CHAPTER I

HISTORICAL INTRODUCTION

Thailand is rich in natural resources espectially in plants. A tremendous number of plants furnish materials for medicine.Some of the plants are harmful or apparently of little or no values, while others seem to be useful. Plants are used in the form of crude drugs and the prescriptions were formulated in the form of multicomponent drugs. Little has been known about the active constituents of the crude drugs or their pharmacological activities. Attempts to have thorough study of local medicinal plants have been initiated. Many of local medicinal plants are official in pharmacopoeia, and are used in folk-medicine, including the plants in the family Convolvulaceae.

Plants in the genus *Erycibe* Roxb. belong to the family Convolvulaceae (Hooker and Jackson, 1885). It is widely distributed throughout India, China, Japan, Indochina and Australia. It is vigorous climber rarely encountered in cultivation. Propagation is usually from seed which has limited viability and must be sown fresh (Elliot and Jones,1984).

According to the Index Kewensis, the 75 species of this genus are shown below:-

Erycibe acutifolia Hayata

E. aenea Prain

Erycibe albida Prain

E. alkiflora Hallier

E. angulata Prain

E. angustifolia Hallier

E. bachmaensis Gagnep.

E. boniana Gagnep.

E. camptobotrya Miq. (*E. Princei*)

E. catonia Vahl.

E. citriniflora Griff. (*E.glomerata*)

E. clemensae V.Ooststr.

E. cochinchinensis Gagnep.

E. copelandii Elmer

E. coriacea Wall.

E. crassiuscula Gagnep.

E. cuprea Gagnep.

E. dubia Elmer

E. elliptilimba Merr.& Chun

E. erimatalia Roem & Schult

E. expansa Wall.

E. fecunda Kerr (*E. elliptilimba* Merr. & Chun)

E. ferruginosa Griff (*E. expansa* Wall.)

E. festiva Prain

E. floribunda Pilger

E. forbesii Prain

E. fragrans Wall.

E. glaucescens Wall.

E. glomerata Blume

E. glomerata Wall.

Erycibe griffithii Clarke

E. hainanensis Merrill

E. hallieriana Elmer

E. halolobula Kerr

E. hellwigii Prain

E. henryi Prain

E. hirsuta H.Hallier

E. induta Pilger

E. integripetala Merrill & Chu

E. javanica Kooler & Valeton

E. laevigata Wall.

E. lateraliflora Elmer

E. leucoxyloides King

E. longipes Gagnep.

E. macrophylla Hallier

E. magnifica Prain

E. maingayi Clarke

E. malaccensis Clarke

E. micrantha Hallier

E. nitidula Pilger

E. noei Kerr

E. obtusifolia Benth.

E. oligantha Merrill

E. paniculata Roxb.

E. papuana Wernham

E. parvifolia Hallier

E. pasaran Elmer

E. peguensis Prain

Erycibe poilanei Gagnep.

E. praecipua Prain

E. princei Wall.

E. rabelii Kerr

E. ramiflora Hallier

E. rheedii Blume (*E. paniculata* Roxb.)

E. sapotacea Hallier

E. sargentii Merrill

E. schlechteri Pilger

E. schmidtii Craib

E. semipilosa Gagnep.

E. sinii How

E. stapfiana Prain

E. subspicata Wall.

E. sumatrensis Merrill

E. terminaliflora Elmer

E. tomentosa Blume

E. wightiana J.Grah (*E. paniculata*)

(Hooker and Jackson, 1885 - 1960)

According to the Thai Plant Names of the Royal Forest Department, there are only nine species of *Erycibe* in Thailand (Smitinand, 1980) as follows:-

Erycibe citriniflora Griff. Kaakeet กากีด (Malay-Krabi); Kaa-tit กาติด (Krabi); Phriu พริ้ว (Chanthaburi).

E. elliptilimba Merr.& Chun, Chaang saan sap man ช้างสับมัน (Nakhon Si Thammarat); Naao duean haa หนาวเดือนห้า (Nong Khai); Horaa โหรา (Pattani).

Erycibe. expansa Wall., ex G. Don Yaan phao khuen ย่านเผาคืน (Songkhla);Lin suea ลิ้นเสือ (Ranong);Saaimaa สายม้า (Satun).

E. fecunda Kerr = *E. elliptilimba* Merr.& Chun

E. griffithii Clarke, Sae wan แซะวัน (Nakhon Si Thammarat, Surat Thani).

E. hololobula Kerr = *E. citriniflora* Griff.

E. noei Kerr, Dang ee thok ดังอีทก (Nakhon Ratchasima).

E. paniculata Roxb., Kaa-bang-duai กาบังดวย (Karen-Lampang),Buk Khruea บุกเครือ (Lampang).

E. rabilii Kerr = *E. elliptilimba* Merr.& Chun

Erycibe subspicata Wall. is a large woody climber; branchlets angular rusty - tomentose. Leaves elliptic,entire and coriaceous. Cymes peduncled subspicate; bracts inconspicuous. Sepals subequal,orbicular,coriaceous,adpressed to the base of the fruit.Corolla yellowish; tube shortly campanulate, densely hairy; limb plaited in bud, glabrous,lobes subbilobed,entire. Stamens on the corolla throat, filaments short; anthers ovate-lanceolate. Ovary globose,1-celled,4-ovuled; style 0, stigma large subglobose 2-lobed. Berry fleshy,1/2 - 2/3 inch elliptic oblong. Albumen scanty,irregularly intruded between the plicate fleshy cotyledons; radical inferior (Hooker,1885).

Several species of *Erycibe* were reported to be used as medicinal plants in many countries mostly in Asia. In Malay Peninsula, a decoction of *E. aenea* Prain is administered as

a protective medicine after parturition. The leaves of *Erycibe malaccensis* Clarke are poulticed and applied to sores, and to the head to treat headache (Perry,1980).

In Indonesia (Sumatra),the roots of *E. rheedii* Bl. (*E. angulata* Prain), after boiling in oil,are rubbed on the abdomen to hasten delivery in labour (Perry,1980).

In Philippines, the leaves of *E. terminiflora* Elm. are used as a remedy for skin rash (Perry, 1980).

The medicinal uses of the Convolvulaceous plants are well documented. The following pages contain a literature survey about the chemical constituents ,medicinal uses and poisonous properties of the plants in the family Convolvulaceae.

Chemical constituents

In 1961, the chemistry of some convolvulaceous resins were investigated by E.J. Shellard.

The resin obtained from Vera Cruz jalap,which was obtained from dried tubercles of *Exogonium purga* Hayne, had been examined chemically and the nature of the hydroxy acids, sugars and volatile acids determined. Convolvulin on alkaline hydrolysis yielded the volatile acids, tiglic, acetic, propionic, isobutyric, isovaleric, methylethylacetic and n-valeric together with a complex oligosaccharidic substance which consisted of two parts. One part, insoluble in ether (convolvulinic acid) consisted of ipurolic acid

(3,11 dihydroxymyristic acid) and convolvulinolic acid (a hydroxypentadecanoic acid) together with the sugars glucose, fucose and rhamnose. The other part, soluble in ether (purginic acid) consisted of ipurolic acid and a hydroxylauric acid with rhamnose only.

Convolvulinolic acid was shown to be a hydroxy pentadecanoic acid (Shellard, 1961).

The ether soluble portion (jalapin) yielded on hydrolysis tiglic, acetic, propionic, isobutyric,isovaleric, methylethylacetic and n-valeric acids, together with jalapinolic acid and the sugars glucose,fucose and rhamnose.

The resin obtained from Brazilian jalap had been examined chemically for hydroxy acids,sugars,and volatile acids. The ether insoluble portion is shown to yield on hydrolysis, two hydroxy acids, one of which was a dihydroxypalmitic acid, and probably 3,12 dihydroxypalmitic acid. The other was a trihydroxymyristic acid. The sugars were glucose and rhamnose and the volatile acids tiglic, acetic, trimethylacetic and n-valeric. The two hydroxy acids had been named operculinolic acid and braziliolic acid respectively (Shellard,1961).

The resins obtained from Tampico jalap, Ipomoea and Scammony root had been examined chemically and the nature of the hydroxy acids,sugars,and volatile acids ascertained.The ether insoluble and soluble portions of the resins from Ipomoea and Scammony root were identical quanlitative. The

volatile acids,in both cases,were tiglic,acetic,and n-valeric while the oligosaccharide acid corresponded to convolvulinic acid from Vera Cruz jalap,i.e.the hydroxy acids were ipurolic and convolvulinolic acids and the sugars were glucose,fucose and rhamnose. The oligosaccharide acid from the ether soluble portions yielded jalapinolic acid together with the same sugars. Tampico jalap resin (which was entirely soluble in ether) differed only by the absence of n-valeric acid from the volatile acids, jalapinolic acid and the sugars glucose,fucose and rhamnose also being present in the resin molecule (Shellard,1961).

In 1969, Matin et al., isolated a glycoside (paniculatin),$C_{30}H_{54}O_{13}$, from the tubers of *Ipomoea digitata* Linn (Matin et al.,1969).

Clavine and ergot alkaloids were separated by gel filtration on Sephadex LH20 from *Ipomoea violacea* L. in 1972 (Nikolin,1972).

In 1973,twenty one ergoline alkaloids were found in fourteen species of *Argyreia spp.* and two closely related genera; *Stictocardia tiliafolia* Haller f. and *Rivea corymbosa*. Hall. (Chao,1973).

In the same year,Jew-ming Chao and Der Marderosian did the chemical analysis on the seeds of *Argyreia nervosa* Bojer ,which contain the highest percentage of indole alkaloid constituents (0.5-0.9%) of the genera of the Convolvulaceae. A total of 19 indole alkaloids were identified by TLC and

paper chromatographic procedures. Nineteen alkaloids were identified to be: agroclavine (1), chanoclavine -I (2),and II(3), elymoclavine (4),ergine (5), ergometrine (6),ergometrinine,isoergine,lysergic acid (7),lysergol (8), lysergine, festuclavine, penniclavine (9), setoclavine (10), isosetoclavine (11), α-hydroxyethalamide, isolysergol, racemic chanoclavine-II, malliclavine, ,isolysergic acid, (Chao,Der Marderosian,1973).

A new glycoside,ipopurpuroside, has been isolated from *Ipomoea purpurea* Roth (Nikolin et al.,1978). Its structure consists of glucose, rhamnose and 6-deoxy-D-glycosidically linked to ricinoleic acid (12),in 1978.

(12) $(CH_3-(CH_2)_5CH(OH)CH_2-CH=CH(CH_2)_7COOH$

From 1979,the genus *Erycibe* began to be interested by the chinese scientists. Baogongteng A (13)($C_9H_{15}O_3N$) and B were isolated from *Erycibe obtusifolia* Benth (Tianrong,1979).

Two years later,the chemical structure of baogongteng A, a new miotic agent isolated from *E. obtusifolia* Benth, was determined by the analysis of proton and carbon-13 NMR and high resolution mass spectral data of baogongteng A and its derivatives in 1981. Consequently, the chemical structure of baogongteng A can be concluded as 2β-hydroxy-6β-acetoxy-nortropane with a levorotation [[a]D^{28} = -7.21].(Tianrong et al.,1981).

Also in 1981, scopoletin (14) and scopolin (15) were

isolated from the stem of *Erycibe. obtusifolia* Benth (Ye, Hui,Zhen,1981).

In 1984, hexadecanol (29.42%), octadecanol (34.54%), monodecanol(10.03%), tetracosanol (18.6%) and hexacosanol (7.38%). The triterpenoids: α-amyrin (37.5%) and β-amyrin (57.5%).The sterol: β-sitosterol(86.86%), campesterol(7.77%) and stigmasterol(5.57%).Fatty acids : palmitic (37.33%) stearic(4.14%), oleic(34.37%),linoleic(14.81%), and linolenic(9.33%) were reported to be fractionated from the petrol extract of *Convolvulus lavatus* (El-Nasr et al.,1984).

Two years later,Chowdhary reported that the benzene extracts of *Convolvulus microphyllus* Sieb. yielded n-tetracontane,n-octacosanol and ß-sitosterol (Chowdhary,1986).

In 1986, Chen et al., reported that baogongteng B and baogongteng C (16)from *Erycibe obtusifolia* Benth. were identified as scopoletin and 2ß,6ß- dihydroxydemethyltropane, respectively.NMR and mass spectrometry were used for the identification (Chen et al.,1986).

Also in 1986,L. Yang et al.isolated five compounds from the stem of *E. elliptilimba* Merr.& Chun. By spectral analysis and chemical reactions four of them had been identified as scopoletin,scopolin,baogongten A and baogongten C. The fifth one,2ß,7ß-dihydroxynortropane,was a new alkaloid named erycibelline (17) (Yang,Tianrong and Zenai,1986).

In 1987,seven known alkaloids (convolvine (18), convo-

lamine (19), phyllalbine (20), convolidine, confoline, convoline,and subhirsine) and the new tropane alkaloids convosine were isolated from the root of *Convolvulus subhirsutum* Regel & Schmalh.by Aripova (Aripova, 1987).

In the same year,Aripova isolated Convolvidine,which is a native alkaloid of *Convolvulus spp.*, from *C. subhirsutum* Regel & Schmalh.(Aripova,1987).

Pharmacological actions

From 1938 - 1940, the pharmocological reports of Convolvulaceous plants were concentrated on the resin part.

In 1938,the convolvulin and jalapin,isolated from the resin part of *Exogonium purga* Hayne, were proved to have an ability to produce lysis of pneumococcus (Valette and Liber, 1938).

In 1940,Jaretzky reported that the resin contents ranged from 0.6-6% of various species of Convolvulaceae was proved to have the carthartic activity. The carthartic activity of the various resins did not differ markedly from that of scammony resin.(Jaretzky and Risse,1940).

In 1969,paniculatin was proved to elevate the blood pressure, show a stimulant effect on myocardium and respiration, a vasoconstrictor and bronchoconstrictor effect, a spasmogenic effect on smooth muscles of gut ,and also an oxytocic activity (Matin et al.,1969).

In 1970, S.Wasuwat reported that there was an active principle (IPA) which was extracted with ether from the water distillate of the dry ground leaves of the *Ipomoea pes-caprae* Roth. IPA was antagonistic to jelly-fish poison and was also mildly antihistaminic (Wasuwat,1970).

In 1973,*Argyreia nervosa* Bojer (Hawaiian Baby Wood Rose) is readily available from the southern parts of Califonia and Florida as well as from Hawaii.The availability of this plant in USA. has led to use by juveniles who seek hallucinatory experiences through ingestion of the seeds. Ylin and Watson reported that each gram of seeds contains approximately 3 mg of total alkaloids of which 0.36 mg is represented to one of the psychoactive constituents, ergine. Several investigators showed wider distribution of the ergoline-type alkaloids in the Convolvulaceae (morning-glory family). These current include the genera *Ipomoea, Argyreia, Cuscuta* and *Stictocordia* (Chao & Der Marderosian,1973).

In 1979, the extraction of *Erycibe obtusifolia* Benth which showed myosis in rabbits and the main constituent was proved to be baogongteng A. Baogongteng A was shown to have the pupil constrictor activity and used for treatment of glaucoma (Yao,Tian-pong,1979).

In 1981, scopoletin and scopolin was proved to exhibit the antiinflammatory and analgesic actions by the scientists in Shianghai (Ye, hui, Zhen,1981).

Also in 1981,a new miotic *Erycibe* alkaloid was isolat-

ed from *E. obtusifolia* Benth. The structure was determined to be baogongteng A. It was effective in treatment of glaucoma (Fang et al.,1981).

Baogongteng A was used in treatment of glaucoma and the miotic activity was ~ 100-fold greater than that of pilocarpine (Shanghai Second Medical College,1981).

Four years later,the pharmacological experiment on Scopoletin could be achieved. Scopoletin purified from the stem of *E. obtusifolia* Benth showed antiinflammatory effects. It inhibited histamine or ovalbumin-induced acute arthritic swelling and formaldehyde-induced subacute arthritic swelling in rats;it also reduced xylene-induced permeability increased in capillary blood vessels of mice but showed no inhibitory effect on leukocyte migration. Scopoletin also inhibited rate connective tissue multiplication induced by cotton ball. It also inhibited histamin-induced contraction of isolated ileum of guinea pig and prostaglandin synthetase activity. Acute toxicity (IV.injection) was > 100 mg/40 ml/kg in mice (Zhu et al.,1984).

In 1986, scopoletin and scopolin can be used as an antirheumatic and an analgesic; baogongteng A can be used as a miotic. For the first time baogongteng C was obtained as a pure colourless oil. Although baogongteng C showed no obvious biological activity,but its O-diacetyl derivative was a strong miotic (Yang,Tianrong and Zenai,1986).

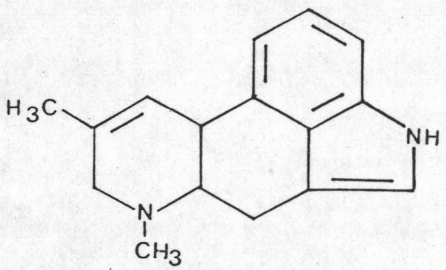
The plant used in this investigation was identified as

Erycibe subspicata Wall. known in Thai as Nao Duan Haa.

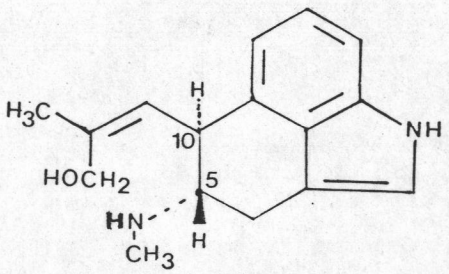
In Thailand,(Nong Khai province) the plant has been used as an analgesic and antipyretic. Side effect of the tunnel vision has also been observed (Pongboonrod,1950).

It is the purpose of this investigation to purify and identify the chemical constituents of *E. subspicata* Wall.and to prove the nature of the structures.Moreover, the chemical characterization of this plant may provide valuable information in the field of chemotaxonomy.

The following three pages contained the chemical structure of the compounds mention in the introductory part.

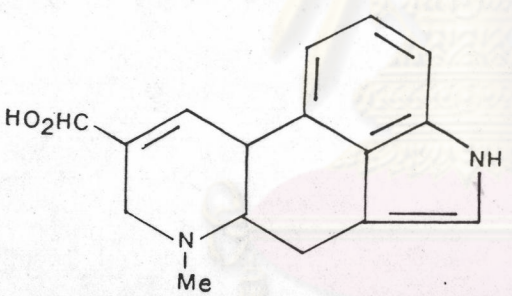


Agroclavine (1)

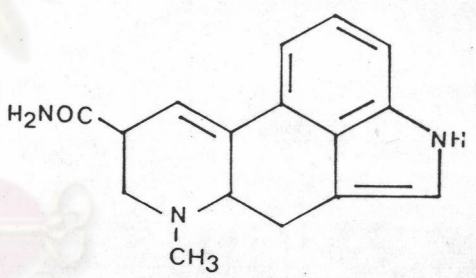


Chanoclavine-I (2)

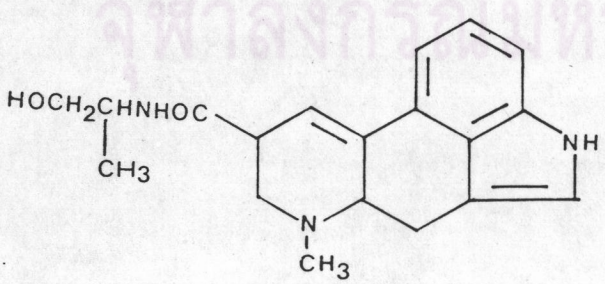
Chanoclavine II = Epimer at position 10 (3)



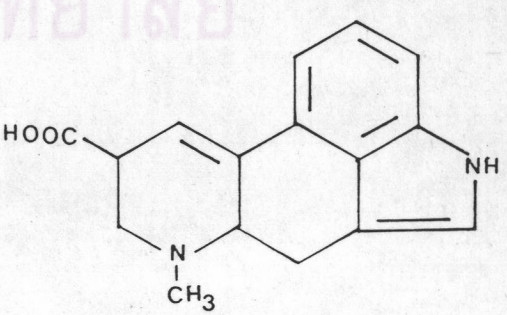
Elymoclavine (4)



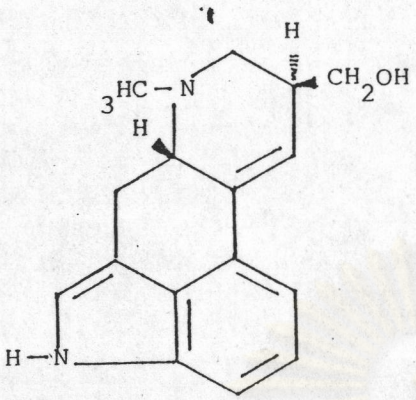
Ergine (5)



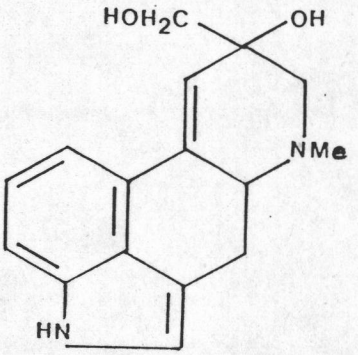
Ergometrine (6)



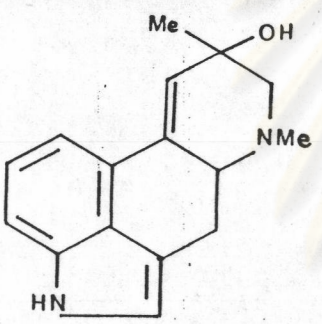
Lysergic acid (7)



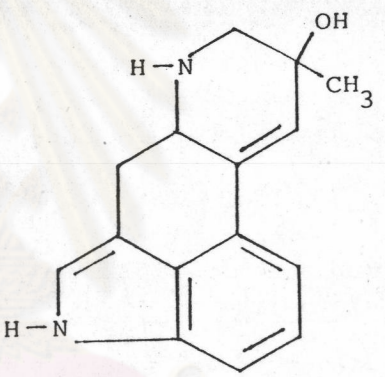
Lysergol (8)



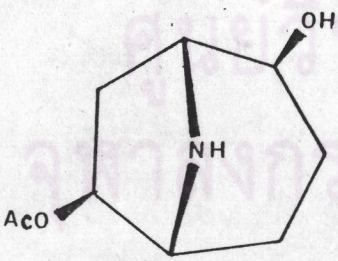
Penniclavine (9)



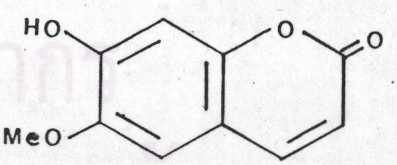
Setoclavine (10)



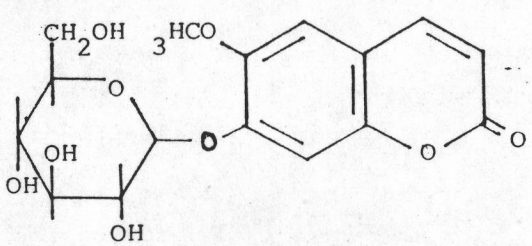
Isosetoclavine (11)



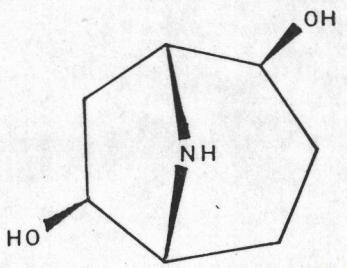
Baogongteng A (13)



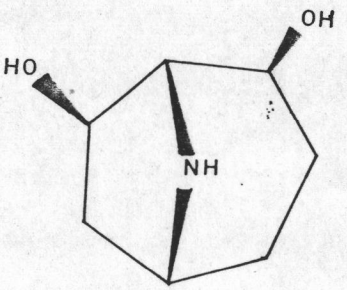
Scopoletin (14)



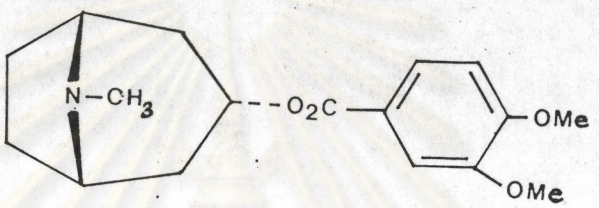
Scopolin (15)



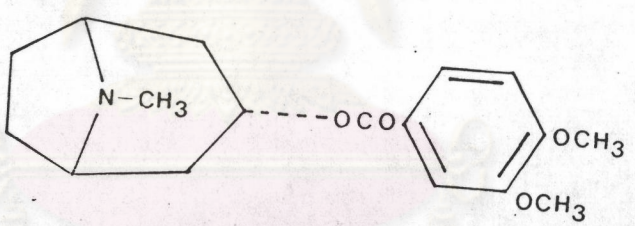
Baogongteng C (16)



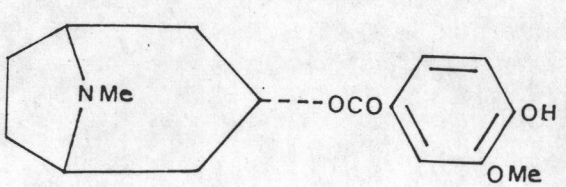
Erycibelline (17)



Convolvine (18)



Convolamine (19)



Phyllalbine (20)