CHAPTER II

HISTORICAL

1. Taxa and Description

The family Alangiaceae is a small family with only one genus (*Alangium*) and about 17 species (Mabberley, 1987). It generally occurs in tropical and subtropical regions of the old world (Keng, 1987). This family is characterized by trees or shurbs, sometimes spiny. Leaves alternate, simple; stipules 0. Flowers hermaphrodite, in axillary cymes; pedicels articulated. Calyx truncate or with 4-10 teeth. Petals 4-10, mostly linear, valvate, at length recurved, sometimes connate at base. Stamens the same number as and alternate with petals or 2-4 times as many, free or slightly connate at the base, more or less villous inside; anthers 2 celled, linear, opening length wise. Disk cushion-like. Ovary inferior, 1-2-celled; style simple, clavate or 2-3-lobed; ovule solitary, pendulous, with 2 integuments. Fruit a drupe crowned by the sepals and disk, 1-seeded stone. Seeds with embryo about equal to endosperm.

Alangium salviifolium is a small tree with more or less spinescent branches; bark light colored; young parts pubescent. Leaves variable 7.5-12.5 by 2.5-5.7 cm, narrowly oblong or ovate-lanceolate, more or less acuminate, subobtuse, entire, glabrous above, pubescent on the nerves and prominently reticulately veined beneath, base rounded or acute; petioles 6-13 mm long, densely pubescent. Flowers few, in axillary fascicles; pedicels 3-6 mm long, densely pubescent, jointed at the top. Calyx turbinate 3 mm long, densely silky pubescent; teeth triangular, 0.85 mm long. Petals 5-10 (usually 6), densely pubescent outside, 1.3-2 cm long and about 5 mm wide, narrowly linear, reflexed. Stamens numerous (usually more than 20), nearly as long as the petals; filaments hairy at base. Style as long as the stamens; stigma very large. Fruit when young ovoid or ellipsoid, becoming nearly globular when ripe 1.3-2 cmdiam., crowned by the persistent calyx-limb, finely pubescent, not or obscurely

ribbed, purplish red; endocarp bony; albumen fleshy outside, friable inside, not at all ruminate; cotyledons foliaceous, flat, not crumpled (Kirtikar and Basu,1933).

2. Chemical Constituents of *Alangium salviifolium*

The compounds that have been found in this plant are listed in Table 1

Table 1 Chemical constituents reported to be present in *Alangium salviifolium*

Chemical compound (The structure is shown in the number of Table 2)	Category	Plant part	References
alamaridine (19)	alkaloid	seed	Bhattacharjya, Mukhopudhyay and Pakrashi, 1986
alamarine (23)	alkaloid	seed	Pakrashi *et al.*, 1980
dihydroalamarine (25)	alkaloid	seed	Pakrashi *et al.*, 1985
dihydroisoalamarine (26)	alkaloid	seed	Pakrashi *et al.*, 1985
isoalamarine (24)	alkaloid	seed	Pakrashi *et al.*, 1980
alancine (15)	alkaloid	stem bark	Chattopadhyay *et al.*, 1984
alangamide (5)	alkaloid	seed	Pakrashi and Ali, 1969
alangicine (10)	alkaloid	root bark	Pakrashi and Ali, 1967
alangidiol	triterpene	leaf	Achari, Pal and Pakrashi, 1975
isoalangidiol	triterpene	leaf	Achari *et al.*, 1975
alangimarckine (32)	alkaloid	leaf root bark	Willaman and Li, 1970
alangimaridine (19)	alkaloid	seed	Pakrashi *et al.*, 1980

Table 1 (continued)

Chemical compound (The structure is shown in the number of Table 2)	Category	Plant part	References
alangimarine (20)	alkaloid	seed	Pakrashi *et al.*, 1980
isoalangimarine, (21)	alkaloid	seed	Pakrashi *et al.*, 1985
alangimarinone (22)	alkaloid	seed	Pakrashi *et al.*, 1985
alangine A	alkaloid	root bark	Bhakuni, Dhar and Dhar, 1960
alangine B	alkaloid mixture	root bark	Bhakuni *et al.*, 1960
alangiside (34)	glucoside	root, leaf, fruit	Shoeb *et al.*, 1975
3-*O*-demethyl-2-*O*-methyl-alangiside,: (36)	glucoside	fruit	Itoh *et al.*, 1994
3-*O*-demethyl-2-*O*-methyl-isoalangiside(39)	glucoside	fruit	Itoh, Tanahashi, and Nagakura, 1995
methylalangiside	glucoside	fruit	Itoh *et al*, 1994
methylisoalangiside (38)	glucoside	fruit	Itoh *et al.*, 1995
isoalangiside (37)	glucoside	fruit	Itoh *et al.*, 1995
demethylneoalangiside, (40)	glucoside	fruit	Itoh *et al.*, 1995
neoalangiside (41)	glucoside	fruit	Itoh *et al.*, 1995
ankorine (14)	alkaloid	leaf	Dasgupta *et al.*, 1965

Table 1 (continued)

Chemical compound (The structure is shown in the number of Table 2)	Category	Plant part	References
betulin	triterpene	kernel	Pakrashi *et al.*, 1968
betulinaldehyde	triterpene	kernel	Pakrashi *et al.*, 1968
betulinic acid	triterpene	kernel	Pakrashi *et al.*, 1968
hydroxylactone A betulinic acid	triterpene	kernel	Pakrashi *et al.*, 1968
bharatamine (33)	alkaloid	seed	Pakrashi *et al.*, 1983
cephaeline (2)	alkaloid	rootbark rootbark, stembark seed	Albright, Van Meter and Goldman, 1965 Willaman and Li, 1970 Achari *et al.*, 1980
demethylcephaeline (4)	alkaloid	stembark	Pakrashi and Achari, 1970
isocephaeline (3)	alkaloid	seed	Achari *et al.*, 1980
emetine (1)	alkaloid	stembark rootbark	Budzikiewicz, Pakrashi and Vorbruggen, 1964
protodehydroemetine (13)	alkaloid	leaf	Willaman and Li, 1970
friedelin	triterpene	leaf	Gupta, Singh and Bhakuni, 1969

Table 1 (continued)

Chemical compound (The structure is shown in the number of Table 2)	Category	Plant part	Referenc
lacinilene C	sesquiterpene	seed	Mukhopudhyay *et al.*, 1987
loganic acid	monoterpene	fruit	Kapil *et al.*, 1971
L: N-benzoylphenyl-alaniol,:	proteid	leaf	Achari, Pal and Pakrashi, 1974
protoemetinol (16)	alkaloid	leaf rootbark	Albright, Van Meter and Goldman, 1965 Willaman and Li, 1970
10-demethylprotoemetinol (18)	alkaloid	seed	Ali *et al.*, 1982
9-demethylprotoemetinol (17)	alkaloid	seed	Ali *et al.*, 1982
psychotrine (6)	alkaloid	rootbark stembark seed	Budzikiewicz *et al.*, 1964 Willaman and Li, 1970 Pakrashi and Ali, 1967
11-hydroxypsychotrine (9)	alkaloid	rootbark	Willaman and Li, 1970
demethylpsychotrine (8)	alkaloid	rootbark stembark	Pakrashi and Ali, 1967 Pakrashi and Achari,
salsoline	alkaloid	seed	Achari *et al.*, 1980

Table 1 (continue)

Chemical compound (The structure is shown in the number of Table 2)	Category	Plant part	References
beta-sitosterol,	steroid	kernel leaf	Pakrashi *et al.*, 1968 Gupta *et al.*,1969
stigmasterol	steroid	leaf	Gupta *et al.*, 1969
tubulosine (27)	alkaloid	rootbark stembark	Albright *et al.*, 1965 Bhakuni, Jain and Chaturvedi, 1983
10-demethyltubulosine (30)	alkaloid	rootbark	Popelak, Haak and Spingler, 1966 a
deoxytubulosine (29)	alkaloid	seed leaf	Battersby *et al.*, 1966
isotubulosine (28)	alkaloid	rootbark	Popelak, Haak and Spingler, 1966 b
venoterpine	monoterpene alkaloid	seed	Achari *et al.*, 1980

3. The Tetrahydroisoquinoline Monoterpene Alkaloids

Among the large number of alkaloids containing an isoquinoline nucleus, there is a small group of alkaloids characterised by an isoquinoline portion and a portion of monoterpenoid origin. A typical member of these alkaloids is emetine which is considered to be derived biosynthetically from 2 molecules of dopamine and one molecule of the monoterpenoid glycoside secologanin. In plants, emetine occurs together with a number of structurally related alkaloids, e.g. cephaeline and

psychotrine of which tubulosine and related base are also included. The latter consists of an isoquinoline portion, a portion of monoterpenoid origin and an indole system originating from tryptamine.

The tetrahydroisoquinoline monoterpene alkaloids occur in only three plant families: Alangiaceae, Icacinaceae, and Rubiaceae (Wiegrebe, Kramer, and Shamma, 1984). *Psychotria ipecacuanha* Stokes (*Cephaelis ipecacuanha* Rich) (Rubiaceae) and *Alangium salviifolium* (Alangiaceae) are the main sources of this group of alkaloids.

Naturally occurring tetrahydroisoquinoline monoterpene alkaloids are classified into 4 types on the basis of their structures, as follows:

1. Benzoquinolizidine
2. Benzopyridoquinolizine
3. Indolobenzoquinolizidine
4. Tetrahydroprotoberberine

1. Benzoquinolizidine

Benzoquinolizidine is a typical skeleton of tetrahydroisoquinoline monoterpene alkaloids. The alkaloids bearing this skeleton, for example, are emetine, cephaeline, ankorine. Their sources and structures are summarised in Table 2 (Structure No.1-18).

2. Benzopyridoquinolizine

Alangimarine, alamarine, and alangimaridine are the first three alkaloids possessing benzopyridoquinolizine skeleton isolated from the weakly basic fraction of the total alkaloids of the seeds of *A. salviifolium* (Pakrashi *et al.*, 1980). Chemical structures and natural sources of alangimarine, alamarine, alangimaridine and other structurally related alkaloids are presented in Table 2 (Structure No.19-26).

3. Indolobenzoquinolizidine

Indolobenzoquinolizidine type is a hybrid structure of an isoquinoline and a β-carboline moiety. The typical alkaloid is tubulosine. It was first isolated by Brauchli *et al.* in 1964 from the Argentinian plant *Pogonopus tubulosus* (DC.) Schumann (Rubiaceae). Subsequently, it was isolated from the South African plant *Cassinopsis ilicifolia* Kuntze (Icacinaceae) (Monteiro *et al.*, 1965) and from the root bark of *A. salviifolium* (Alangiaceae) (Battersby, 1965). Structures of tubulosine typed-alkaloids are shown in Table 2 (Structure No.27-32).

4. Tetrahydroprotoberberine

Pakrashi *et al.* in 1983 reported the presence of bharatamine as a unique tetrahydroisoquinoline monoterpene alkaloid of tetrahydroprotoberberine skeleton. The alkaloid was isolated from the seeds of *A. salviifolium* and its structure (shown in Table 2) was established by an equivocal synthesis (Structure No.33).

Table 2 Structures of naturally occurring tetrahydroisoquinoline monoterpene alkaloids (Structurally related glucosides are also included)

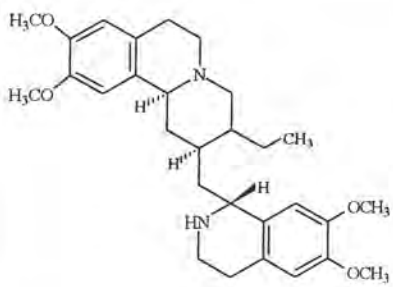
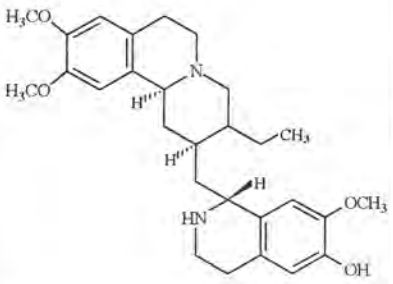
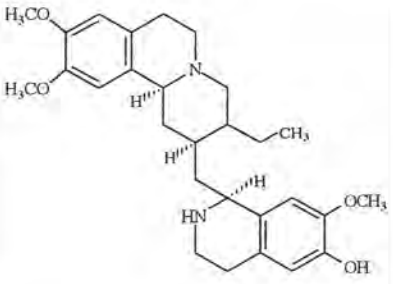
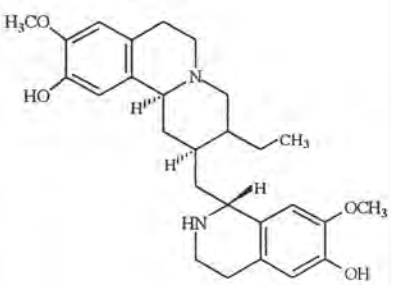
Name and structure	Sources	References
1. emetine 	*Alangium salviifolium* Wang.[a] *Cephaelis acuminata* Karsten[b] *Psychotria granadensis* Benth. ex Oerst[b] *C. ipecacuanha* Stokes	Budzikiewicz, Pakrashi and Vorbruggen, 1964 Grag and Gear, 1972
2. cephaeline 	*A. salviifolium* Wang. *C. acuminata* Karsten *P. granadensis* Benth. ex Oerst *C. ipecacuanha* Stokes	Budzikiewicz, Pakrashi and Vorbruggen, 1964 Grag and Gear, 1972
3. isocephaeline 	*A. salviifolium* Wang.	Achari *et al.*, 1980
4. demethylcephaeline 	*A. salviifolium* Wang.	Pakrashi and Achari, 1970

Table 2 (continued)

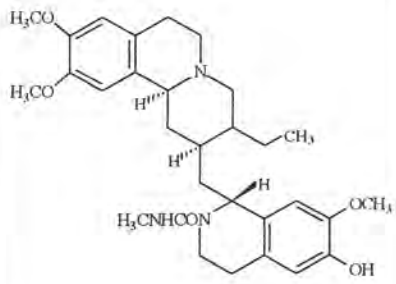
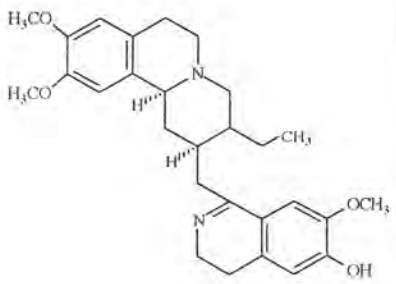
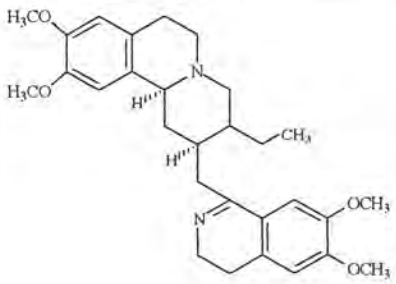
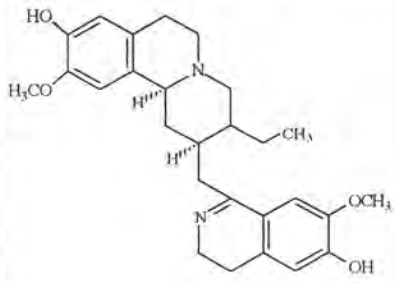
Name and structure	Sources	References
5. alangamide 	*A. salviifolium* Wang.	Pakrashi and Ali, 1969
6. psychotrine 	*A. salviifolium* Wang. *C. ipecacuanha* Stokes	Budzikiewicz, Pakrashi and Vorbruggen, 1964 Brindley and Pyman, 1927
7. O-methylpsychotrine 	*P. granadensis* Benth. ex Oerst *C. ipecacuanha* Stokes	Battersby, Davidson and Harper, 1959
8. demethylpsychotrine 	*A. salviifolium* Wang.	Pakrashi and Ali, 1967

Table 2 (continued)

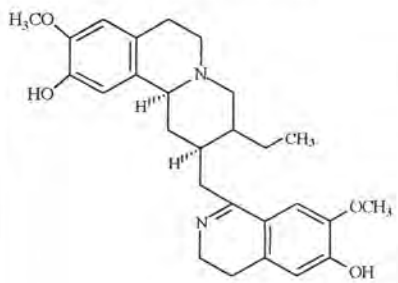
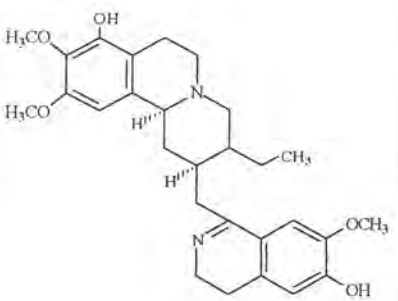
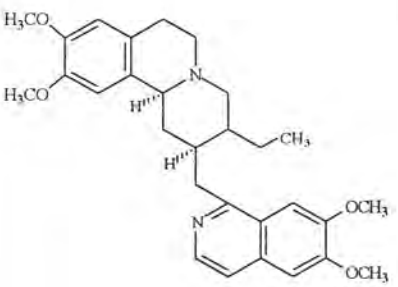
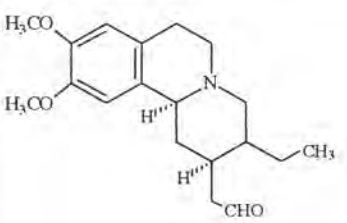
Name and structure	Sources	References
9. 11-hydroxypsychotrine 	*A. salviifolium* Wang.	Willaman and Li, 1970
10. alangicine 	*A. salviifolium* Wang.	Pakrashi and Ali, 1967
11. emetamine 	*P. granadensis* Benth. ex Oerst *C. ipecacuanha* Stokes	Battersby, Davidson and Harper, 1959
12. protoemetine 	*C. ipecacuanha* Stokes	Battersby, Davidson and Harper, 1959

Table 2 (continued)

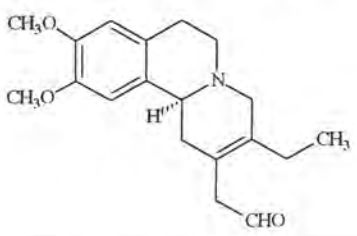
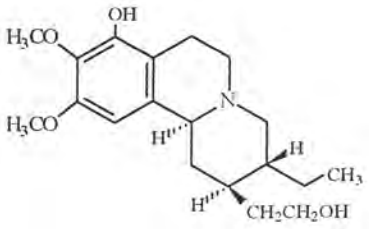
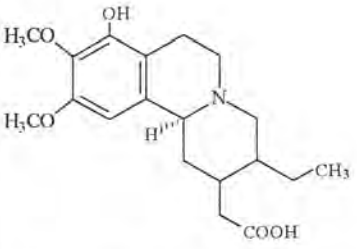
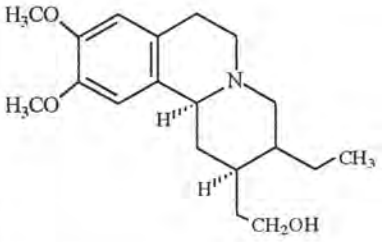
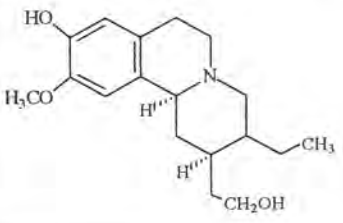
Name and structure	Sources	References
13. dehydroprotoemetine 	*A. salviifolium* Wang.	Willaman and Li, 1970
14. ankorine 	*A. salviifolium* Wang.	Battersby *et al.*, 1966
15. alancine 	*A. salviifolium* Wang.	Chattopadhyay *et al.*, 1984
16. protoemetinol 	*A. salviifolium* Wang.	Albright, Van Meter and Goldman, 1965
17. 9-demethylprotoemetinol 	*A. salviifolium* Wang.	Ali *et al.*, 1982

Table 2 (continued)

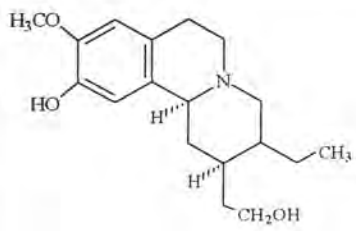
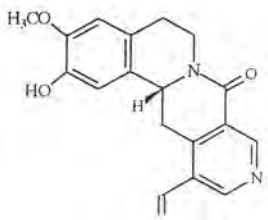
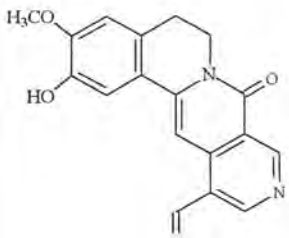
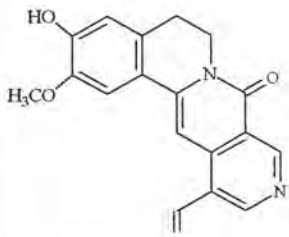
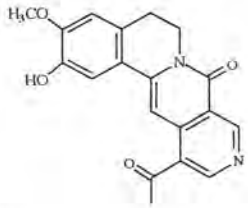
Name and structure	Sources	References
18. 10-demethylprotoemetinol 	*A. salviifolium* Wang.	Ali *et al.*, 1982
19. alangimaridine 	*A. salviifolium* Wang.	Pakrashi *et al.*, 1980
20. alangimarine 	*A. salviifolium* Wang.	Pakrashi *et al.*, 1980
21. isoalangimarine 	*A. salviifolium* Wang.	Pakrashi *et al.*, 1985
22. alangimarinone 	*A. salviifolium* Wang.	Pakrashi *et al.*, 1980

Table 2 (continued)

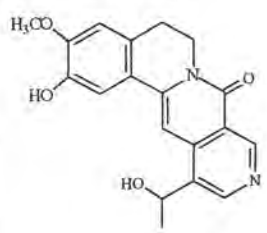
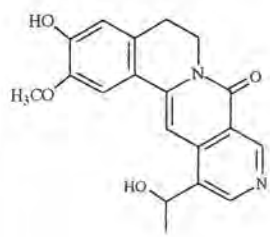
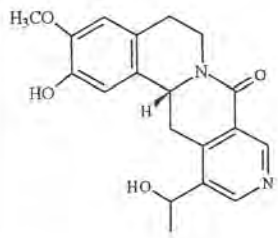
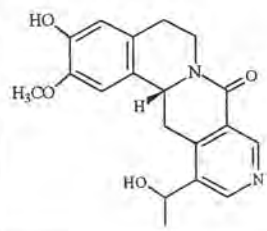
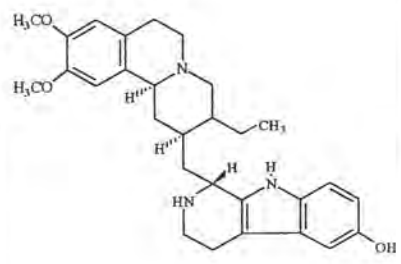
Name and structure	Sources	References
23. alamarine 	*A. salviifolium* Wang.	Pakrashi *et al.*, 1980
24. isoalamarine 	*A. salviifolium* Wang.	Pakrashi *et al.*, 1985
25. dihydroalamarine 	*A. salviifolium* Wang.	Pakrashi *et al.*, 1985
26. dihydroisoalamarine 	*A. salviifolium* Wang.	Pakrashi *et al.*, 1985
27. tubulosine 	*A. salviifolium* Wang. *Pogonopus tubulosis* (DC.) Schumann[b]	Albright, Van Meter and Goldman, 1965 Brauchli *et al.*, 1964

Table 2 (continued)

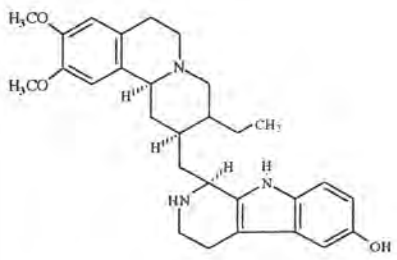
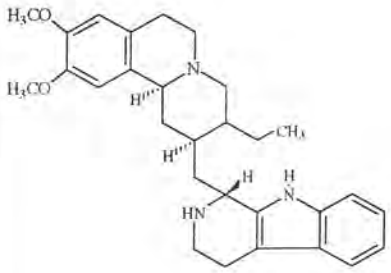
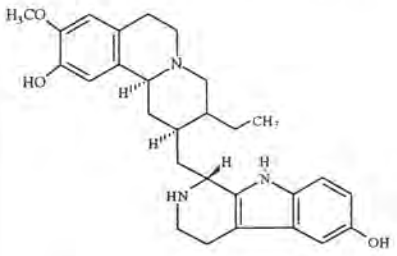
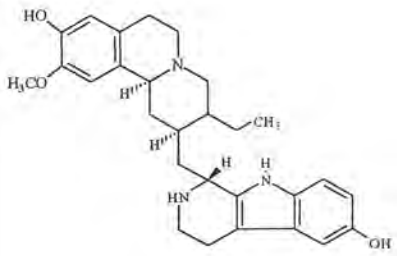
Name and structure	Sources	References
28. isotubulosine 	*A. salviifolium* Wang.	Popelack, Haack and Spingler, 1966 b
29. deoxytubulosine 	*A. salviifolium* Wang. *Cassinopsis ilicifolia* Kuntze[c]	Battersby *et al.*, 1965 Monteiro *et al.*,1965
30.10-demethyltubulosine 	*A. salviifolium* Wang.	Popelack, Haack and Spingler, 1966 a
31. 9-demethyltubulosine 	*A. vitiense* (A. Gray) Baillon	Kan-Fan *et al.*, 1985

Table 2 (continued)

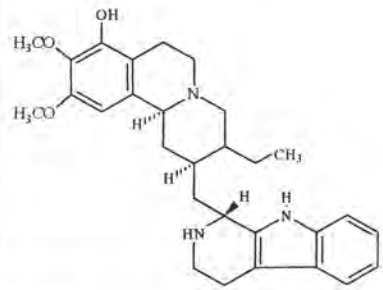
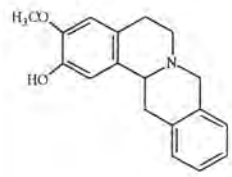
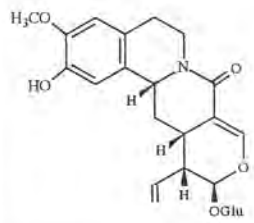
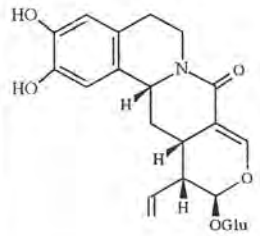
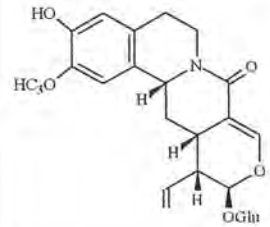
Name and structure	Sources	References
32. alangimarckine 	*A. salviifolium* Wang.	Pakrashi, 1964
33. bharatamine 	*A. salviifolium* Wang.	Pakrashi *et al* , 1983
34. alangiside 	*A. salviifolium* Wang.	Shoeb *et al*., 1975
35. demethylalangiside 	*C. ipecacuanha* Stokes	Itoh, Tanahashi and Nagakura, 1991
36. 3-*O*-demethyl 2-*O*-methylalangiside 	*A. salviifolium* Wang. *C. ipecacuanha* Stokes	Itoh *et al*., 1994

Table 2 (continued)

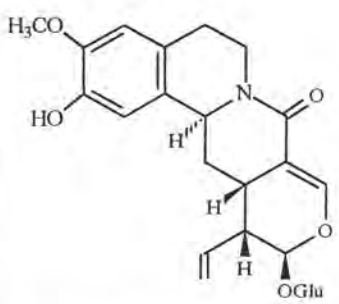
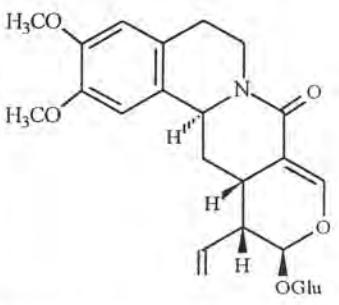
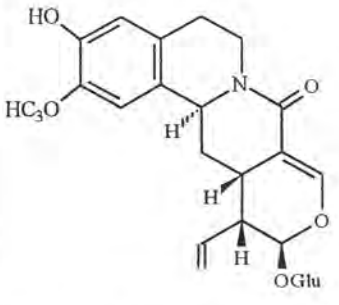
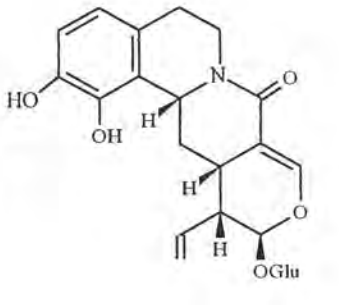
Name and structure	Sources	References
37. isoalangiside 	*A. salviifolium* Wang.	Itoh, Tanahashi, and Nagakura, 1995
38. methylisoalangiside 	*A. salviifolium* Wang.	Itoh, Tanahashi, and Nagakura, 1995
39. 3-*O*-demethyl 2-*O*-methylisoalangiside 	*A. salviifolium* Wang.	Itoh, Tanahashi, and Nagakura, 1995
40. demethylneoalangiside 	*A. salviifolium* Wang.	Itoh, Tanahashi, and Nagakura, 1995

Table 2 (continued)

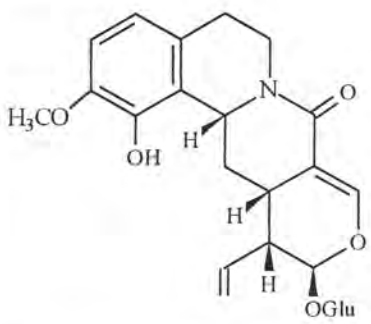
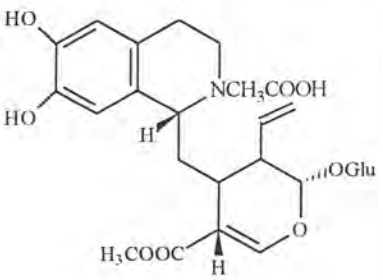
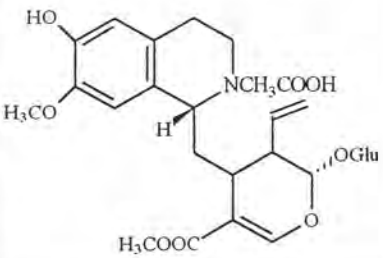
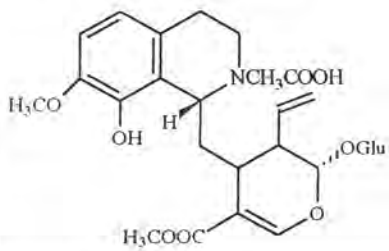
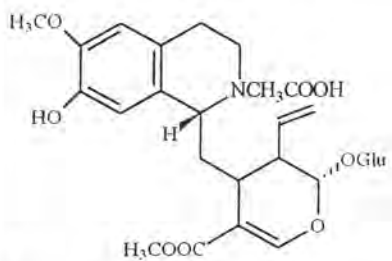
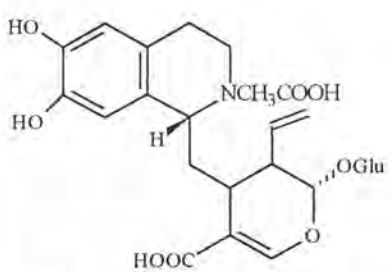
Name and structure	Sources	References
41. neoalangiside 	*A. salviifolium* Wang.	Itoh, Tanahashi, and Nagakura, 1995
42. ipecoside 	*C. ipecacuanha* Stokes *C. acuminata* Karsten	Grag and Gear, 1972
43. 7-*O*-methylipecoside 	*C. ipecacuanha* Stokes	Itoh *et al.*, 1994
44. neoipecoside 	*C. ipecacuanha* Stokes	Itoh and Tanahashi, 1989

Table 2 (continued)

Name and structure	Sources	References
45. methylneoipecoside 	*C. ipecacuanha* Stokes	Itoh and Tanahashi, 1989
46. 6-*O*-methylipecoside 	*C. ipecacuanha* Stokes	Itoh, Tanahashi and Nakagura, 1991
47. ipecosidic acid 	*C. ipecacuanha* Stokes	Itoh, Tanahashi and Nakagura, 1991
48. 3,4-dehydroneoipecoside 	*C. ipecacuanha* Stokes	Itoh, Tanahashi and Nakagura, 1991

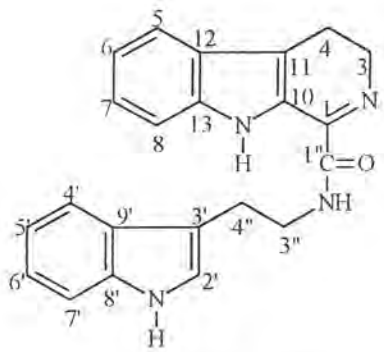
[a]The genus *Alangium* belongs to the family Alangiaceae

[b]The genera *Cephaelis, Psychotria* and *Pogonopus* belong to the family Rubiaceae.

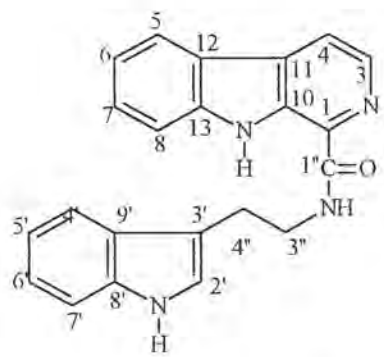
[c]The genus *Cassinopsis* belongs to the family Icacinaceae.

The alkaloids alangiobussine and alangiobussinine are not classified as tetrahydroisoquinoline monoterpene alkaloids since they do not posses isoquinoline moiety. They were isolated for the first time very recently from the leaves of *Alangium bussyanum* by Diallo *et al.*,1995 and their structures were established on the basis of spectroscopic analyses and confirmed by partial synthesis.

The structures and numbering system of alangiobussine and alangiobussinine are given below:



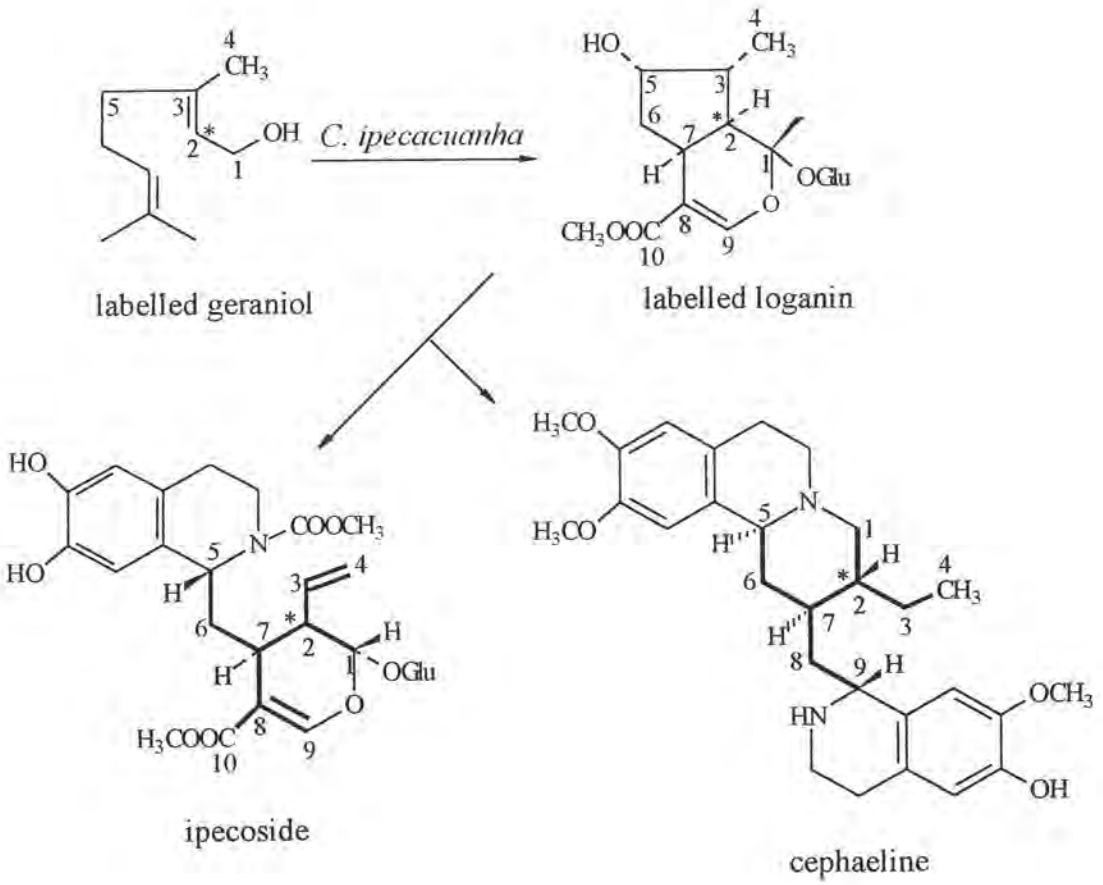
alangiobussine



alangiobussinine

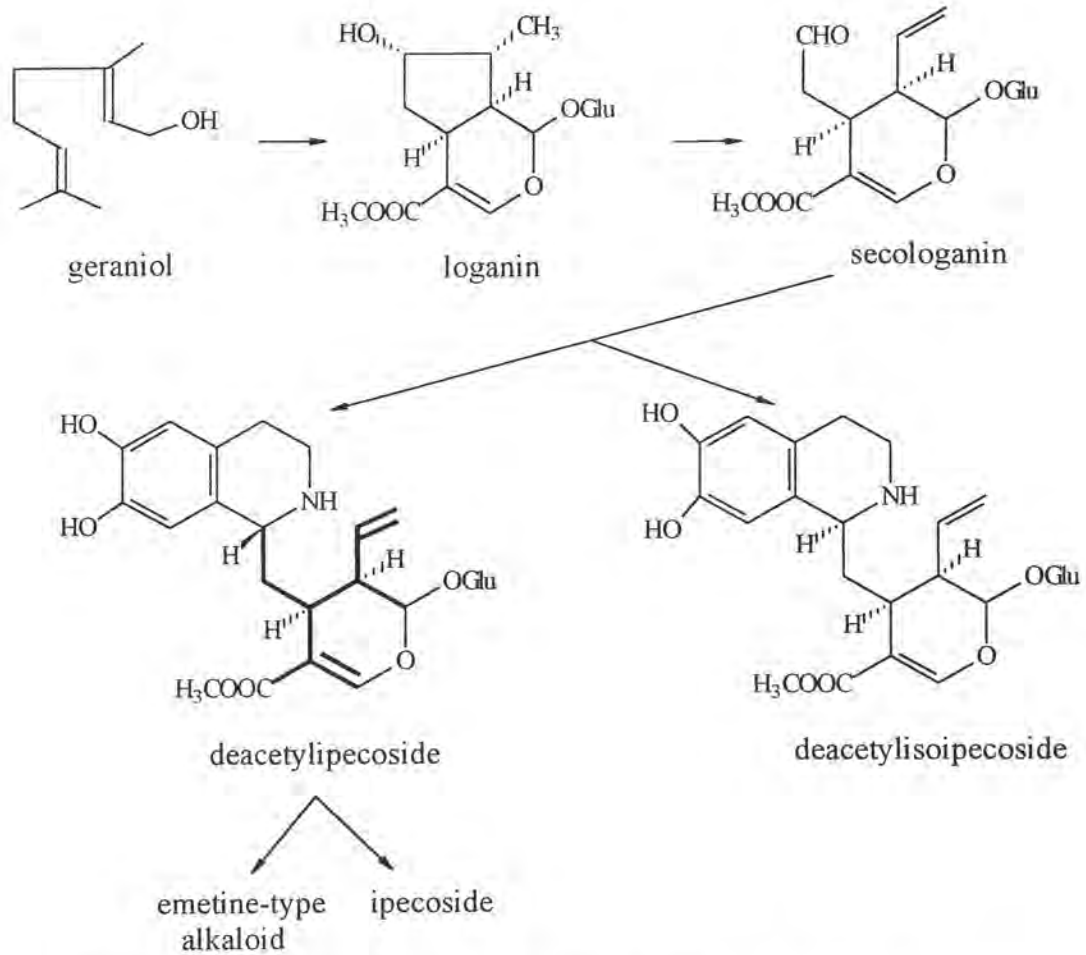
4. Biosynthesis of Tetrahydroisoquinoline Monoterpene Alkaloids and Glucosides

Using feeding experiments, Battersby and Gregory (1968) have firmly established that in *Cephaelis ipecacuanha,* geraniol is converted into loganin which can then act as a precursor for ipecoside and cephaeline. The C_9 unit of the ipecac alkaloids and the C_{10} unit of ipecoside are therefore of monoterpenoid origin (Scheme 1).



Scheme 1 Experimental biosynthesis of ipecoside and cephaeline.

Further studies by Battersby, Burnet, and Parson (1969) and Battersby and Parry (1971) have demonstrated that loganin is cleaved to secologanin which undergoes condensation with 3,4-dihydroxyphenylamine (dopamine) to form deacetylipecoside as a major product together with its isomer. It is deacetylipecoside and not deacetylisoipecoside which can be biologically converted into ipecoside, cephaeline and emetine. Since the alkaloids possess α-configuration, an inversion of configuration was postulated (Scheme 2).

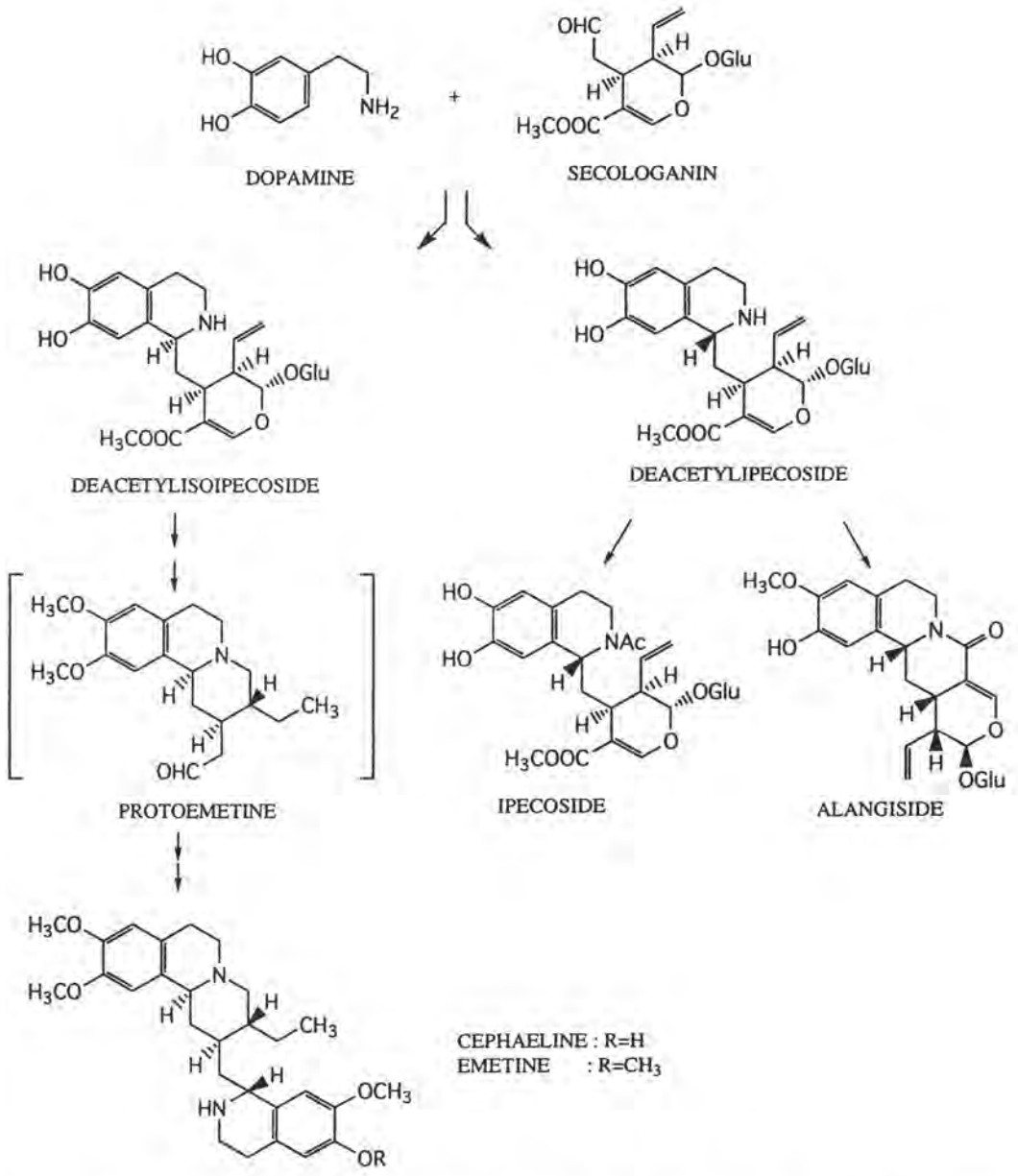


Scheme 2 Biosynthetic pathway of emetine-type alkaloid and ipecoside through deacetylipecoside.

Nagakura *et al.* (1978) established the role of secologanin as precursor for this type of compounds by feeding (7-^{3}H) secologanin into seedlings of *C. ipecacuanha* and apical shoot tips of *A. salviifolium*. Incorporation of labelled secologanin into alkaloids and glucosides was demonstrated. This clearly confirms earlier observation in *C. ipecacuanha* (Battersby and Parry, 1971). Furthermore it was found that the tritium atom at the C-7 of secologanin was retained during the formation of the metabolites both with α- and β-configuration.

The synthesis of (1-^{3}H, 3-^{14}C) -1α-deacetylisoipecoside and 1β-deacetylipecoside made it possible to reinvestigate the biosynthesis of the alkaloids and glucosides by precursor feeding experiment using *C. ipecacuanha* and *A. salviifolium* as experimental plants. Similar results were obtained in both plants, that is 1β-epimer deacetylipecoside was exclusively and specifically incorporated into the nitrogenous glucosides ipecoside in *C. ipecacuanha* and alangiside in *A. salviifolium*, both possessing the β-configuration. Incorporation into the alkaloids emetine and cephaline has not been observed. In contrast the epimer with 1α-configuration, deacetylisoipecoside was incorporated into the alkaloids with retention of configuration (Nagakura et al.,1978).

As shown in Scheme 3, the biosynthetic pathway suggested by Nagakura *et al.* (1978) involves the condensation of dopamine and secologanin with the formation of both deacetylipecoside and deacetylisoipecoside. While the β-epimer deacetylipecoside is acetylated in *C. ipecacuanha* to give ipecoside or lactamized in *A. salviifolium* to alangiside, the α-epimer deacetylisoipecoside is further transformed, most likely via protoemetine as intermediate, to several tetrahydroisoquinoline monoterpene alkaloids including cephaeline and emetine, all possessing α-configuration.



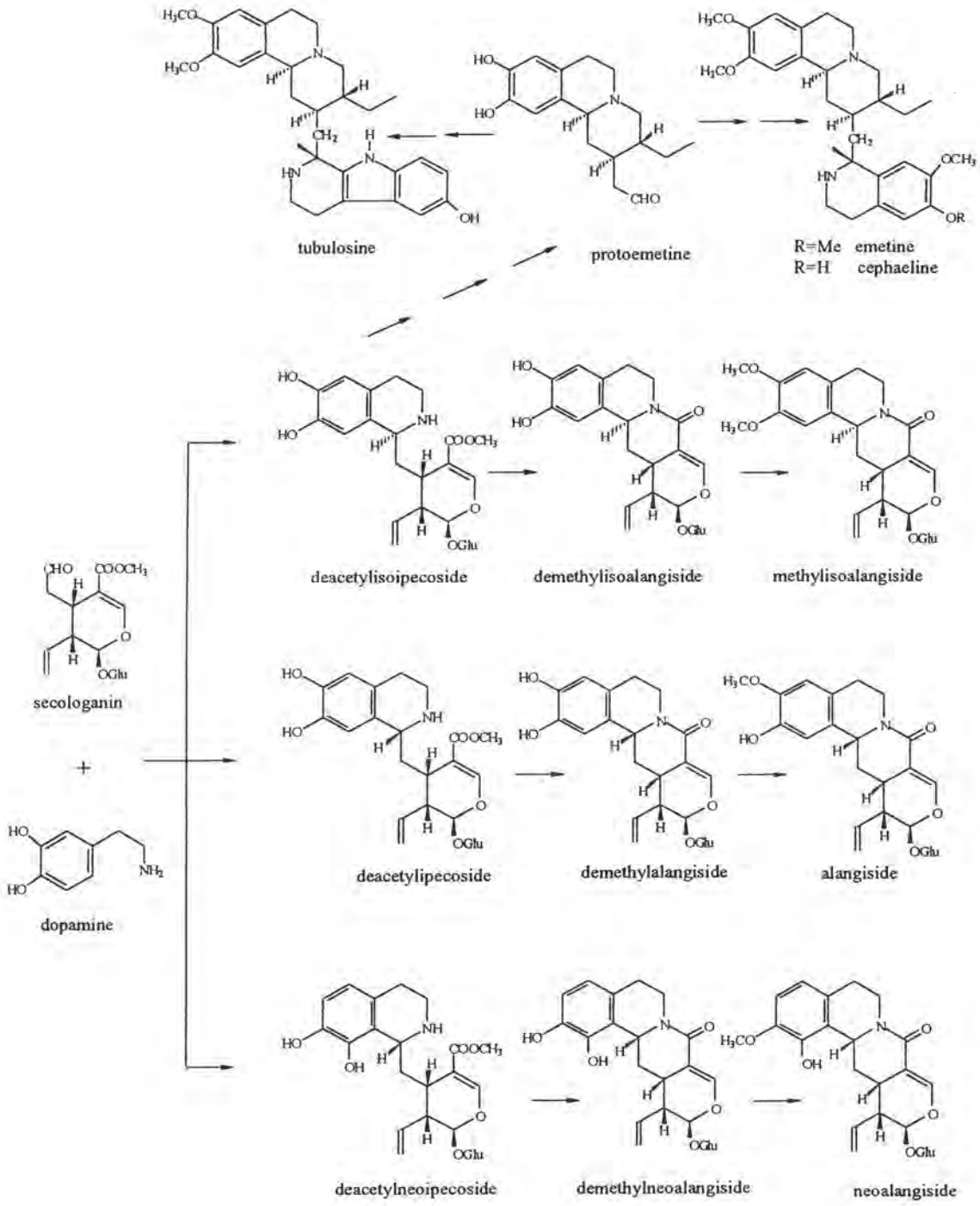
Scheme 3 Proposed biosynthetic sequence for the biosynthesis of cephaeline, emetine and the alkaloidal glucoside and alangiside.

Recently, a number of tetrahydroisoquinoline monoterpene glucosides have been isolated. Almost all of the glucosides possess β-H at the chiral center. However, reinvestigation of the fruit of *A. salviifolium* (Itoh, Tanahashi, and Nagakura 1995) reported the isolation of glucosides with the same stereochemistry as the alkaloids emetine and cepheline. This strongly supports the intermediacy of deacetylisoipecoside in the biosynthesis of the alkaloids. Deacetylisoipecoside could be transformed to alkaloids such as emetine, cephaeline and tubulosine or cyclised to demethylisoalangiside, which can be further transformed to other nitrogenous glucosides possessing α-configuration.

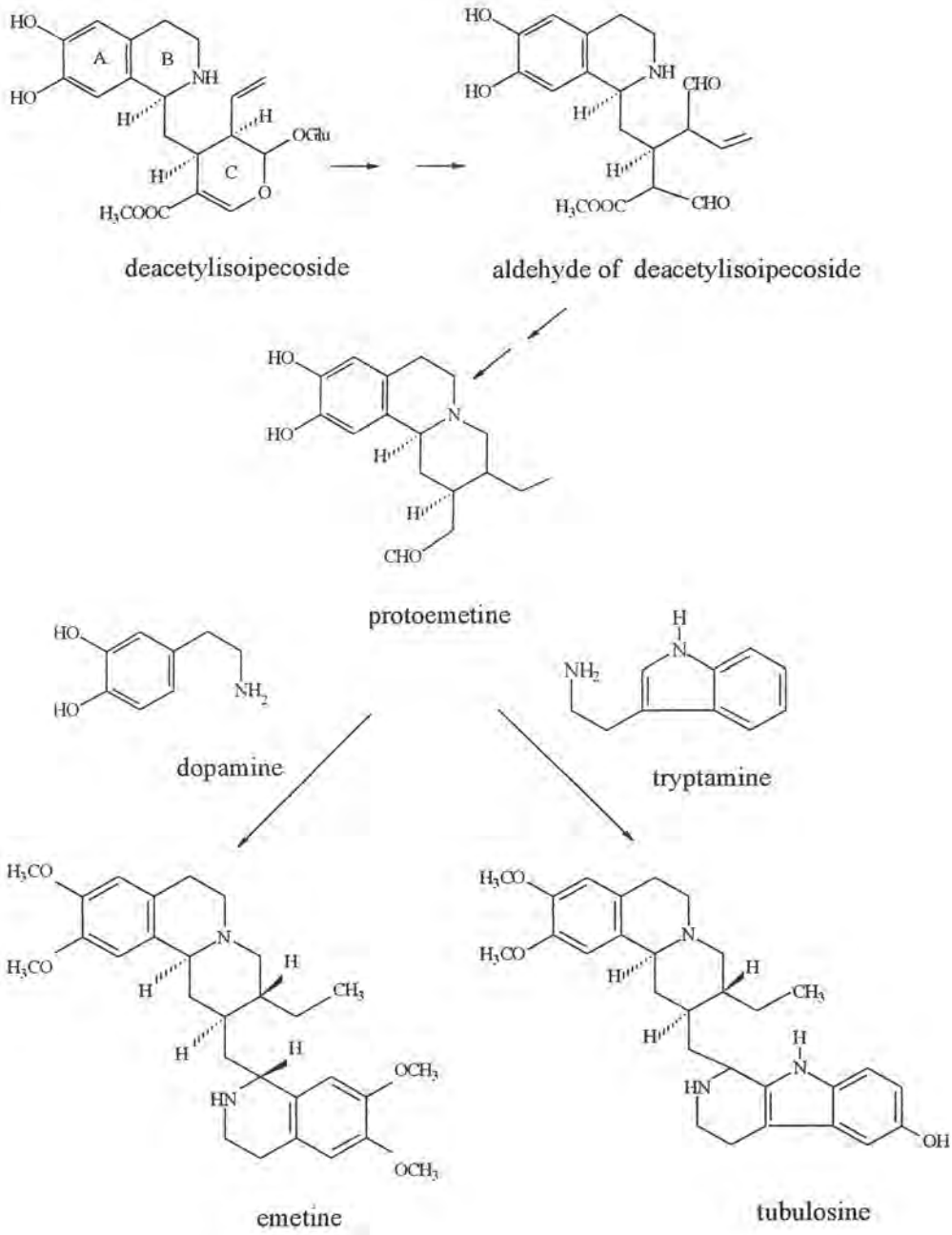
The glucosides with an unusually cyclised isoquinoline nucleus, demethylneoalangiside and neoalangiside, were also isolated. They are obviously biosynthesized *via* deacetylneoipecoside which was previously postulated as a precursor for neoipecoside in *C. ipecacuanha* (Itoh, Tanahashi, and Nagakura, 1991).

It could, therefore, be assumed that the condensation of dopamine and secologanin could give rise to 3 different compounds: deacetylipecoside, deacetylisoipecoside and deacetylneoipecoside (Scheme 4).

The β-carboline alkaloid tubulosine has also been demonstrated to derive from deacetylisoipecoside via protoemetine (Bhakuni, Jain, and Chaturvedi, 1983). Enzymic hydrolysis of deacetylisoipecoside and opening of ring C could yield the dialdehyde. Condensation of the appropriate aldehyde function with the secondary amine group, followed by reduction of the corresponding iminium intermediate could give rise to the protoemetine skeleton. It would then condense with a second molecule of dopamine to form emetine or with tryptamine (derived from tryptophan) to form β-carboline alkaloid tubulosine (Scheme 5).

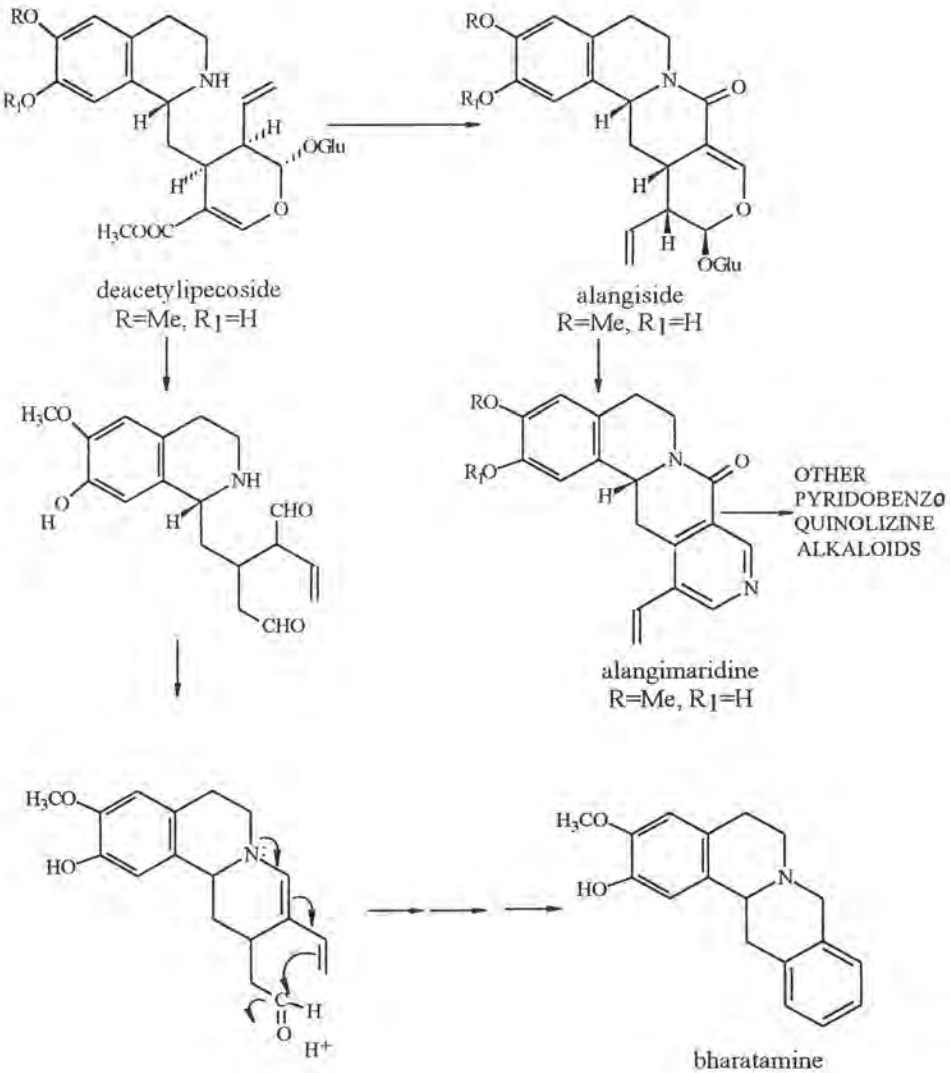


Scheme 4 Proposed biosynthetic sequence for the biosynthesis of the alkaloids and nitrogenous glucosides in *A. salviifolium.*



Scheme 5 Protoemetine acts as intermediate for emetine and tubulosine biosynthesis.

It has been proved that lactamisation of deacetylipecoside could yield alangiside (Nagakura *et al.*, 1978). Pakrashi *et al.* (1985) have proposed that hydrolysis of the glucosidic bond of alangiside followed by amination could afford alangimaridine. Biochemical transformation of alangimaridine could lead to alangimarine, alangimarinone, and dihydroalamarine. Isoalangimarine, isoalamarine and dihydroisoalamarine could then be derived from the isomeric glycoside, 3-*O*-demethyl-2-*O*-methylalangiside which has recently been isolated from *A. salviifolium* by Itoh *et al.* in 1993 (Scheme 6).



Scheme 6 A feasible biosynthetic route for the formation of pyridobenzoquinolizine alkaloids and bharatamine.

The genesis of bharatamine, the unique tetrahydroprotoberberine alkaloid found in *A. salviifolium*, could be conceivable through cyclisation of deacetylipecoside or its equivalents because its upper moiety emanates from tyrosine and its lower half is very probably of terpenoidal derivation (Pakrashi *et al.*, 1983).

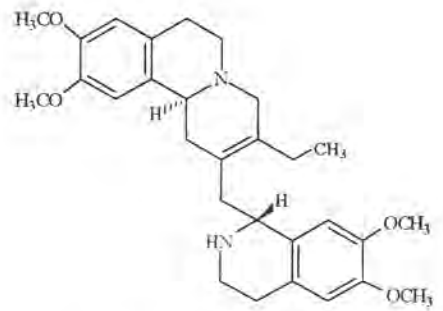
5. Biological Activities of Tetrahydroisoquinoline Monoterpene Alkaloids

Alangium salviifolium is a rich source of alkaloids structurally related to those isolated from *Cephaelis ipecacuanha*. It has been used in indigenous systems of medicine for the treatment of leprosy, syphylis, various skin disorders and dysentery. The bark is a good substituent for ipecac root in the treatment of amoebic dysentery and the active principle is emetine.

Emetine is considered to be one of the most potent amoebicidal agents and is used in the initial treatment of severe cases of acute amoebic dysentery (Gilman, Goodman, and Gilman, 1980). It is administered by injection of the hydrochloride salt or may be given orally as the bismuth iodide complex (Reynolds, 1989). The severe side effects include abdominal cramp, dizziness, fainting, vomiting, neuromuscular and cardiovascular effects and pain at the site of injection. Emetine is concentrated in the liver and is still employed as treatment for amoebic hepatitis either alone or with chloroquine. Emetine has also been used as a mild emetic, although this is not a common treatment. The emetine effect is local and is due to irritation of the gastrointestinal lining and musculature (Gilman, Goodman, and Gilman, 1980; Reynolds, 1989).

Emetine and some structurally related compounds have been tested for their *in vitro* activity against *Entamoeba histolytica* (NIH200) and cytotoxicity to guinea pig ear keratinocytes (GPK) (Keene *et al*, 1987). Emetine exhibited IC_{50} value of 0.07 μg/ml for amoebicidal activity and 0.02 μg/ml for GPK cytotoxicity. The ratio of GPK cytotoxicity to amoebicidal activity is 0.29. The less than 1 value of the ratio reflects the highly cytotoxic nature of the compound (Keene *et al.*, 1986). A synthetic

compound, 2,3-dehydroemetine, has been shown to be 2-3 times less active than



2,3-dehydroemetine

emetine in amoebicidal activity (IC_{50} 0.16 μg/ml) but its cytotoxicity to GPKs (IC_{50} 0.02μg/ml) is equal to that of emetine (Keene *et al*, 1987). Removal of the 9,10-dimethoxy substituents from emetine has been found to result in a 52-fold loss of amoebicidal activity (IC_{50} 3.7μg/ml) and 270-fold loss of cytotoxicity (IC_{50} 5.4 μg/ml) (Keene *et al*, 1987).

Tubulosine has the same overall stereochemistry as emetine but differs in having a hydroxy substituted tetrahydro-β-carboline moiety in the lower portion of the molecule. This change has been shown to result in a 23-fold loss of amoebicidal activity (IC_{50} 1.6 μg/ml) but retention of cytotoxicity (IC_{50} 0.04 μg/ml) (Keene *et al*, 1987).

Antitumor activity of emetine, cephaeline, tubulosine and *O*-methyltubulosine in rodent tumor has been reported as inactive in solid tumors but active against the L1210 and P388 leukemia cell lines (Brossi, 1985). Typical increases in life span (ILS) values have been found as follows: cephaeline, 30-60% in L1210 and 50% in P388; tubulosine, 30% in L1210 and 80% in P388; and *O*-methyltubulosine, 40-50% in L1210 and 60-80% in P388.

The cardiovascular effects and antiinflammatory activities have also been studied. The alkaloid AL-60 from the stembark has been found to exert a biphasic action on blood pressure of cats injected intravenously with either chloralose-urethane or sodium nembutal anesthesia. The action appeared to be dose-dependent, sustained and prolonged (Dutta and Pakrashi, 1962). The alkaloid AL-60 has later been found to be a mixture of psychotrine, cephaeline, and demethylcephaeline (Pakrashi and Achari,1970).

The effect of various concentrations of total alkaloid from the seeds has been investigated by intravenous injection of overnight fasted cats anasthetized with nembutal (Dutta and Pakrashi, 1962). The extract in low doses (0.1-1 mg/kg) showed a transient biphasic action on carotid blood pressure. Marked and prolonged hypotension was observed at a dose of between 1.6-8 mg/kg while with 16 mg/kg pressure was reduced to zero with complete inhibition of the respiration. After a few seconds the pressure again registered a gradual rise and was maintained at 30-40 mm below the normal level and normal respiration was restored.

A total alkaloid fraction isolated from the leaves has been screened for antiinflamatory activity against formalin-induced arthritis in albino rats, using betamethasone (5γ/100g/day) as the reference compound (Prasad, Bhattacharya and Das, 1966). Betamethasone reduced the foot volume, necrosis of the feet, and tenderness following formalin injection, while extracts from *A. salviifolium* leaves increased the inflammatory reaction during the first five days and then significantly reduce foot volume from the eleventh day. This is collaborated by the fact that the leaves are used in the indigenous systems of medicine to relieve rheumatic pains when applied in the form of a poultice.