ISOQUINOLINE ALKALOIDS

PHENETHYLISOQUINOLINES
COLCHICUM ALKALOIDS

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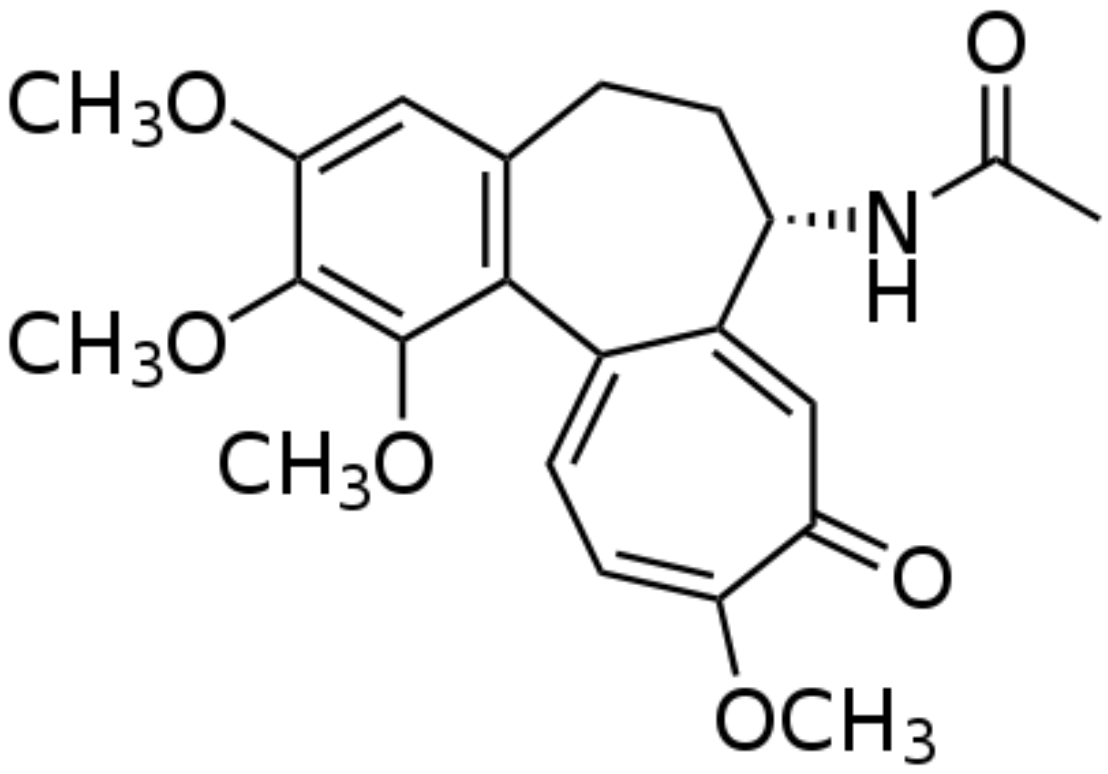
Autumn crocus, acı çiğdem
Colchicum autumnale L., Liliaceae
Colchici semen/ cormus

An industrial source of colchicine, used to the specially cure the acute attack of gout, especially the seeds of the autumn crocus or meadow saffron, namely colchicum seeds were the subject of monographs in some pharmacopoeias.

The autumn crocus , known to the Greeks for its toxicity, was used in the Byzantine empire since the fifth century to treat gout. It appeared at the end of eighteenth century in the form of a tincture “ two parts of roots (cormus) in four parts of rectified wine. Colchicine was crystallized by chemists Laborde and Houdé in 1884. The formula was established by Dewar in 1945.



Colchicine

Colchicum autumnale is a herbaceous plant of the damp meadows of Europe. It is thought to have originated on the eastern banks of the Black Sea (from Colchide, which is a part of Georgia today). It doesn't grow in Turkey and Cyprus.

Also known as meadow saffron, it is characterized by a peculiar vegetative cycle. In october, the corm grows a group of two to six trimerous flowers with a purplish-pink perianth, which blossoms in the six lobes spread out at the apex of a very long and narrow tube (10-15 cm) , with the ovary remaining at the level of the corm, underground., following the winter resting season, oblong and linear leaves appear.

At the same time, the fertilized ovary of fruit emerges from the ground and completes its maturation : it is a small septicidal three-lobed, three-celled capsule vaguely reminiscent of a walnut (hence the risk of intoxication of young children). The species is perennial : each year , a replacement corm develops at the expence of the parent.

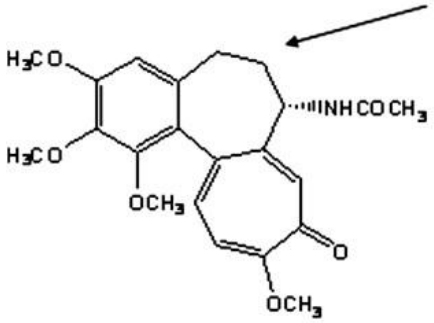
The drug : *Colchicum* seeds are small : their diameters does not exceed 3 mm. They are globulous and particularly hard.

Sources of colchicine : The drug supply essentially comes from harvesting wild plant (in central and eastern Europe).

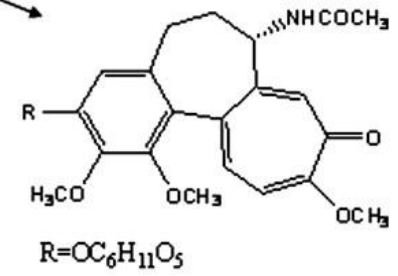
Colchicine can also be extracted from an Indian Liliaceae, *Gloriosa superba* L., which is reported to contain , on average 9% colchicine.

Gloriosa superba

Chemical composition : The contrentration of total alkaloids is variable, from 0.3 to 1.2%. About 20 alkaloid-type compounds have been isolated from the drug. Most of them occur only in small quantities. Almost of them are amides that are weakly or not basic Some occur as glycosides (colchicoside 0.4%)

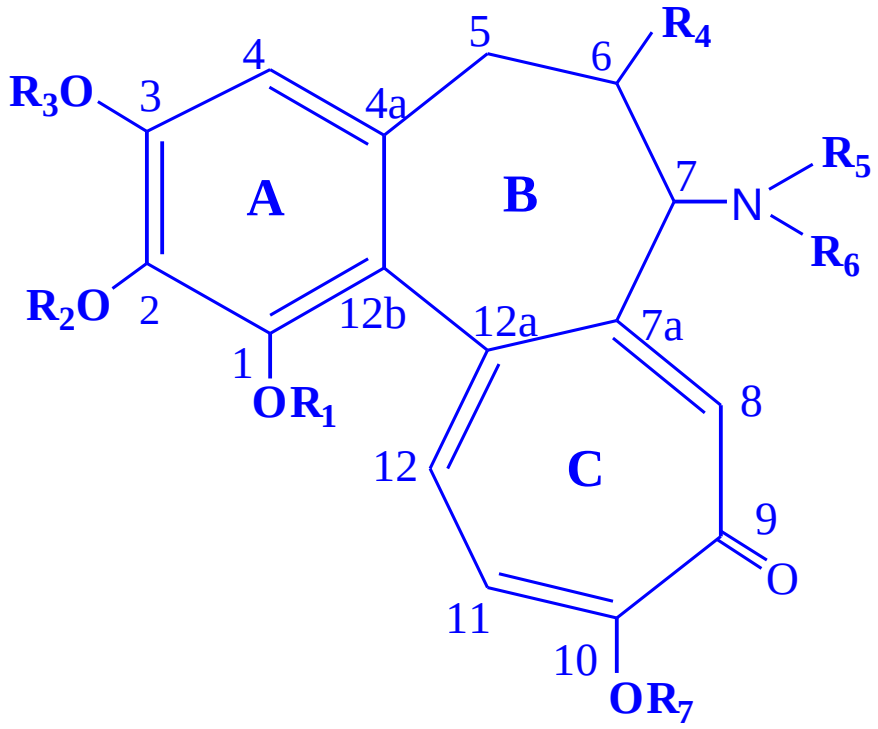


Colchicine

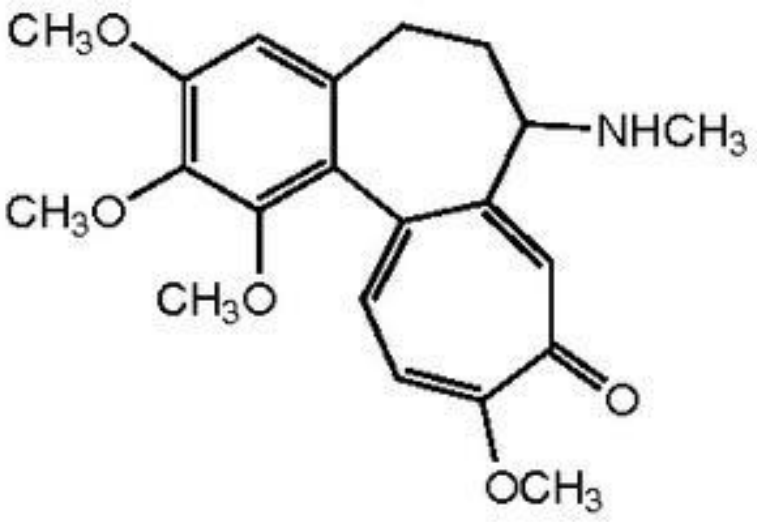


Colchicoside

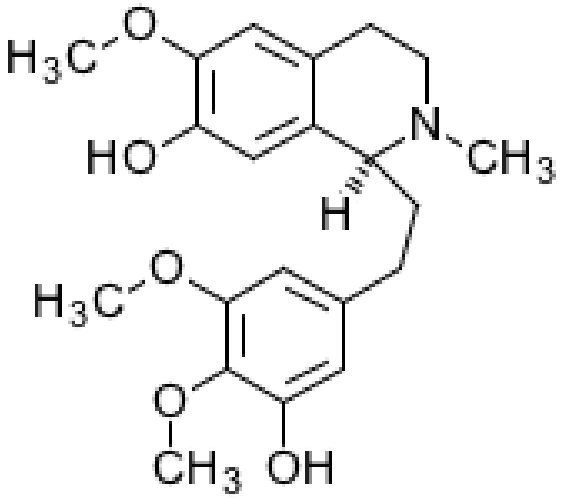
Structurally they have in common a tropolone nucleus (tropolone alkaloids), in other words a tricyclic structure comprising two heptagonal rings; their nitrogen atom is exocyclic.



The other important alkaloids are demecolcine and autumnaline.

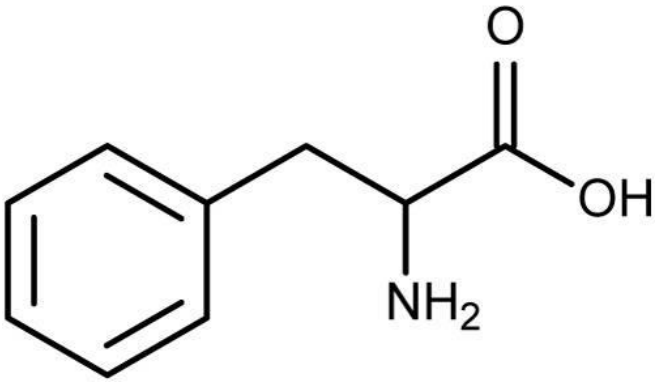


demecolcine

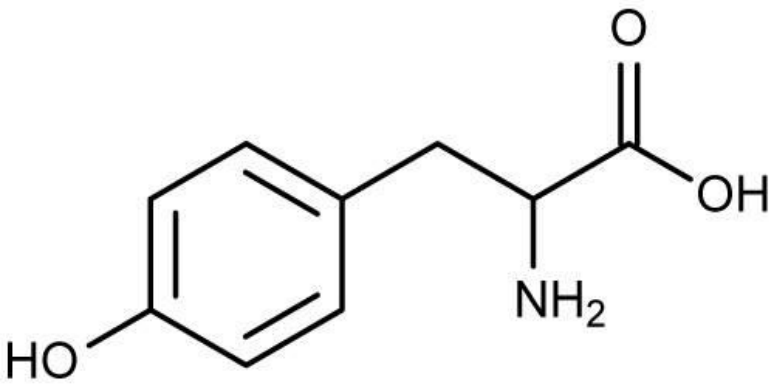


autumnaline

Biosynthetic origin : The biosynthesis of these alkaloids are not obvious. But of course phenylalanine and tyrosine are incorporated



phenylalanine



tyrosine

Pharmacological activity : The autumn crocus is very toxic : ingested, it (the corms) kills by suffocation, like the mushrooms. The ingestion of all part of the plant causes swallowing difficulties, abdominal pains with diarrhea, muscle cramps, hypotension, and respiratory difficulties. In case of serious intoxication, death occurs by respiratory arrest or cardiovascular collapse, several days after intoxication.

Colchicine blocks mitosis at the metaphase stage by preventing the formation of the mitotic spindle. In vegetable cells, it inhibits the separation of the two batches of doughter chromosomes, which remain attached by their common centromeres, and tetraploid form as a result; agricultural research sometimes uses colchicine to create polyploid strains. The cellular toxicity of colchicine is too great, so it cannot be used as an antitumor agent.

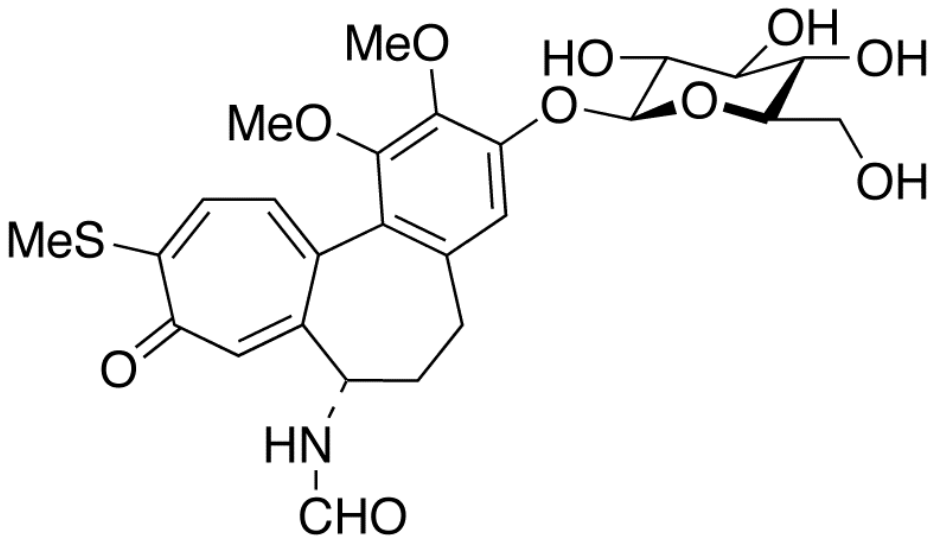
Anti-inflammatory Properties : Colchicine is an anti-inflammatory spesific to the microcrystalline arthritis caused by sodium urate crystals : it is particularly efficacious in the treatment of the acute attack of gout.

Colchicine Toxicity : The toxic dose in humans is around 10 mg ; the ingestion of doses greater than 40 mg is always fatal within three days of the ingestion of the alkaloid. After a latency of three to five hours , the intoxicated patient experiences abdominal pains, hypokalemia, and metabolic acidosis. Death generally occurs after one week.

Uses : *Colchicum* seeds and corm are used for the extraction of colchicine. Colchicine is prescribed orally and indicated in the treatment of gout : it is efficacious in over 95% cases if it is taken as soon as the first symptoms are experienced. The guidelines for prescription are as follows : 3 mg on the first day (in three single doses), 2 mg in two doses on the second and third day, 1 mg on the following days up to a maximum dose of 10 mg. Other indications of colchicine are : to prevent the acute attack of gout in cronic patients, Behçet's disease (1 mg/day for these other indications)

Contraindicated in the case of renal insuffiency, severe hepatic incuffiency, and pregnancy, colchicine has side effects, particularly gastrointestinal problems, nausea, vomiting, and especially diarrhea.

Derivative related to colchicine : Thiocolchicoside : This compound prepared by semisynthesis is the sulfur-containing analog of the naturally-occuring glycosidic alkaloid namely colchicoside. Pharmacologically it is said to be a muscle relaxant. It is not a curare and it acts through a central effect on the spastic hypertony of the skletal muscle.



About 40 *Colchicum* species grow wildly in Turkey, most of them are autumn-flowering species. Especially *Colchicum speciosum* growing in the north-aestern part of Turkey and rich in colchicine,can be used instead of *C.autumnale*.

Colchicum speciosum

Colchicum baytopiorum

Colchicum bivonae

Colchicum cilicicum

Colchicum umbrosum

Colchicum bornmuelleri

Colchicum variegatum

Merendera sp.

Colchicum troodi ***Colchicum pusillum***

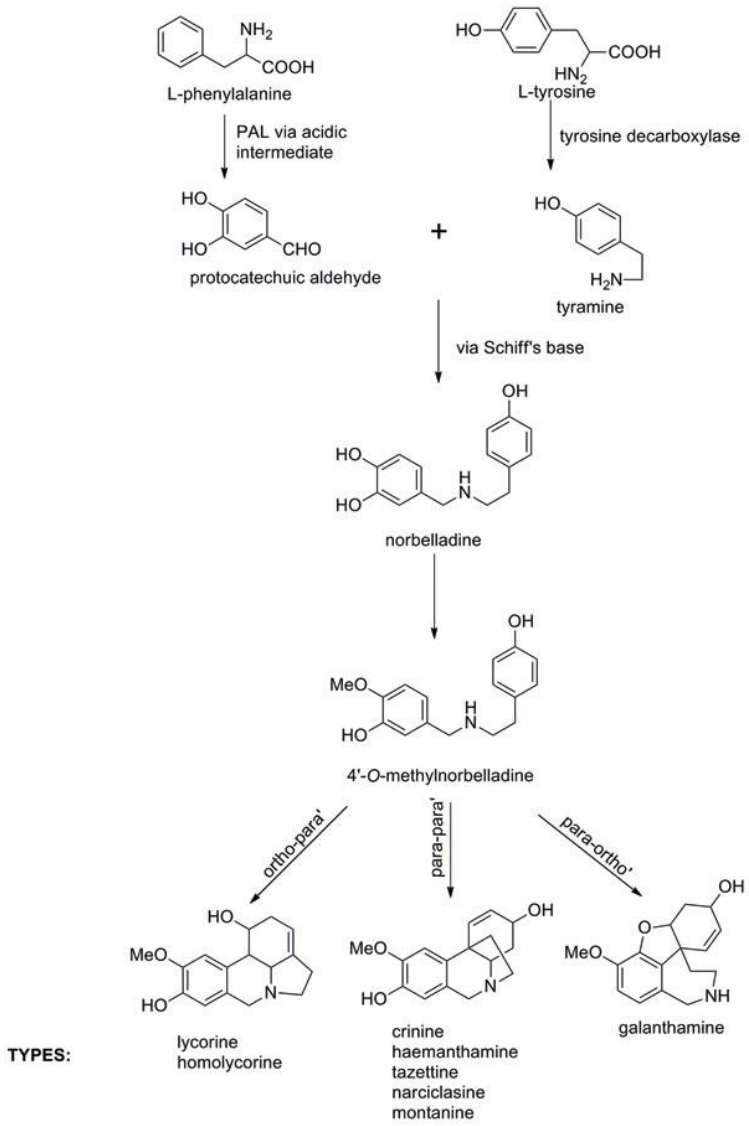
Grow in Cyprus

Isoquinoline alkaloids

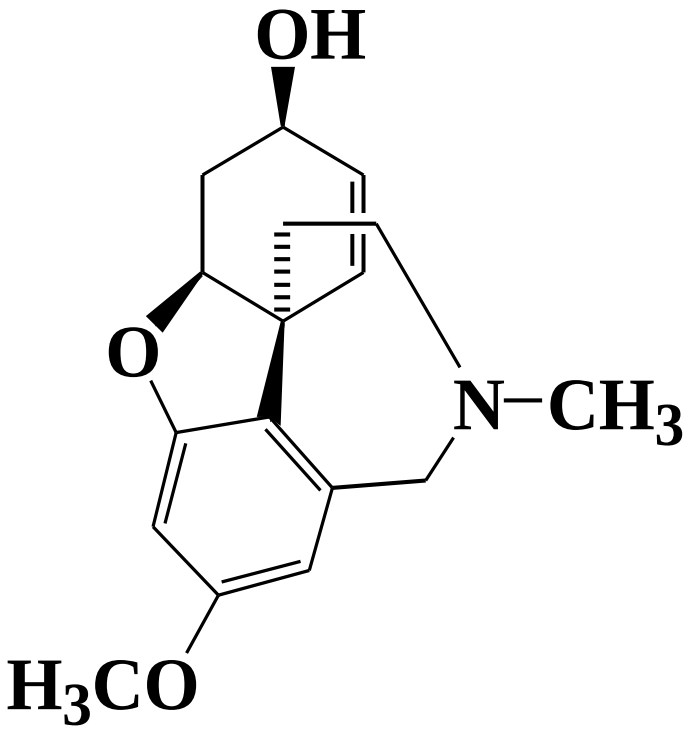
Alkaloids of the Amaryllidaceae

These alkaloids are not used in therapeutics, nor are the different species that contain them. Especially very beautiful park and garden plants, *Galanthus, Leukojum* and *Narcissus* species contain these alkaloids, and most of the alkaloids are very toxic. Galanthamine is the most important alkaloid among them. They are also named as fenanthridine alkaloids

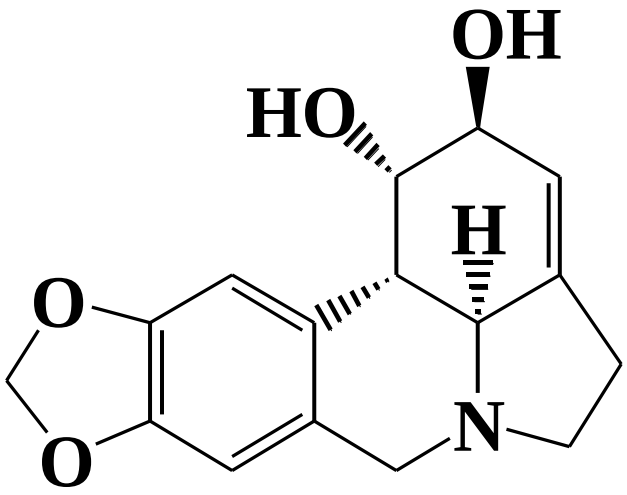
The biosynthesis of these alkaloids is rather complex. The important amino acids are again phenylalanine and tyrosine.


L-phenylalanine
L-tyrosine
PAL via acidic intermediate
tyrosine decarboxylase
protocatechuic aldehyde
tyramine
via Schiff's base
norbelladine
4'-O-methylnorbelladine
ortho-para'
para-para'
para-ortho'
lycorine
homolycorine
crinine
haemanthamine
tazettine
narciclasine
montanine
galanthamine

TYPES:



GALANTHAMINE



LYCORINE

Serious intoxications are rare. The ingestion of the bulbs, like that of leaves, which can be mistaken for leek, rapidly induces nausea and vomiting followed by profuse diarrhea. The symptoms normally subside rapidly. *Narcissus* also cause cutaneous reactions (dermatitis). The most common toxic principle is lycorine, a cholin esterase inhibitor, which at low doses, causes salivation, vomiting, diarrhea, and at higher doses paralysis and collapse. Lycorine and related compounds are also cytotoxic. Lyco betain acetate, produced by oxidation of lycorine, are sometimes used in China for ovarian cancer.

Galanthamine : It was isolated from various snowdrops (*Galanthus*) and found in several genera of the same family (*Narcissus, Leukojum*). This alkaloid can be extracted from *Leukojum aestivum* , in which it represents up to 2% of the dry weight. It can also be prepared by synthesis.

Galanthamine is an acetylcolinesterase inhibitor. Injected into animals (or humans) previously curarized by alcuronium or gallamine, it ends the neuromuscular block. It is less active than neositigmine or pyridostigmine and it induces a few muscarine-type side effects (hypersalivation, nausea, bradycardia).

It is thought that galanthamine could, by inhibiting acetylcolinesterase , can be used in Alzheimer's disease an also in polio. A lot of experiments show that the compound is well tolerated and is not hepatotoxic.

Galanthus nivalis

kardelen

Leucojum aestivum

Göl zambağı

Narcissus tazetta

nergis

Grows also in Cyprus

Isoquinoline Alkaloids

Monoterpenoid Isoquinolines

Ipecacuanha (Ipecacuanhae radix)

Cephaelis sp. (Rubiaceae)

Cephaelis ipecacuanha

İpeka kökü

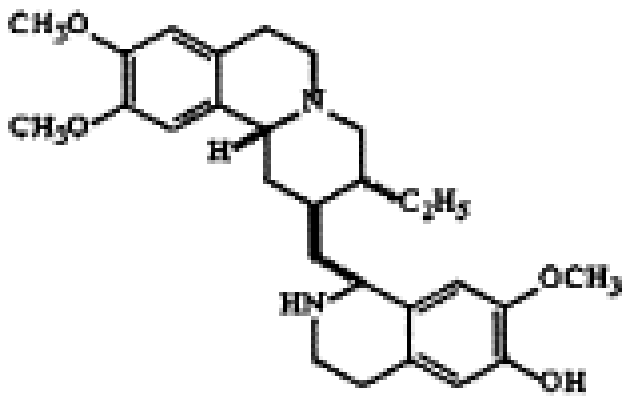
The latest edition of the European Pharmacopoeia provides the following definiton for this drog : “Ipecacuanha consists of the fragmented and dried underground organs of *Cephaelis ipecacuanha*, Matto Grosso ipecacuanha or of *Cephaelis acuminata*, known as Costa Rica ipecauanha, or of a mixture of both species.

The term ipecac is of Native American origin. The drug used by Native Americans for its emetic and antidysenteric properties, was introduced in Europe at the end of the sixteenth century.

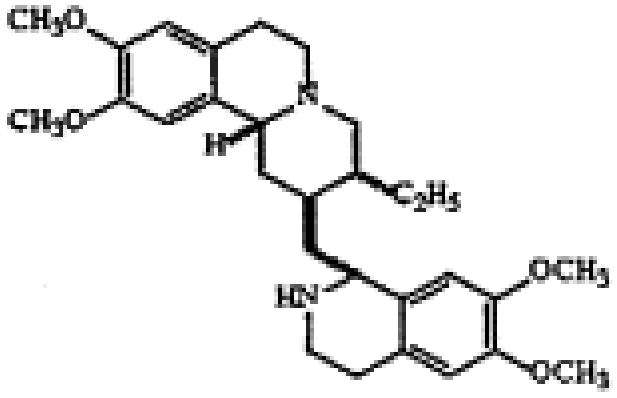
Cephaelis acuminata

The plants : Ipecacuanhas are small perennial subshrubs (20-40 cm) bearing opposite decussate leaves with laciniate stipules between te petioles, and with white flowers gathered into compact cymes. Rio or Brazilian Ipecac (from Matto Grosso) grows wild in the damp forests of southern Brazil and of Bolivia : after uprooting the plant, the majority of the roots crops. The roots are dried (sun, fire) and cut before exportation. Cultivation has been attempted in Brazil and other tropical areas (Malaysia, Burma, India), but only with limited sucsess (3-4 year delay before harvest). Cartagena, Nicaragua or Panama Ipecac, as it names indicate, essencially comes from Central Amerika (Costa Rica).

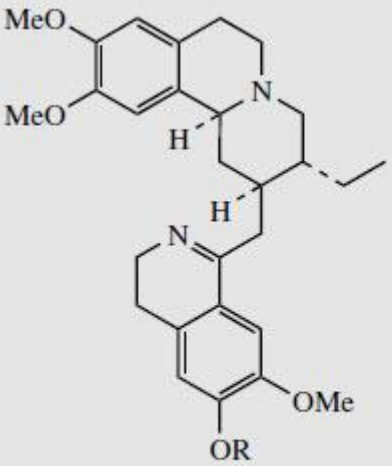
Chemical composition : The active principles localized in the cortex of the root and rhizome , are isoquinoline alkaloids at a concentration ranging from 2 or 2.5% for Rio Ipecac, or from 2 to 3.5% for Cartagena Ipecac. Emetine is by far the major constituent of Rio Ipecac (60-70% of the total alkaloids), but it repsesents only 30 to 50% of the total alkaloids of Cartagena Ipecac. The other alkaloids have similar structures (cephaeline, psychotrine, o-methylpsychotrine). The drugs also contain a large amount of starch (30-40%), an allergenic glycoprotein, and monoterpenoid isoquinoline glycosides such as ipecoside.



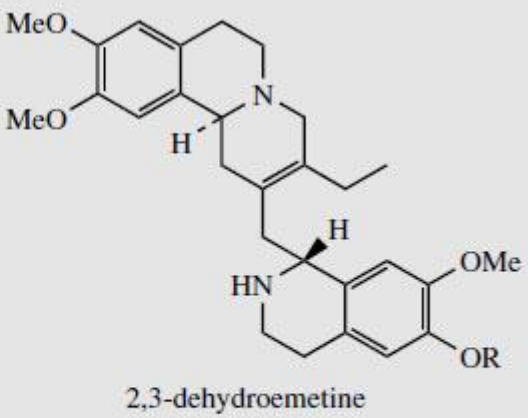
Cephaeline



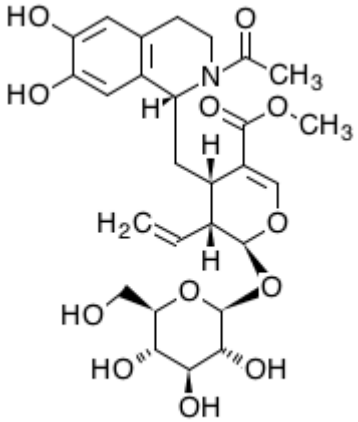
Emetine



R = Me, *O*-methylpsychotrine
R = H, psychotrine

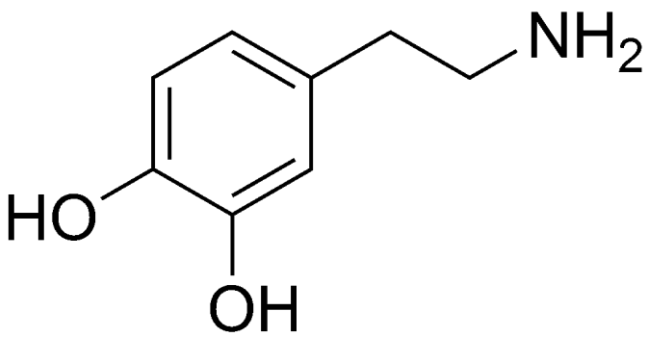


2,3-dehydroemetine

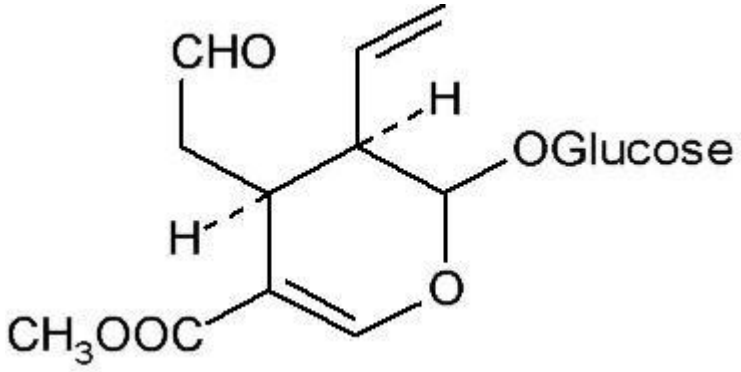


ipecoside

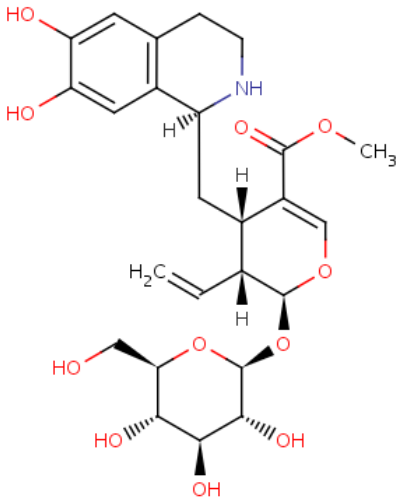
Biosynthetic Origin of the Ipecac Alkaloids : These monoterpenoid isoquinoline alkaloids are rare : they are found in *Cephaelis* and some other Rubiaceae and also Alangiaceae, Icacinaceae. Their pathway of formation resembles that of the monoterpenoid indole alkaloids characteristic of the Apocynaceae, Loganiaceae, and also of many Rubiaceae
(*Corinanthe, Pausynistalia*). The first step in the process in the condensation of the molecule of dopamine with a seco-iridoid, secologanin, to form desacetylisoipecoside.



dopamine

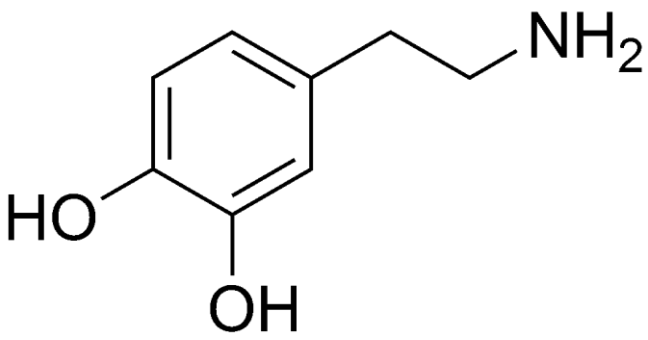


secologanin

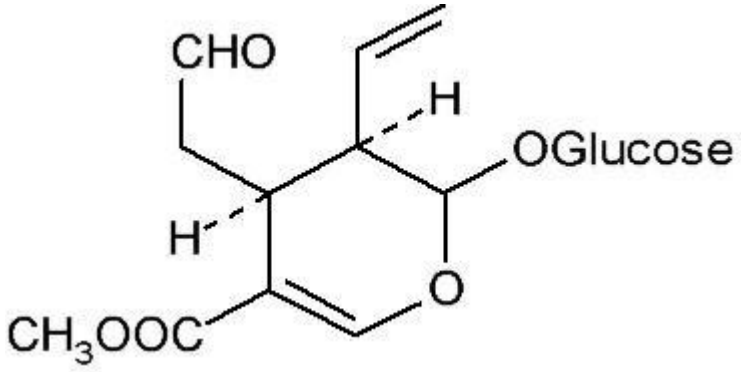


deacetylisoipecoside

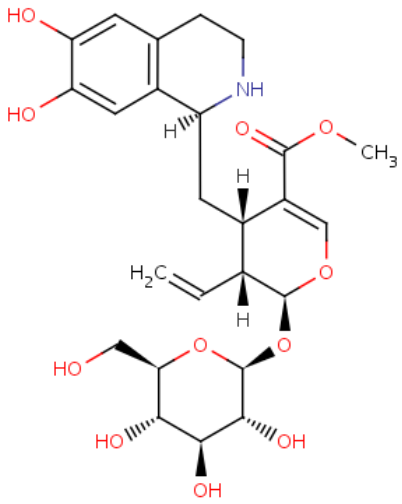
The hydrolysis of deacetylisopecoside leads to an unstable aglycone : the dihydropyran ring opens and the aldehyde reacts with the secondary amine to form ring C. Subsequently, the molecule loses a carboxymethyl group and undergoes a condensation with a second molecule of dopamine.



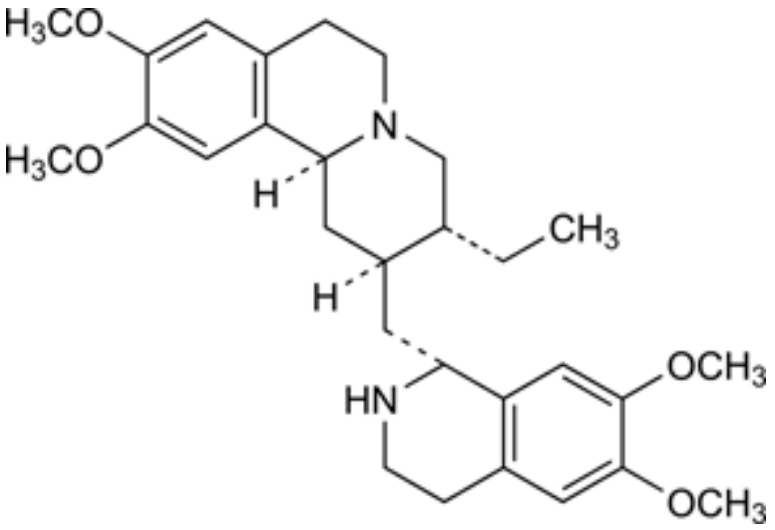
dopamine



secologanin

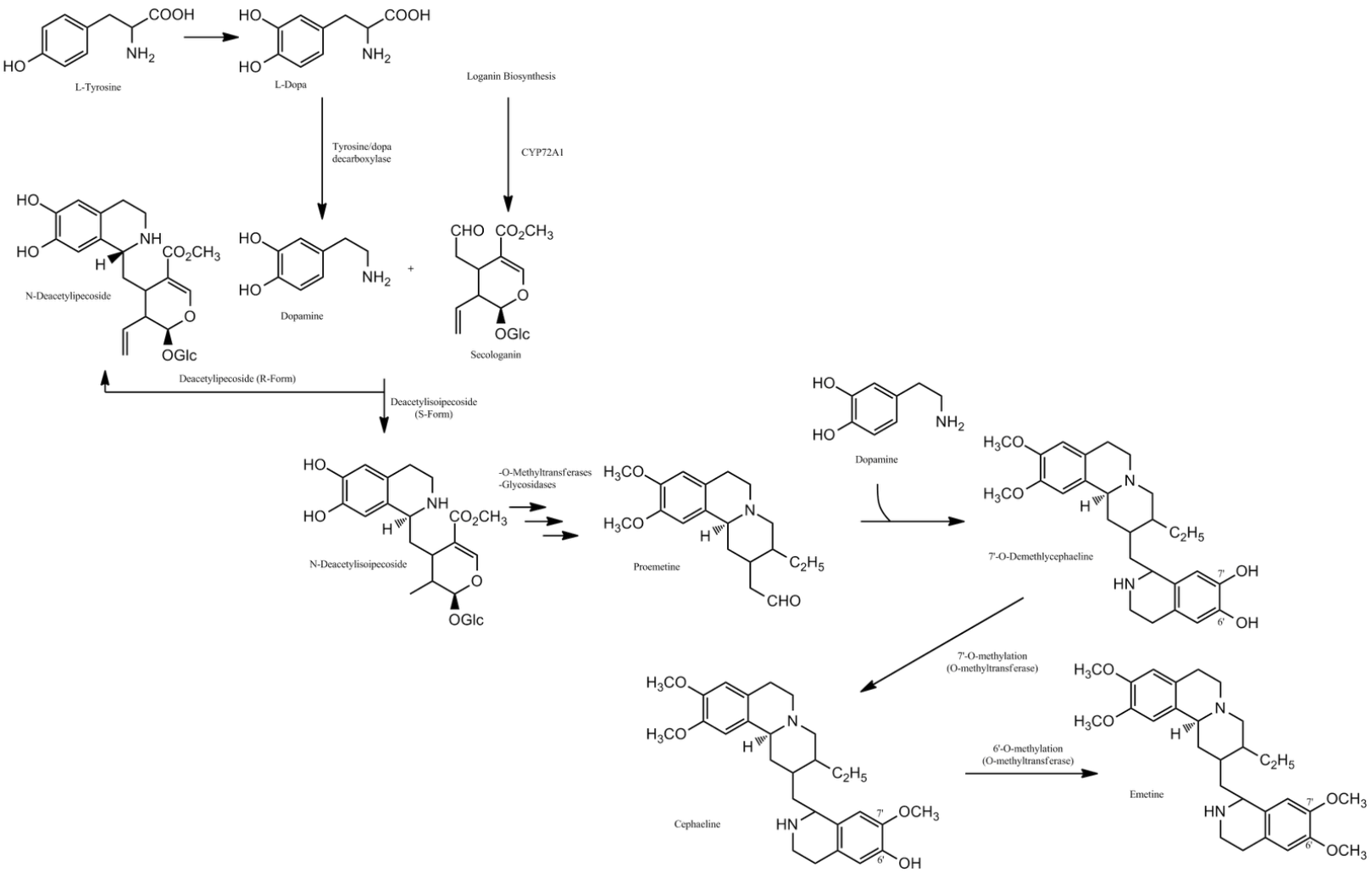


deacetylisoipecoside



emetine

Proposed Biosynthesis of Emetine



Tests : The assay includes a TLC analysis of a chloroform extract prepared in the presence of aqueous ammonia. The chromatogram is examined under UV light after spraying with a iodine solution in chloroform heating at 60°C; the intensity of the light blue fluorescent band due to cephaeline (cepheline) allows the distinction between the two *Cephaelis* species.

The quantitation is achieved by classic methods : alkaloid extraction (diethyl ether) after alkalinization (NH_4OH), solvent evaporation, redissolution in ethanol, heating to 100°C, evaporation, dissolution, and titration of the excess acid with a sodium hydroxide solution of known concentration. The drug must contain not less than 2% alkaloid expressed emetine.

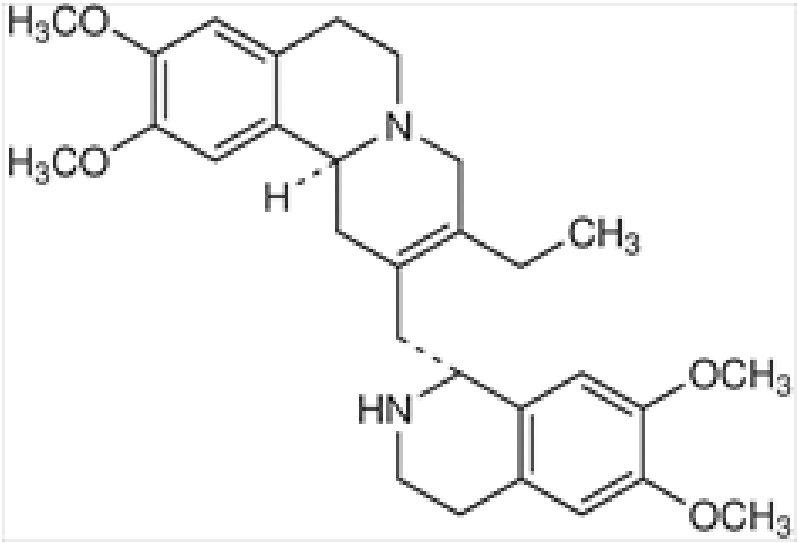
In addition, emetine can be characterized by a color reaction : in the presence of potassium chlorate or hydrogen peroxide emetine gives red color.

Pharmacological activity : Ipecac preparations, when administered orally at low doses , are emetics. The emetic activity is due at first to a direct peripheral stimulation (excitation of the sensory fibers of the glossopharingeal and vagus nerve), and secondarily , to the stimulation exerted on the brain stem centers that control vomiting. Cephaeline is the main alkaloid responsible for the emetic activity, whereas emetine is mostly en expectorant.

Emetine is an amebicide which destroys the motile forms of the ameba, *Entamoeba histolytica,* the species responsible for amebis dysentery; its activity on the cysts only appears at concentrations that are toxic for humans. Emetine inhibits protein synthesis in animal and vegetable cells, and protozoa. It can inhibit the synthesis of DNA. It kills viruses, but is not an antibacterial.

Emetine is toxic for humans : cardiac toxicity (arrhythmias), hypotension, muscular weakness, and gastrointestinal distress are common side effects. It is excreted in urine at a particularly slow rate (60 days).

Uses : Emetine is no longer used in therapeutics. It was formerly obtained by extraction, and the yield used to be increased by methylating cephaeline. It has been replaced by a synthetic derivative, dehydroemetine, whose subacute and chronic toxicity are decreased by lower accumulation. The synthetic alkaloid remains on the market in spite of the predominant use of metronidazole, secnidazole, and related compounds.

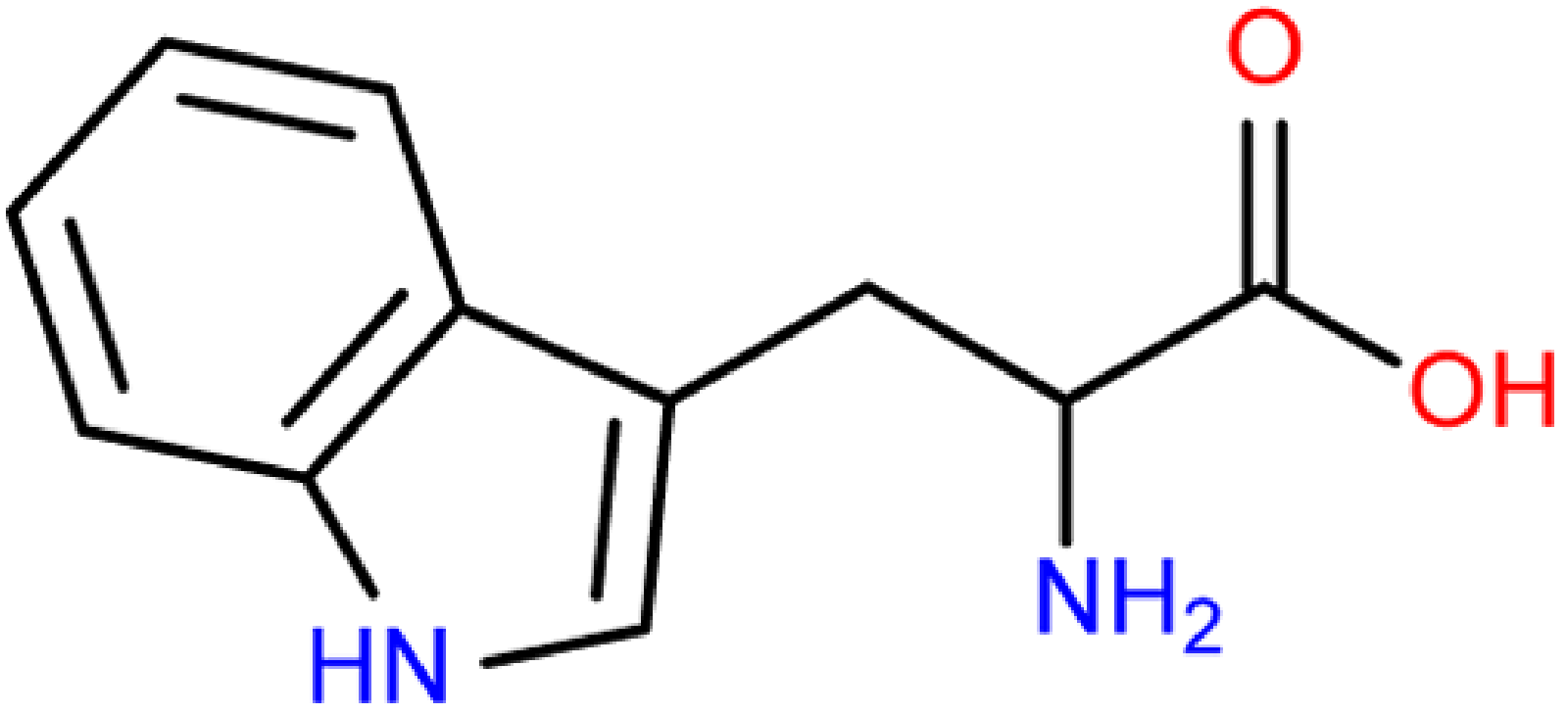


Dehydroemetine is indicated in case of acute intestinal amebiasis, serious colic amebiasis, , hepatic amebiasis, hepatobiliary distomatosis . The main side effects are gastrointestinal distress (nausea, diarrhea), cardiovascular symptoms (hypotension, tachicardia) and neuromusculer problems.

The drug is still to prepare ipecac powder and mostly syrups.

Ipecac syrup is used as an emetic in the tereatment of intoxications . The syrup must be used as soon as the intoxication is diagnosed.

Alkaloids Derived from Tryptophan



A very large groups of alkaloids – undouptely the largest of all- the group of alkaloids arising from the metabolism of tryptophan was thoroughly studied following the isolation, in 1953, of reserpine, the antihypertensive and tranquilizing constituent of the roots of an Apocynaceae, *Rauwolfia serpentina.* Several years later, the therapeutical interest of these indole-type structures was confirmed when the antitumor properties of the binary alkaloids of the *Catharanthus roseus*, were demonstrated.

Tryptophan is the percursor of these alkaloids, bur except for simple amines it is not the only one : acetate, mevalonate, secologanin, and other elements can be combined with tryptamine.

Thus for groups of alkaloids can be distinguished, including the tryptamines.

1. **Simple Amines and Carboline Alkaloids**
   Tryptamine derivatives that have hallucinogenic properties , is devoid of pharmacological interest : ß-carboline alkaloids

2. Indolines Arising from the Cyclization of Tryptamine

Essencially Calabar bean alkaloids

3. Ergoline Derivatives

They are highly specific to a few rare higher vegetables (Convolvulaceae) and to the Ascomycetes fungi.

4. Monoterpenoid Indole Alkaloids

Monoterpenoid Indole Alkaloids are by far the largest group. They incorporate a C_{10} (or C_9) monoterpenoid unit, and their distribution is limited to a small number of Angiosperm families, mainly the Apocynaceae, Rubiaceae, and Loganiaceae

Tryptamines, ß-Carboline Alkaloids

Generalities : Hallucinogens are substances capable of causing “substantial and transient modifications of perceptions, thought and mood” and are classified among psychoactive substances, a less restrictive term applicable to the hallucinogens but also opium, alcohol, and solvents, and even to the psychoactive component of the action of the Solanaceae alkaloids

Except for indian hemp, whose properties are in fact markedly different, hallucinogenic plants owe their activity to nitrogen-containing substances. In most cases responsible are indoles.

Principal Hallucinogenic Drugs : Hallusinogenic drugs have been known since the dawn of time, and their use , rooted in the social life of all the primitive civilizations, has been the source of mystico-religious practices and the basis of initation rites. For example the sorcerers (shaman or other) had been used them to remove the bad spirits; this is close to exorcism.

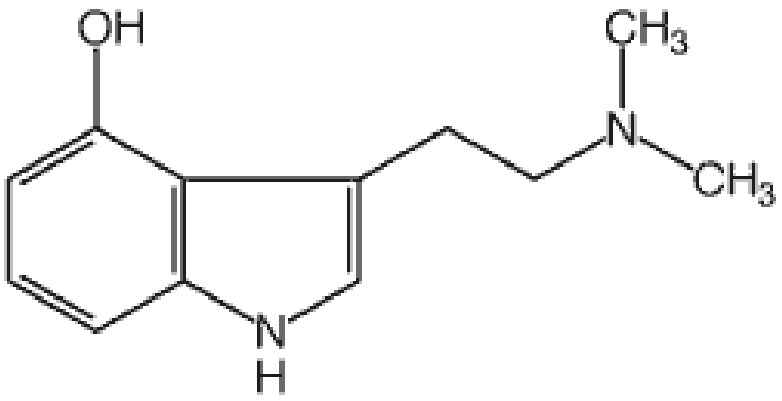
AGARICACEAE (Hallucinogenic, Central Amerikan)

The *teonanacatl* used by the Aztecs of the pre-Columbian America, and still used in some areas of Mexico, is not a well definied drug, but rather a group of mushrooms from the genera *Conocybe, Panaeolus, Psilocybe,* and *Stropharia.* Those most often used are *Stropharia cubensis* and *Psilocybe aztecorum*.

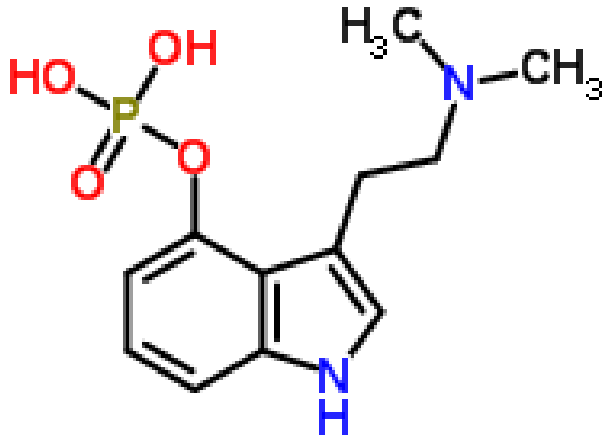
It is known that the active principles of these Agaricaceae are derivatives of tryptamine : psilocin and psilocybin.

Stropharia cubensis

Psilocybe aztecorum



Psilocin



Psilocybin

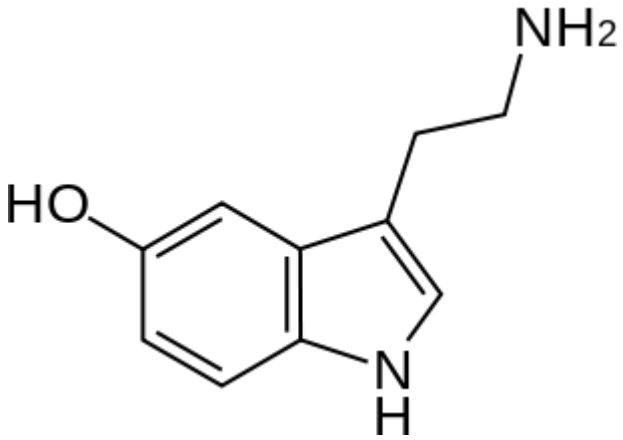
Psilocybin, which is phosphorylated 4-hydroxy-N,N-dimethyltryptamine, is active orally at doses ranging from 100 to 150 µg/kg. It causes few physical effects (mydriasis, muscle relaxation), but it induces substantial psychic effetcs: after an agitation, dizziness, and anxiety phase, hallucinations appear.

MYRISTICACEAE (South American)

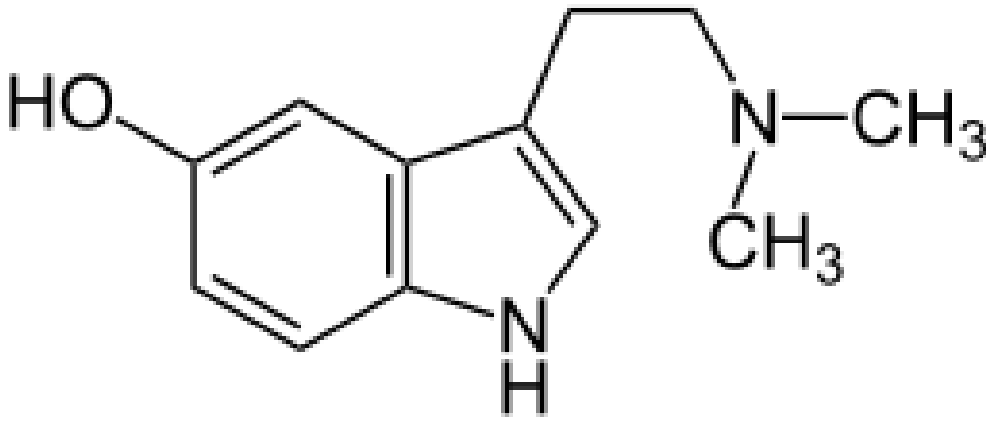
These are trees with yellow flowers from the genus *Virola* (*Virola elongata, V.calophylla*). The method of preparation of the active resin can vary greatly; often the powder is prepared from the bark soaked with the red resin which flows after the bark is peeled : the internal layers and the resin are scraped, dried over a fire, and pulverized; sometimes the bark is boiled and the resin collected and concentrated. Known under various names (yakee, parica, nyakvana…).

Virola elongata

The drug contains derivatives of tryptamine (N,N-dimethyltryptamine, serotonine, bufotenine).
The drug has a marked effect : intense agitation, and excitability, followed by depression and sometimes loss of consciousness.



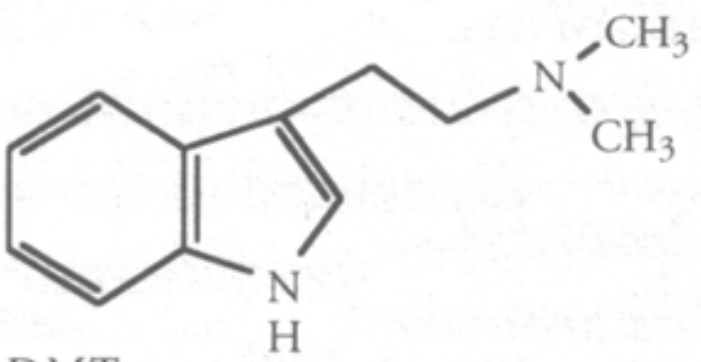
Serotonine



Bufotenine

MIMOSACEAE (South American)

The drug, known as yopo or niopo, consists of the seeds of *Anadenanthera peregrina*, and contains N,N-dimethyltriptamine and bufotenine.



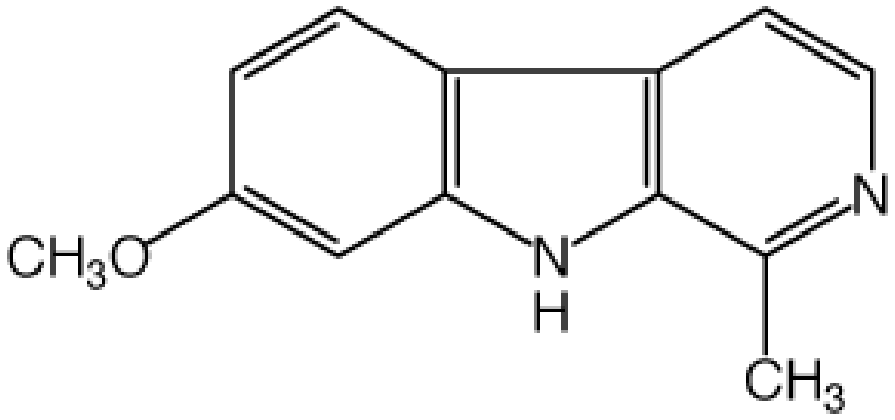
DMT
(N, N-Dimethyltryptamine)

MALPIGHIACEAE (South American)

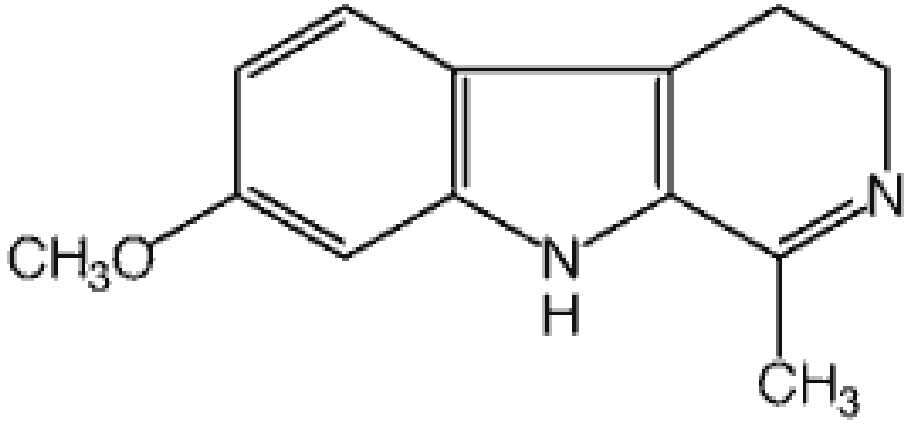
The drug named ayahuasca, obtained from the bark of *Banisteriopsis caapi*, is used in the northwest Amazon region: it is shaved and macerated in cold water, or in some areas chewed directly.

It contains 0.5% total alkaloids, the main compounds are ß-carboline derivatives, harman alkaloids (harmine, harmaline, harmol…).

Reputed as “telepathic”, this drug was used during religious ceremonies to gain the knowledge of the “true reality”.



Harmine



Harmaline

ZYGOPHYLLACEAE, *Peganum harmala*

Peganum harmala is a herbaceous plant, wide spread especially in Central Anatolia. Its seeds contain 3-4% alkaloids (harmine, harmaline, harmol…). It is known that throwing the seeds into a fire releases psycoactive vapors. In anatolia one believes that the dried fruits hanging on walls, protect the humans against “evil eye”.

üzerlik

CONVOLVULACEAE

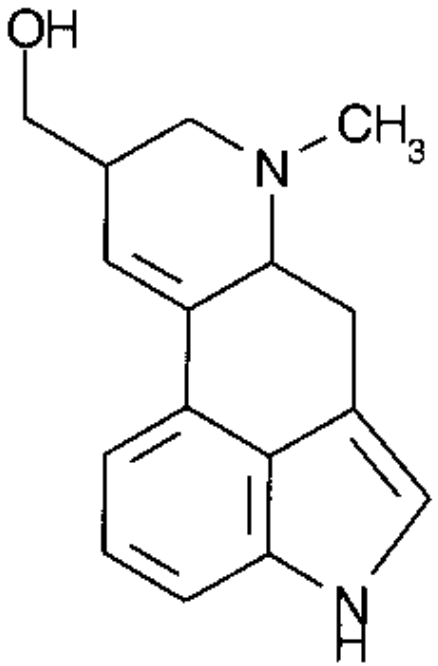
Especially some Mexican Convolvulaceae plants contain hallucinogenic alkaloids. The most important plants are *Turbina corymbosa* and *Ipomea tricolor* (*I. violacea*). They continue to be used in certain regions of Mexico to predict the future and to diagnose and cure diseases.

Turbina corymbosa

Ipomea tricolor

The active substances in the seeds of these convolvulus arise, like the previous ones, from the metabolism of tryptophan via tryptamine : ergine, lysergol).

The concentrations of total alkaloids are generally low (*T. corymbosa* : 0.012%, *I. tricolor* : 0.06%).



Lysergol

Calabar Bean Alkaloids

Calabar Bean ,

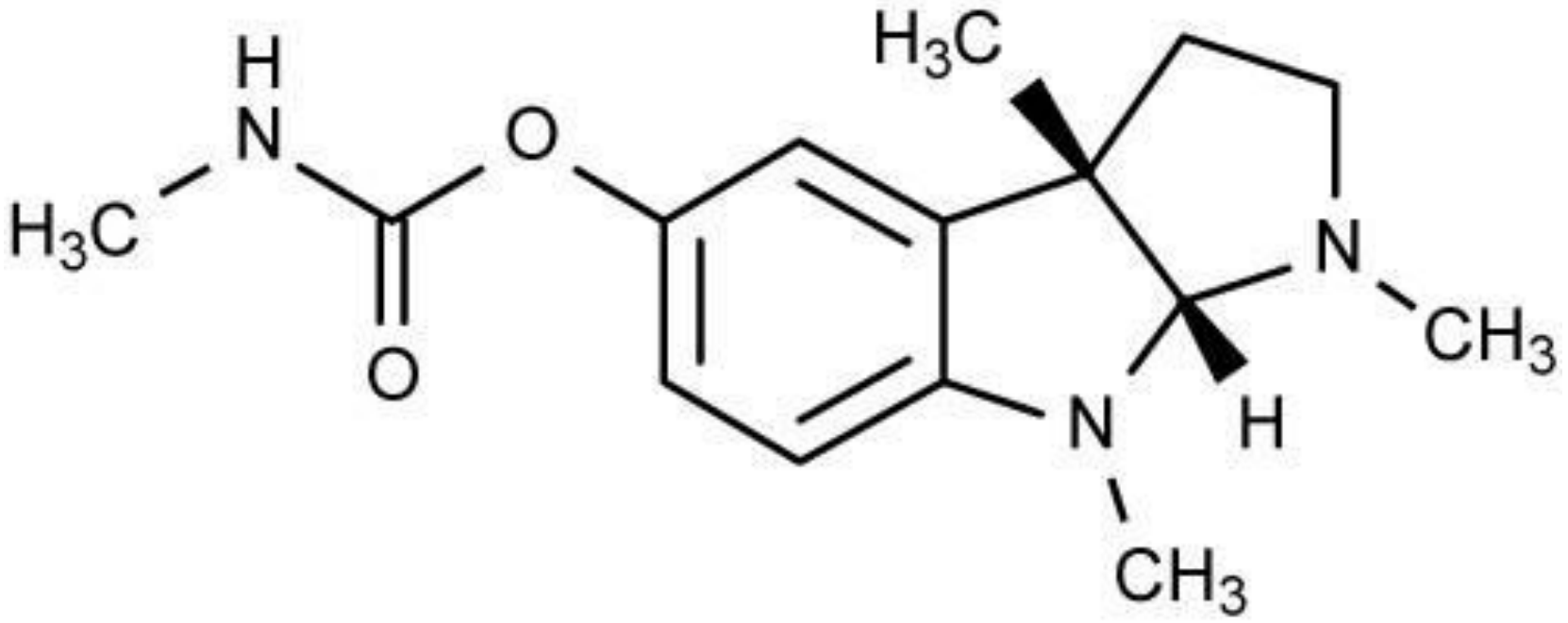
Faba calabarica, Physostigmati semen

Physostigma venenosum **(Fabaceae)**

Physostigma venenosum

The seed of this vine was formerly official. It is a source of physostigmine, a cholinesterase inhibitor (also known as eserine).

Chemical Composition : The seeds contain alkaloids (0.2-0.3%), chiefly represented by (-)-physostigmine (eserine), occuring alongside norphysostigmine, eseramine, physovenine and geneserine.



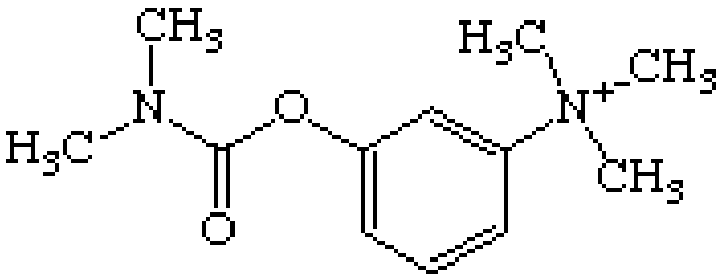
Physostigmine = Eserine

Properties and Uses : Traditionally, Calabar beans were used, in the regions where the plant grows wild, as an ordeal poison.

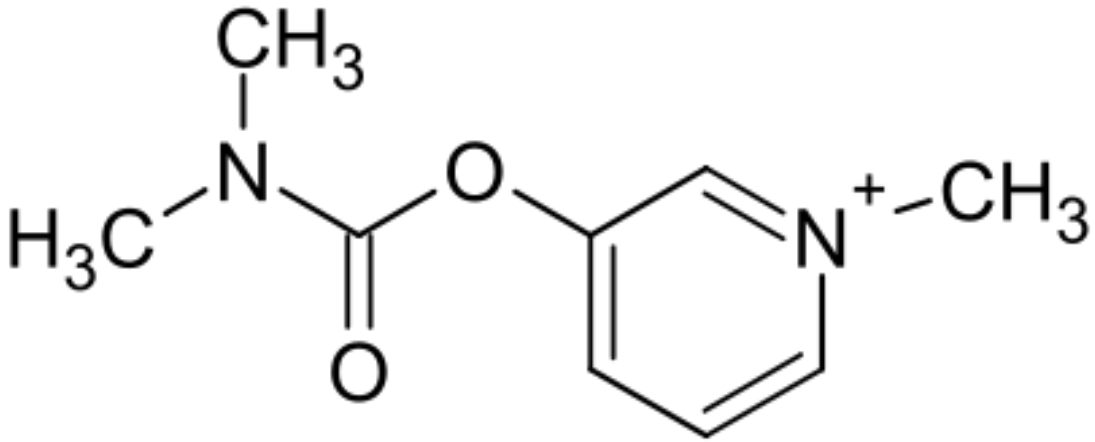
Physostigmine is a reversible cholinesterase inhibitor its affinity for the enzyme is 10.000 times greater than that of acetylcholine. It behaves as a parasympathomimetic, causing myosis, sialorrhea, rhinorrhea, bradycardia, hypotension, bronchospasms, nausea, vomiting, abdominal cramps, and central effects.

Physostigmine can be used as an antidote for parasympatholytic poisoning (by Solanaceae such as stramonium or belladonna). Many authors emphasize that this treatment must be applied with good judgement, because the risk of overdose and several side effects.

Other derivatives : In therapeutics, physostigmine has been replaced by synthetic antycholinesterases, neostigmine and prydostigmine.



Neostigmine



Prydostigmine

The therapeutic indications of these compounds are myasthenia, post-operative intestinal or bladder atony, stubborn constipation, and post-operative recovery after curarization with competitive neuromusculer blocking agent. Asthma, parkinsonism, and obstruction of the digestive or urinary tract are contraindications.

Like other cholinesterase inhibitors, physostigmine has been tested to treat the impairment of cognitive skills characteristic of Alzheimer's senile domentia. The results were rather contradictory.

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