrhythmic Anti-caries Antidiarrheic Antifibrillant Antifungal Antiheparinic Antihipoxic Antihistaminic Anti-inflammatory Antimicrobial Antimitotic Antiparasitic

Table 4 (continue)

Berberine*				Antitumoral Antiulcer Blocking R factors Cholagogue Cholecystokinetic Choler toxin antagonist Choleretic CNS depressant Competitive adrenalytic Cytotoxic Decrease blood level of cholesterol Decrease blood level of T_4 Decrease Ca^{+2}available in intracellular receptors Decrease urinaty volume Ganglionic stimulant block Hypoglycemic Hypothermia Increase bilirubin excretion Increase lachrymal secretion

Table 4 (continue)

Berberine*				Increase the action of antitumorals Increase the activity of the UDP-glucuronyl transferase Inhibition of acetylcholinesterase Inhibition of alcohol dehyddrogenase Inhibition of aldehyde reductase I Inhibition of cation-dependent ATP-phosphohydrolase Inhibition of diamine oxidase Inhibition of lactic fermentation Inhibition of NADH oxidase Inhibition of reverse transcriptase Inhibition of RNA synthesis Inhibition of tryptophanase

Table 4 (continue)

Berberine*				Inhibition of tyrosine decarboxylase Inhibits enterotoxins Inhibits the action of carcinogens Inhibits the synthesis of DNA Intestinal antisecretory Local anesthetic Mutagenic Mydriatic Negative chronotropic Parasympatholytic Parasympathomimetic Phototoxic Pilomotor erection Positive chronotropic Positive inotropic Ptosis Sedative Spasmolytic Spermicide Sympatholytic Uterotonic Vasodilator

Table 4 (continue)

Berberrubine * (9-Berberobine)	-O-CH_2-O-		OH	OMe	Antimicrobial Antitumoral Ganglionic stimulant block Hypotensive Negative chronotropic Parasympatholytic Parasympathomimetic
O-Butylberberrubine	-O-CH_2-O-		OBu	OMe	Hypotensive Inhibition of cardiac function Negative chronotropic Parasympatholytic
Columbamine *	OH	OMe	OMe	OMe	Antimicrobial Inhibition of butyrylcholinesterase Uterotonic
Coptisine *	-O-CH_2-O-		-O-CH_2-O-		Anti-inflammatory Antimicrobial Cytotoxic Inhibition of acetylcholinesterase

Table 4 (continue)

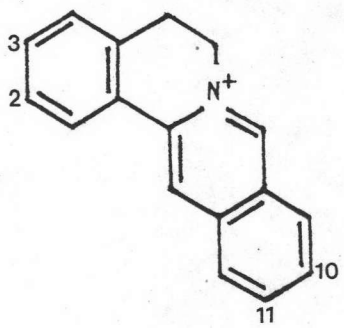
Coptisine*					Inhibition of alcohol dehydrogenase Spasmolytic Uterotonic
O-Dodecylberberrubine	-O-CH_2-O-		OD	OMe	Hypotensive
Jatrorrhizine *	OMe	OH	OMe	OMe	Antiarrhythmic Anti-inflammatory Antimicrobial Inhibition of butyrylcholinesterase Spasmolytic Uterotonic
O-Octylberberrubine	-O-CH_2-O-		OOCt	OMe	Hypotensive
Palmatine *	OMe	OMe	OMe	OMe	ACTH-like Anti-inflammatory Antimicrobial Antiparasitic Antipyretic Antitumoral Hypotensive

Table 4 (continue)

Palmatine*					Inhibition of acetylcholinesterase Inhibition of reverse transcriptase Parasympatholytic Spasmolytic Sympatholytic Uterotonic
O-Pentylberberrubine	$-O-CH_2-O-$		OP	OMe	Hypotensive Negative chronotropic Parasympatholytic

Table 4 (continue)

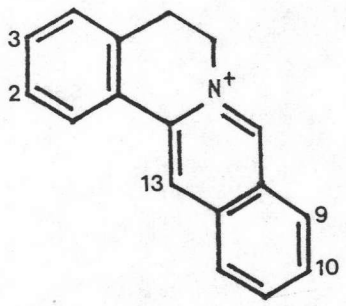
Quaternary pseudoprotoberberines



	Structure				
Name	2	3	10	11	Activity
Pseudocoptisine	-O-CH_2-O-		-O-CH_2-O-		Inhibition of acetylcholinesterase
Pseudoepiberberine *	OMe	OMe	-O-CH_2-O-		Inhibition of acetylcholinesterase

Table 4 (continue)

Quaternary protoberberines substituted at carbon 13



	Structure					
Name	2	3	9	10	13	Activity
Corysamine *	-O-CH_2-O-		-o-CH_2-O-		Me	Inhibition of alcohol dehydrogenase
Dehydrocavidine *	OMe	OMe	-O-CH_2-O-		Me	Analgesic Anticonvulsant Antimicrobial Increase the levels of hepatic glucogen Inhibits uterine contractions Negative inotropic Spasmolytic

Table 4 (continue)

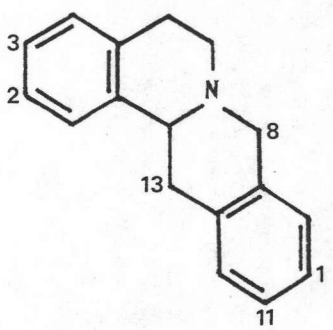
Dehydrocorydaline *	OMe	OMe	OMe	OMe	Me	Adrenalytic Anticonvulsant Antihipoxic Antitumoral Antiulcer Decrease urinary excretion of sodium Hypotensive Increase coronary flow Increase hypoxia tolerance Increase myocardial uptake Inhibition of reverse transcriptase Negative inotropic Peristaltic stimulant Protective effects on myocardial necrosis Protects pituitary induction Sedative Spasmolytic Uterotonic

Table 4 (continue)

13-Methylberberine	-O-CH_2-O-	OMe	OMe	Me	Antiarrhythmic Antihipoxic Inhibition of acetylcholinesterase Inhibition of reverse transcriptase
13-Methylberberrubine	-O-CH_2-O-	OH	OMe	Me	Antitumoral
13-Methylpalmatrubine	OMe OMe	OH	OMe	Me	Antitumoral
13-Allylberberrubine	-O-CH_2-O-	OH	OMe	All	Antiulcer Inhibition of butyrylcholinesterase
8-Benzylberberine	-O-CH_2-O- 8=Ben	OMe	OMe		Antimicrobial
13-Ethylberberine	-O-CH_2-O-	OMe	OMe	Et	Inhibition of acetylcholinesterase Inhibition of alcohol dehydrogenase
13-Propylberberine	-O-CH_2-O-	OMe	OMe	Pr	Antidiarrheic Miocardial stabilizer

Table 4 (continue)

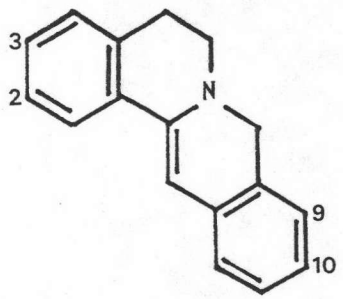
Pseudoprotoberberine methylated at carbon 8 or 13



	Structure						
Name	2	3	8	10	11	13	Activity
Dihydrocoralyne	OMe	OMe	Me	OMe	OMe	-	Antileukemic
13-Methylpseudoberberine	-O-CH_2-O-		-	OMe	OMe	Me	Antitumoral Inhibition of reverse transcriptase

Table 4 (continue)

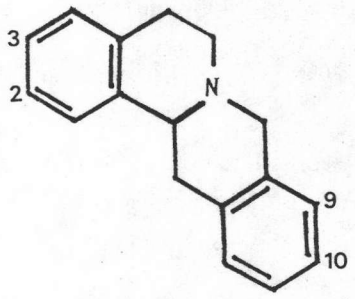
7-Dihydroprotoberberines



	Structure				
Name	2	3	9	10	Activity
Dihydroberberine	-O-CH_2-O-		OMe	OMe	Uterotonic
Dihydropalmatine *	OMe	OMe	OMe	OMe	Uterotonic

Table 4 (continue)

Tetrahydroprotoberberines



Name	Structure				Activity
	2	3	9	10	
(-) Aequaline * ((-) Discretamine)	OMe	OH	OMe	OH	Dopaminergic antagonist
(-) Corypalmine) * ((-) Tetrahydrojatrorrhizine)	OMe	OH	OMe	OMe	DA_2 antagonist Dopaminergic antagonist Spasmolytic
(+) Corypalmine ((±) Tetrahydrojatrorrhizine)	OMe	OH	OMe	OMe	Monoanimes depletor in brain Spasmolytic Tranquillizer

Table 4 (continue)

(+) 2,3-Dihydroxy 9,10-dimethoxy tetrahydroprotoberberine	OH	OH	OMe	OMe	Inhibition of dopamine-sensitive adenylate cyclase
(-) 2,3-Dihydroxy 9,10-dimethoxy tetrahydroprotoberberine	OH	OH	OMe	OMe	Inhibition of -sensitive adenylate cyclase Inhibition of dopamine-sensitive adenylate cyclase
(+) 2,3-Dihydroxy 9,10,11-trimethoxy tetrahydroprotoberberine	OH	OH	OMe	OMe 11-OMe	Inhibition of S-sensitive adenylate cyclase
(+) 9,10-Dihydroxy tetarhydroprotoberberine	-	-	OH	OH	Inhibition of dopamine-sensitive adenylate cyclase
(-) 9,10-Dihydroxy tetrahydroprotoberberine	-	-	OH	OH	Inhibition of dopamine-sensitive adenylate cyclase

Table 4 (continue)

(+) 9,10-Dimethoxy 10-methylthio tetrahydroprotoberberine	OMe	OMe	-	SMe	Tranquillizer
(+) 9,10-Dimethoxy tetrahydroprotoberberine	-	-	OMe	OMe	Inhibition of dopamine-sensitive adenylate cyclase
(-) 9,10-Dimethoxy tetrahydroprotoberberine	-	-	OMe	OMe	Inhibition of dopamine-sensitive adenylate cyclase
(-) Isocorypalmine * ((-)tetrahydroprotoberberine)	OH	OMe	OMe	OMe	Antitumoral Dopaminergic antagonist
(-) Kikemanine * ((-) Corydalmine)	OMe	OMe	OMe	OH	Dopaminergic antagonist
Nandinine *	-O-CH_2-O-		OH	OMe	Uterotonic
(-) Scoulerine *	OH	OMe	OH	OMe	Dopaminergic antagonist Sedative
Scoulerine	OH	OMe	OH	OMe	Antiemetic Antitussive

Table 4 (continue)

(-) Stepholidine *	OH	OMe	OMe	OH	Analgesic Antipyretic Antiserotoninic DA_2 agonist Dopaminergic antagonist Hypotensive Increase the action of analgesic Inhibition of catecholamine uptake Monoamines depletor in brain Sedative Spasmolytic
(±) 2,3,9,10,11-Pentamethoxy tetrahydroprotoberberine	OMe	OMe	OMe 11-OMe	OMe	Tranquilizer
(+) Tetrahydroberberine *	-O-CH_2-O-		OMe	OMe	Dopaminergic antagonist Inhibition of dopamine-sensitive adenylate cyclase

Table 4 (continue)

(-) Tetrahydroberberine *	-O-CH_2-O-	OMe	OMe	Antipsychotic Clonic spasm Ganglionic stimulant block Hypotensive Inhibition of -sensitive adenylate cyclase Sedative Spasmogenic
(±) Tetrahydroberberine	-O-CH_2-O-	OMe	OMe	Analgesic DA_2 agonist Emetic Hypothermia Monoamines depletor in brain Sedative Spasmolytic
Tetrahydroberberine	-O-CH_2-O-	OMe	OMe	Analgesic Antipsychotic Antitussive Ataraxic

Table 4 (continue)

Tetrahydroberberine				CNS depressant Curare-like Dopaminergic antagonist Ganglionic stimulant block Hypotensive Inhibition of conditioned reflexes Sedative Tranquillizer Uterotonic
(-) Tetrahydrocoptisine *	$-O-CH_2-O-$	$-O-CH_2-O-$		Antipsychotic Neuroleptic Sedative
(±) Tetrahydrocoptisine	$-O-CH_2-O-$	$-O-CH_2-O-$		DA_2 agonist Monoamines depletor in brain Tranquilizer

Table 4 (continue)

(+) Tetrahydropalmatine *	OMe	OMe	OMe	OMe	CNS stimulant Dopamine depletor Inhibition of catecholamine uptake
(-) Tetrahydropalmatine *	OMe	OMe	OMe	OMe	Analgesic Antiarrhythmic Catalepsic Dopaminergic antagonist Hyperthermic Hypnotic Increase the action of analgesic Increase the action of CNS deperssant Increase the threshold of hippocampal convulsive action Inhibition of catecholamine uptake Inhibition the activation of the reticular system

Table 4 (continue)

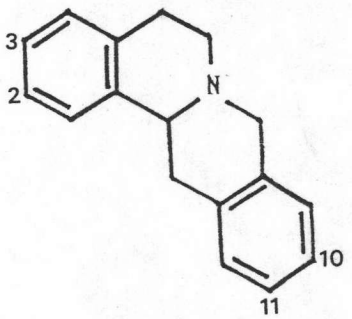
(-) Tetrahydropalmatine*					Monoamine depletor in brain Sedative Spasmolytic Supperssed the cortical and subcortical reaction Supperssed the period of after affect Tranquillizer
(±) Tetrahydropalmatine	OMe	OMe	OMe	OMe	ACTH-like Antiarrhythmic Antimicrobial Ca^{+2} antagonist Decrease the speed of neuronal depolarization Hypotensive Monoamines depletor in brain Sedative Serotonergic antagonist Spasmolytic

Table 4 (continue)

Tetrahydropalmatine	OMe	OMe	OMe	OMe	CNS depressant Inhibition of NADH oxidase Sedative Tranquillizer Uterotonic
(+) 2,3,9,10-Tetrahydroxy tetrahydroprotoberberine	OH	OH	OH	OH	Inhibition of dopamine-sensitive adenylate cyclase
(-) 2,3,9,10-Tetrahydroxy tetrahydroprotoberberine	OH	OH	OH	OH	Dopaminergic antagonist Inhibition of dopamine-sensitive adenylate cyclase
(±) 3,9,10-Trimethoxy tetrahydroprotoberberine	-	OMe	OMe	OMe	Tranquillizer

Table 4 (continue)

Tetrahydropseudoprotoberberines



	Structure				
Name	2	3	10	11	Activity
(+) 10-Acetyl 2,3,11-trimethoxy tetrahydroprotoberberine	OMe	OMe	OAc	OMe	Analgesic Hypotensive Vasodilator
Coreximine * (Coramine)	OH	OMe	OMe	OH	Respiratiory stimulant
(-) 10,11-Dihydroxy tetrahydroprotoberberine	-	-	OH	OH	Inhibition of dopamine sensitive adenylate cyclase
(±) 2,3-Dimethoxy 10,11-methylenedioxy tetrahydroprotoberberine	OMe	OMe	$-O-CH_2-O-$		Analgesic Hypotensive Vasodilator

Table 4 (continue)

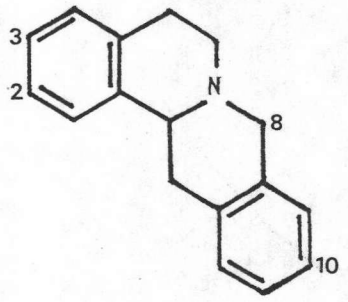
(+) 3-Hydroxy 10,11-dimethoxy tetrahydroprotoberberine	-	OH	OMe	OMe	Hypotensive
(+) 2-Methoxy 3,10,11-trihydroxy tetrahydroprotoberberine	OMe	OH	OH	OH	Dopaminergic antagonist
(+) 3-Methoxy 2,10,11-trihydroxy tetrahydroprotoberberine	OH	OMe	OH	OH	Dopaminergic antagonist
(+) 11-Methoxy 2,3,10-trihydroxy tetrahydroprotoberberine	OH	OH	OH	OMe	Dopaminergic antagonist
(±) 2,3-Methylenedioxy 9,10,11-trihydroxy tetrahydroprotoberberine	$-O-CH_2-O-$		OH	OH 9-OH	Inhibition of dopamine-sensitive adenylate cyclase
(-) 2,3,10,11-Tetrahydroxy tetrahydroprotoberberine	OH	OH	OH	OH	Dopaminergic antagonist Inhibition of monoamine oxidase

Table 4 (continue)

(+) 2,3,10,11-Tetrahydroxy tetrahydroprotoberberine	OH	OH	OH	OH	Inhibition of - sensitive adenylate cyclase
2,3,10,11-Tetrahydroxy tetrahydroprotoberberine	OH	OH	OH	OH	Inhibition of catecholamine uptake
(±) 2,3,11-Trihydroxy tetrahydroprotoberberine	OH	OH	-	OH	Inhibition of - sensitive adenylate cyclase Inhibition of dopamine-sensitive adenylate cyclase
(±) 3,10,11-Trihydroxy tetrahydroprotoberberine	-	OH	OH	OH	Hypotensive
(-) Xylopinine*	OMe	OMe	OMe	OMe	Dopaminergic antagonist
(±) Xylopinine	OMe	OMe	OMe	OMe	Analgesic Hypotensive Vasodilator
Xylopinine	OMe	OMe	OMe	OMe	Antitussive Sympatholytic

Table 4 (continue)

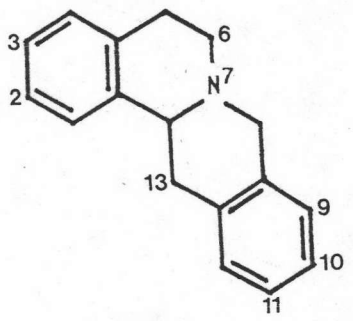
Tetrahydroprotoberberines oxygenated at C-8



	Structure				
Name	2	3	8	10	Activity
(±) 2,3,10-Trimethoxy 8-oxo tetrahydroprotoberberine	OMe	OMe	O	OMe	Tranquillizer

Table 4 (continue)

Tetrahydroprotoberberines methylated at carbon 13



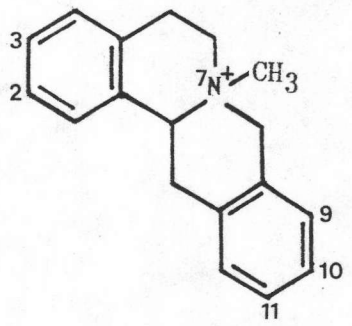
	Structyre						
Name	2	3	9	10	11	13	Activity
(+) Cavidine*	OMe	OMe	-O-CH_2-O-		-	Me	Spasmolytic
Corydaline*	OMe	OMe	OMe	OMe	-	Me	CNS depressant Uterotonic
2,3-Methylenedioxy 10,11-dimethoxy 13-methyl tetrahydro-protoberberine	-O-CH_2-O-		-	OMe	OMe	Me	Cytotoxic

Table 4 (continue)

Ophiocarpine*	$-O-CH_2-O-$		OMe	OMe	-	Me	Uterotonic
(±) 13-Cianoxylopinine	OMe	OMe	-	OMe	OMe	CN	Hypotensive Vasodilator
2,3-Methylenedioxy 10,11-dimethoxy 13-hydroxymethyl tetrahydro protoberberine	$-O-CH_2-O-$		-	OMe	OMe	CH_2OH	Cytotoxic

Table 4 (continue)

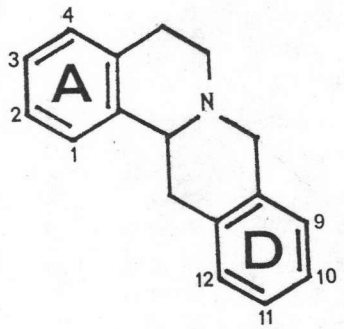
Tertahydroprotoberberine with N-methylated



Name	Structure						Activity
	2	3	7	9	10	11	
N-Methylisocorypalmine	OH	OMe	Me	OMe	OMe	-	Positive inotropic
N-Methylxylopinine	OMe	OMe	Me	-	OMe	OMe	Curare-like

Table 4 (continue)

Tetrahydroprotoberberines with uncommon oxygenation patterns on rings A and D



	Structure								
Name	1	2	3	4	9	10	11	12	Activeity
Capauridine*	OH	OMe	OMe	-	OMe	OMe	-	-	Uterotonic
Capaurine*	OH	OMe	OMe	-	OMe	OH	-	-	Uterotonic
(±) 4-Formyl-xylopine	-	OMe	OMe	CHO	-	OMe	OMe	-	Analgesic Hypotensive Sedative

Table 4 (continue)

(+) 2,3,10,11,12-pentamethoxy tetrahydro-protoberberine	-	OMe	OMe	-	-	OMe	OMe	OMe	Tranquillizer
(+) 1,2,3,10-tetramethoxy tetrahydro-protoberberine	OMe	OMe	OMe	-	-	OMe	-	-	Tranquillizer
(+) 1,3,10-trimethoxy tetrahydro-protoberberine	OMe	-	OMe	-	-	OMe	-	-	Tranquillizer
(±) 3,4,10-trimethoxy tetrahydro-protoberberine	-	-	OMe	OMe	-	OMe	-	-	Tranquillizer

4.2 Pharmacology of aprophine alkaloids

The aporphine alkaloids display a wide range of pharmacologic activities, although none are commercial items.

1,2 - Methylenedioxyaporphine increases arterial blood pressure, but higher doses cause strychnine - like convulsions. The methohydroxide salt has a curare - like action. (Cordell, 1981)

Isothebaine increased intestinal muscle tone in rabbits and also amplified uterine contractions in the rat. Other activities observed include decreased motor activity and analgesia (mice), and an anti-inflammatory effect(rats). (Cordell, 1981) and depress central nervous system. (Shamma, 1972)

Glaucine and dicentrine cause narcosis in animals, and with larger doses convulsions. (Shamma, 1972). Glaucine reduced blood pressure and inhibited respiration in cats and had antitussive effects resembling codeine, but of longer duration.

In rats and cats a potentially useful hypoglycemic effect was observed at 12-mg/kg doses. Dehydroglaucine has antibacterial activity. (Cordell, 1981)

Corydine has central nervous system depressant and hypotensive activity and blocks transmission of nerve impulse. The corresponding 11-demethyl derivative, corytuberine , accelerates respiration and stimulates secretions.

Bulbocapnine antagonizes the effects of apomorphine and amphetamine, depresses the central nervous system, and causes catalepsy in mice. Xylopine has sedative and analgesic activity and isoboldine is an insect-feeding inhibitor.

Apomorphine although not a natural product has been quite well studied, it has hypotensive activity and is a powerful emetic, suitable for rapid emesis after ingestion of poisons. Of more interest from a therapeutic point of view is its stimulation of the dopaminergic system in rats and mice, and consequently its potential anti-Parkinsonism activity. Also of interest are reports that it can decrease serum prolactin levels. (Cordell, 1981)

Apocodeine may have useful emetic activity. Boldine is only slightly toxic and does not cause addiction. It has mild sedative, diuretic, and antispasmodic action, and also increases the secretions of the liver and salivary glands. Laurifoline chloride has some hypotensive activity, while corytuberine accelerates respiration and slow the pulse. Xylopine is supposed to possess sedative and analgesic activity. (Shamma, 1972)