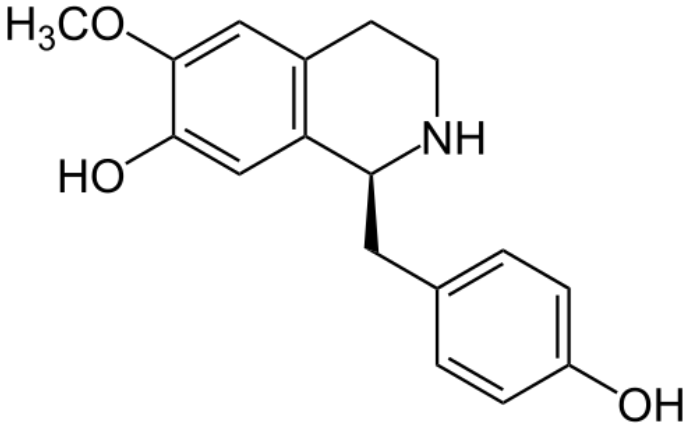
Bisbenzyltetrahydroisoquinolines

Prof. Dr. Ali Hikmet Meriçli

Bisbenzyltetrahydroisoquinolines and aporphine-benzyltetrahydroisoquinoline «dimers» represent over 400 compounds occuring in about ten families, chiefly in the Menispermaceae (*Cocculus, Tiliacora*), the Ranunculaceae (*Thalictrum*), the Berberidaceae (*Berberis, Mahonia*), but also Monimiaceae, Annoaceae or Lauraceae.

There are approximately thirty classes of compounds. Almost all of the known bisbenzyltetrahydroisoquinolines arise from the intermolecular oxidative coupling of two coclaurine (or N-methylcoclaurine) units.



coclaurine

Pharmacologically, these compounds are of limited interest : although several have interesting potential : antitumor properties of tetrandine (leukemia), antituberculosis activity of cepharanthine, antimalarial properties of pycnamine. Some also have a curare-like activity.

CURARE

The term curare is the phonetic transcription of the Caribbean Word «ourari» originally from Guyana. The natives of South America formerly used these preparations to coat the tip of blow darts, or else, but less often, the tip of arrows. For the hunter there are many advantages to these curares :

- The effect is so immediate that the animal cannot flee,
- The muscle relaxation induced by the poison prevents parrots, small monkeys, which are sometimes high in the trees.
- Curare is toxic only by the parenteral route, so that the game caught with it can be consumed safely.

Curares are hunting poisons in forest areas, and are not known to have been used as war poisons. The symptoms of curare poisoning (a paralysis that progresses rapidly and, upon reaching the diaphragm. Causes death by respiratory arrest, without having altered the consciousness or sensitivity of the victim at any (point).

The action of curares on skletal muscle was studied in detail during the nineteenth century even while their botanical origin was still shrouded in mystery. It took a long time to unravel the latter, as well as the structure of the alkaloids, which was elucidated only about fifty years ago.

Classification of Curares :

- Tube-curare from Brasil and Peru, poured into bambou tubes, and used as arrow poison
- Pot-curare poured into clary pots of various shapes, rare and specific upper Orinoco and upper Amazon basins
- Calabash-curare, poured into the fruits of various Bignoniaceae, originally from Colombia, Venezuela, and Guayana, and used as arrow poison

Later, curares for pharmaceutical application were prepared in their countries of origin, from the barks of the fresh plants, by maceration in water. After a lixiviation-type step, the solution was concentrated into a soft extract and poured into one kilogram tins which were then shipped overseas for the extraction of the active substances.

Botanical origin : Tube-curares from the upper Amazon basin (Brasil, Peru) are chiefly composed of extracts of stems of Menispermaceae of the genus *Chondrodendron* (*C. tomentosum*) and of the very close genus *Curarea* (*C. toxicofera*)

Calabash-curares owe their activity to extracts of trunk barks of various shrub or vine species of the genus *Strychnos* (Loganiaceae), including *S. toxifera, S. letalis*.

Pot-curares almost always contain a mixture of extracts of Menispermaceae and Loganiaceae.

Chondrodendron tomentosum

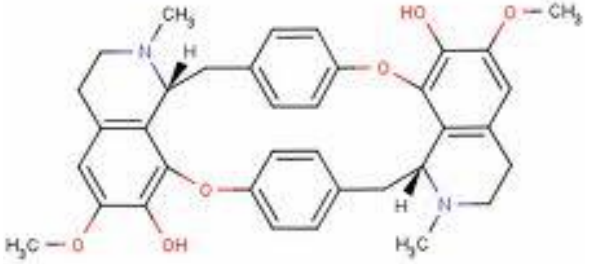
Curarea toxicofera

Strychnos toxifera

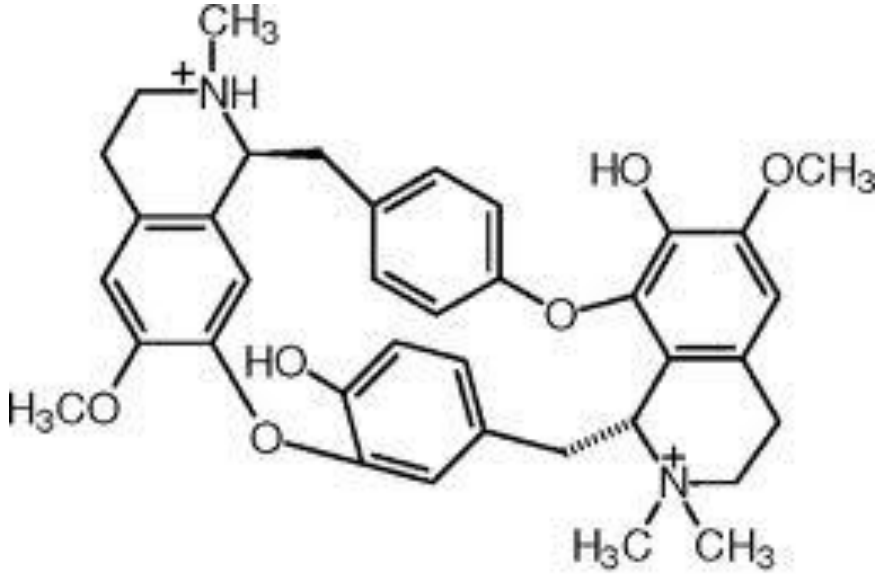
Chemical Composition : **The active principles of the curares from Menispermaceae and Loganiaceae are very different** : **the former are of the isoquinoline type**, **whereas the latter of the indole type**; both types, however are quaternary ammonium salts. Since their pharmacological activities are identical, we shall not dissociate them, even though, biosynthetically, **the alkaloids of Loganiaceae are tryptophan derivatives.**

Menispermaceous Curares

This curares contain from 2 to 10% bisbenzyltetrahydroisoquinoline alkaloid, a very common structure type in this family. The curare molecule is (+)-tubocurarine, a quternary ammonium structure. The other alkaloids are tertiary bases (-)-curine, (+)-isochondrodenrine, and (+)-chondrocurine.



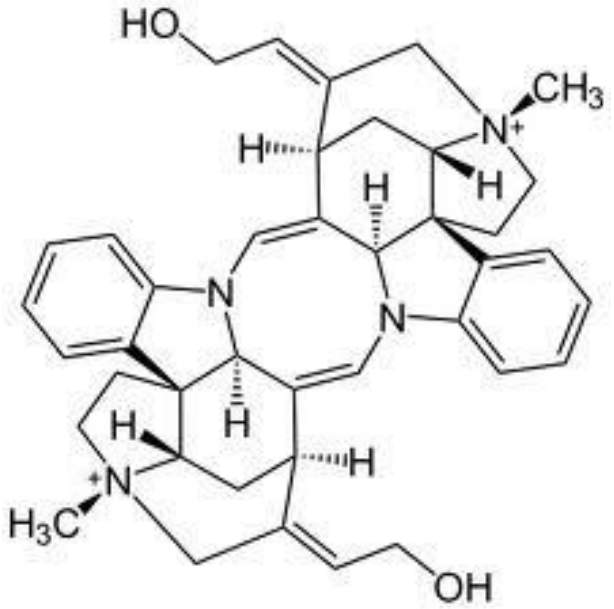
(+)-isochondrodendrine



(+)-tubocurarine

Loganiaceous Curares

In this case, the active constituents are symmetrical bisindoline, bis quartery ammonium alkaloids, arising from the «doubling» of a strychnane-type unit : C-toxiferine, C-curarine, C-alkaloid G and others. These alkaloids represent 8 to 10% of the weight of the curare.



C-toxiferine

Pharmacological Activity : Naturally-occuring curares are non-depolarizing (or competitive, or stabilizing) neuromuscular blocking agents. Active only the parenteral-route, they compete with acetylcholine for the colinergic receptors at the motor end-plate and prevent the formation of the action potential, without modifying nerve conduction elsewhere and without preventing muscular contraction in response to direct stimulation.

Uses : Tubocurarine remains the pharmacological reference for this class. Currently, a semisynthetic derivative of C-toxiferine is used : N,N'-diallylnortoxiferiniumdichloride(= alcuronium chloride INN). Alcuronium chloride is used (IV) as an adjunct in anesthesia, particularly to achive muscle relaxation during surgical procedures.

OTHER NATURALLY-OCCURING SUBSTANCES WITH CURARE-LIKE ACTIVITY

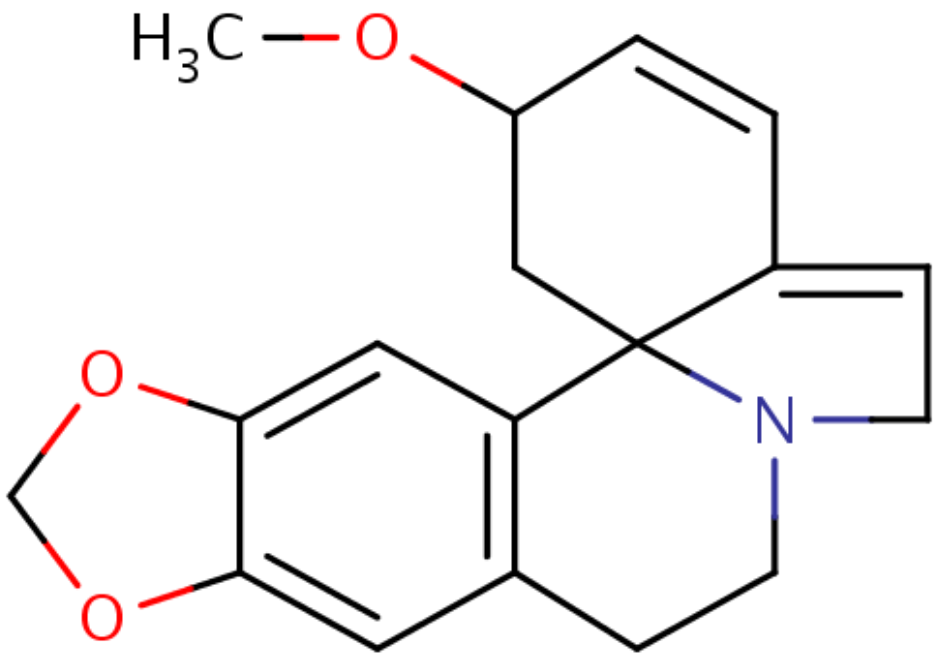
Erythrina Alkaloids

This alkaloids have a structure which is very different from that of the curares. We describe them at this point only because they fit from a pharmacological point of view. In a sense, they are 1-benzyltetrahydroisoquinolines having undergone a particular intramolecular oxidative coupling.

Erythrina are tropical Fabaceae, often arborescent, which grow in South America, Africa, and the tropical regions of Asia.

Erythrina crista-galli

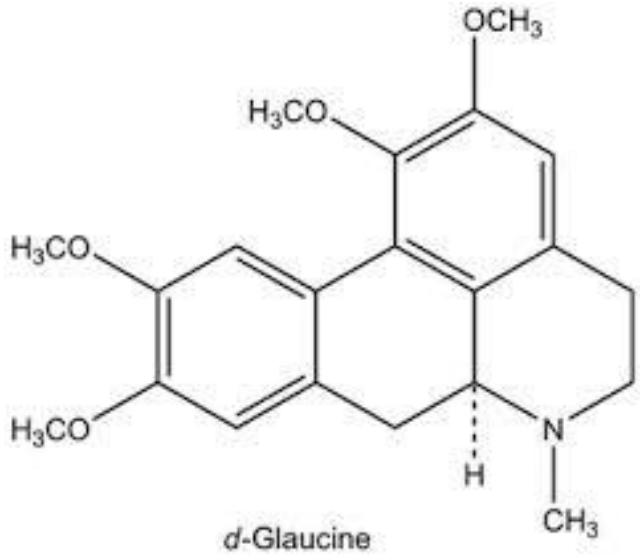
Most of the species in this genus contain tetracyclic isoquinoline alkaloids which are structrally very similar : erythraline, erysodine, erythratidine, β-erythroidine and others.



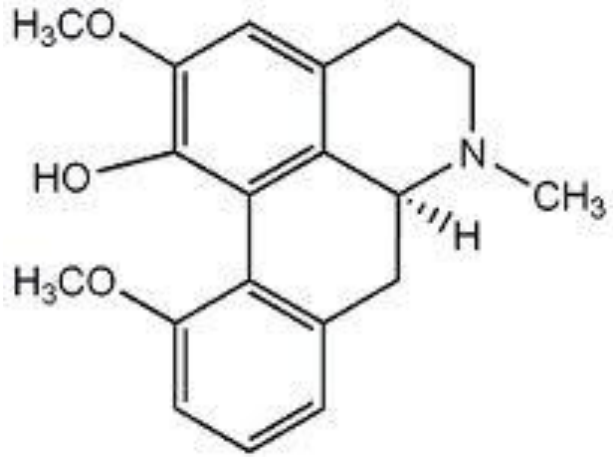
eryhthraline

Aporphinoids

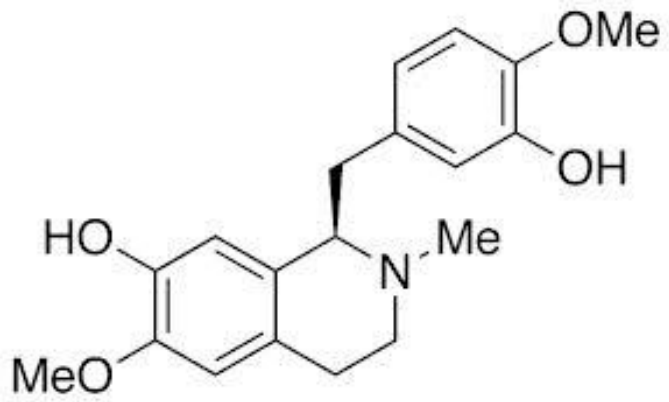
A very large group of more than 500 alkaloids (proaporphines, aporphines, and derivatives) occur frequently mostly in certain archaic families (Monimiaceae, Lauraceae, Magnoliaceae, Ranunculaceae…)



d-Glaucine



isothebaine



reticuline

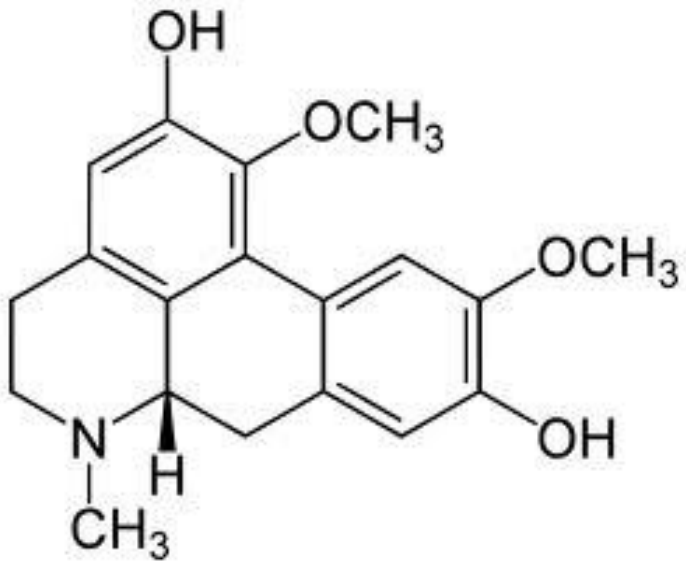
Boldo

Peumus boldus

Boldo folium

Monimiaceae

Chemical Composition : The dried drug contains 10 to 30 ml/kg essential oil (limonene, cineole, camphor), flavonoids and alkaloids. The alkaloids (0.2-0.5%) are aporphinoids, and include boldine (chief constituent), isoboldine, isocorydine and laurolitsine.



boldine

Boldo extracts, and boldine extracted from the tree leaves and bark are ingredients of proprietary drugs used for the adjunct treatment of dyspepsia and heart burn.

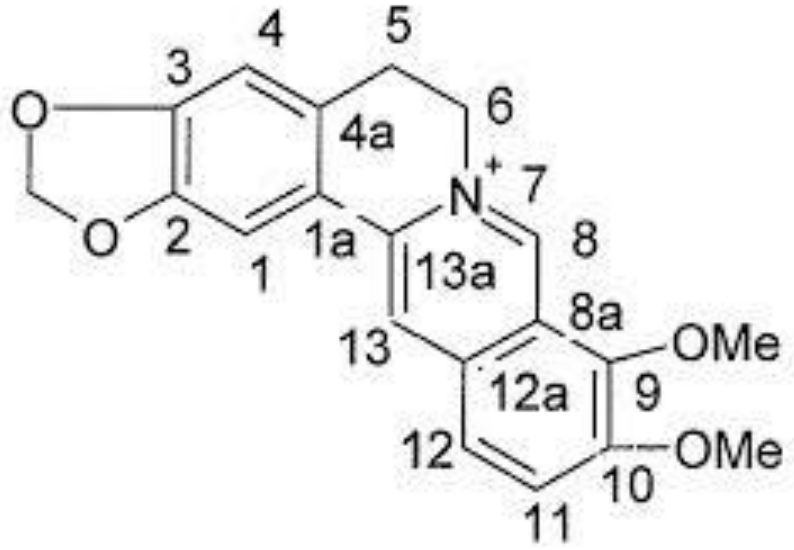
The German Commission E lists uses of boldo based on activities as a «spasmolitic, choleretic, and stimulant of gastric secretions» : gastrointestinal problems such as cramps and dyspepsia. Boldo is contraindicated in case of obstruction of the biliary tract of serious liver disease.

Protoberberines and Derivatives

GENERALITIES

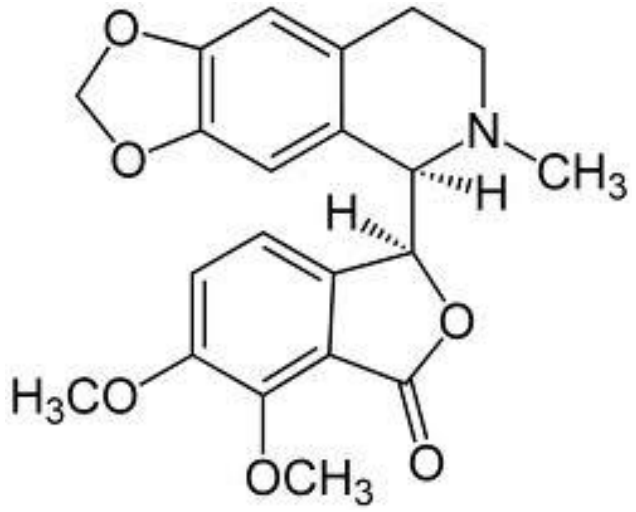
Protoberberines are fairly widespread quaternary and tertiary tetracyclicalkaloids, found in Berberidaceae, Menispermaceae, Ranunculaceae, and also in Annonaceae and Papaveraceae. Their biogenetic potential is substantial, particularly through the protopines, which arise from the cleavage of the bound between C-14 and the nitrogen atom.

Like the other isoquinoline alkaloids, the protoberberines are formed from a benzyltetrahydroisoquinoline : the C-8 carbon atom comes from the oxidative cyclization of the N-methyl group of a molecule of this type.



berberine

orientalidine



hydrastine

Goldenseal

Hydrastidis rhizoma

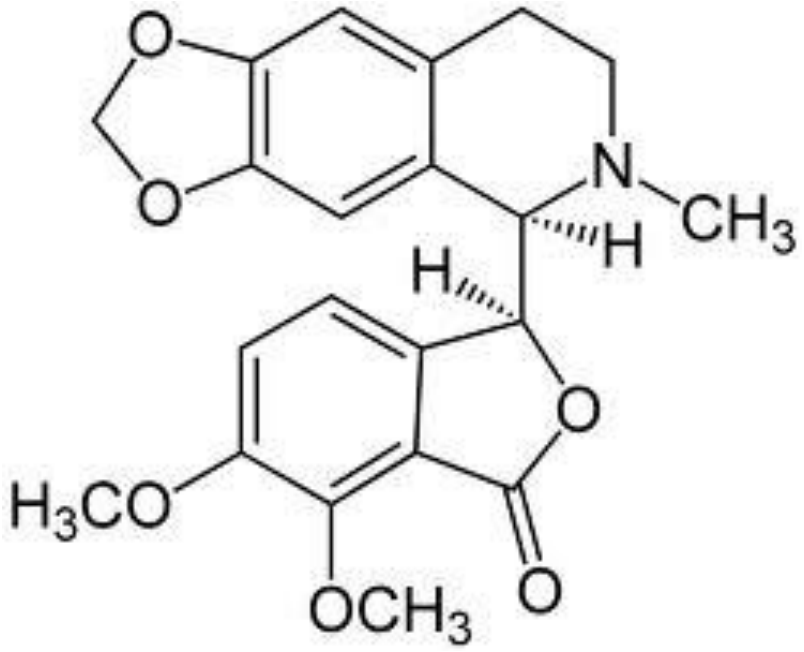
Hydrastis canadensis

Ranunculaceae

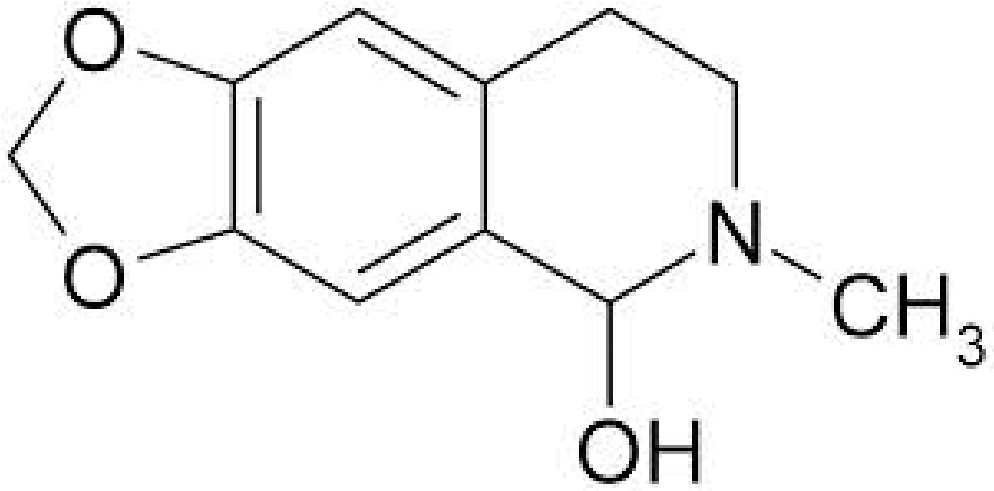
Chemical composition : The chief components of the drug are isoquinolines : hydrastine (a phthalyltetrahydroisoquinoline) and berberine, a bright yellow quaternary ammonium protoberberine.

Pharmacological Activity and Uses : Berberine is a bacteriostatic at low doses and a bactericide at higher doses. It is also a fungicide, and it is toxic for various protozoa. It decreases intestinal peristaltis.

Hydrastinine chloride is combined with synephrine and chlorhexidine in eye drops used to treat conjunctival hypertermia of allergic or seasonal origin, and eye strain due to environmental irritations.



hydrastine



hydrastinine

Fumitory **Şahtere** **Fumariae herba**

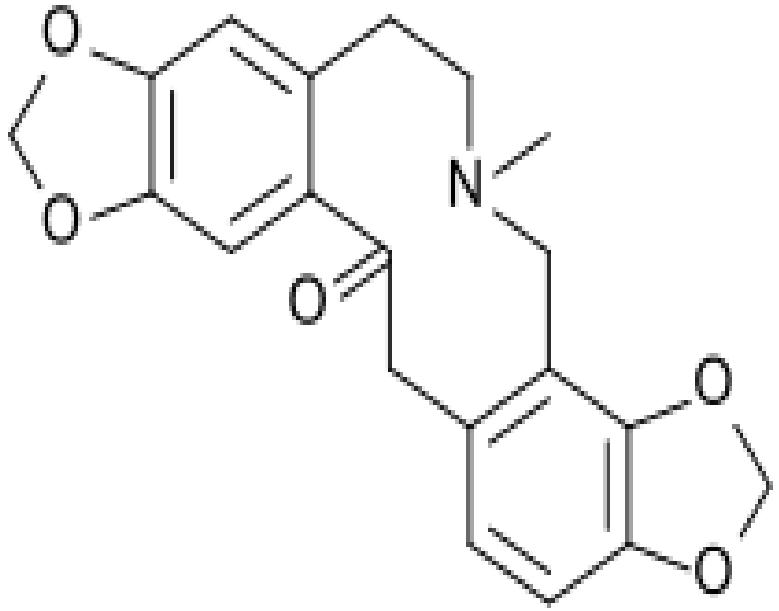
Fumaria officinalis **Fumariaceae**

Fumaria densiflora *Fumaria parviflora*

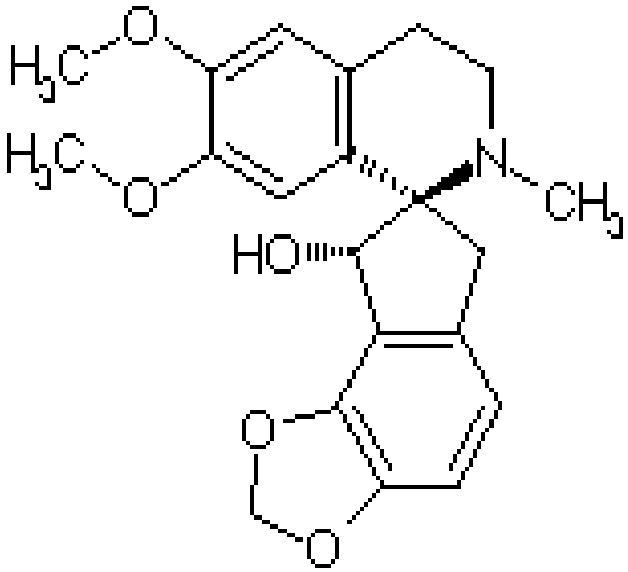
grow in Cyprus

Chemical Composition : The principal alkaloid of Fumariae herba is protopine together with spiro-benzyltetrahydroisoquinolines (fumaricine, fumariline).

Pharmacological activity : The drug and and especially protopine is a spasmolitic, an anticholinergic, an antiarrhythmic, and an antibacterial. The German Commission E monograph states that the the drug can be used for constipation and spastic biliary pain.



Protopine



Fumaricine

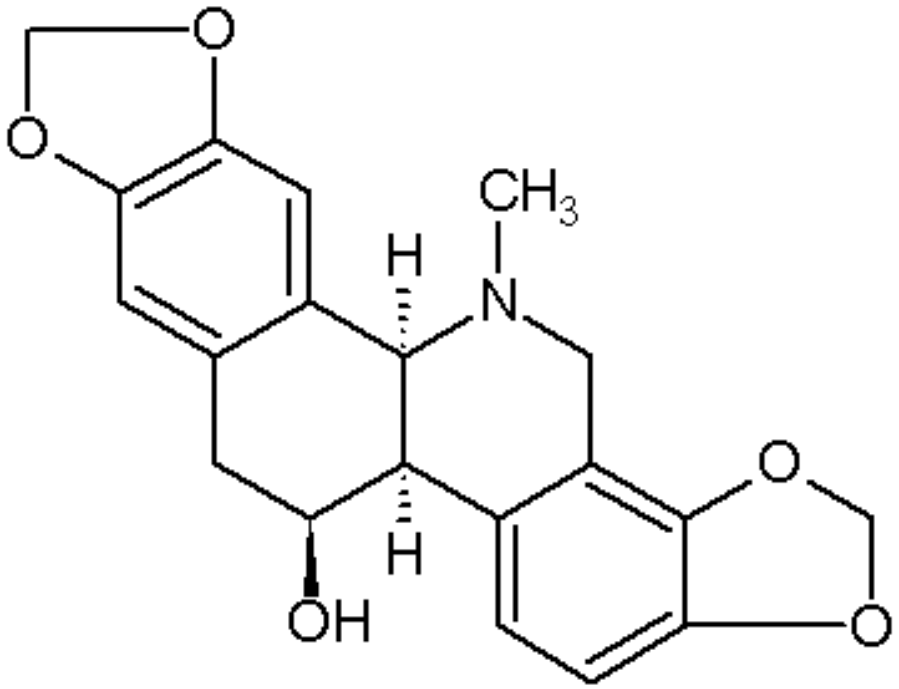
Celandine **Kırlangıç otu** **Chelidonii herba**

Chelidonium majus **Papaveraceae**

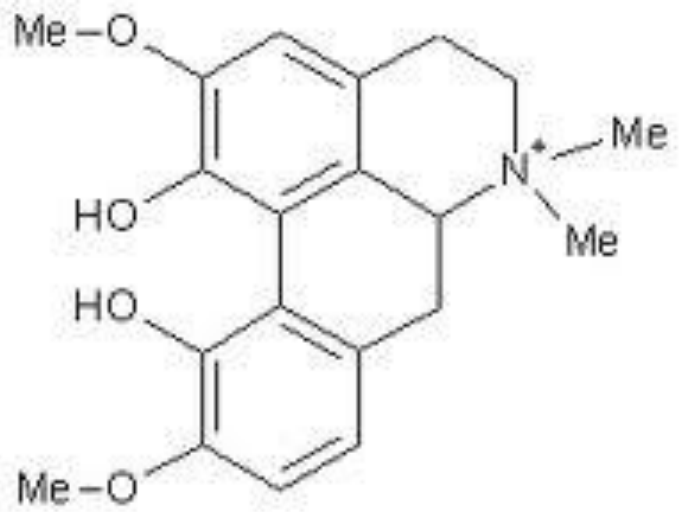
The plant is a perennial herb growing widespread in Europe, when damaged, the plant tissues produce an orange colored caustic latex.

The whole plant contains about 30 alkaloids concentrated in the subterranean part, up to 2%. The chief alkaloids are benzophenanthridines (chelidonine, chelerythrine, sanguinarine). These occur alongside protopines, protoberberines (berberine, coptisine, stylopine), and magnoflorine.

In folk medicine,celandine latex is a remedy for warts. According to the German Commission E monograph, the drug is described as a mild spasmolytic for the upper digestive tract, with an effect similar to that of papaverine. The plant is used for cramp-type gastrointestinal and biliary disorders.



chelidonine



magnoflorine

Bloodroot

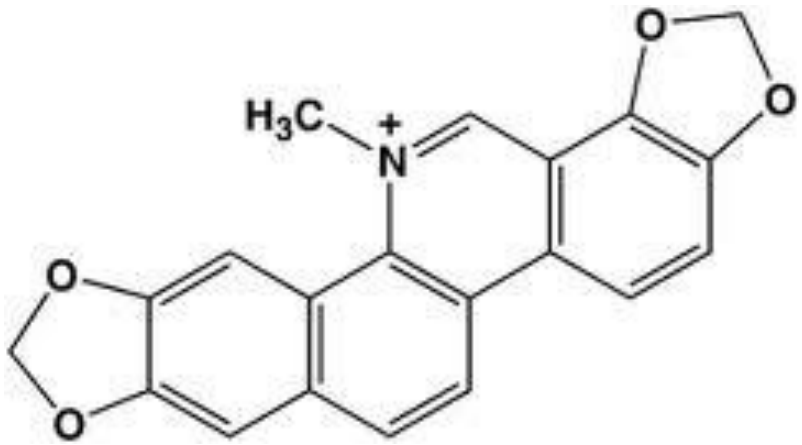
Sanguinariae radix

Sanguinaria canadensis

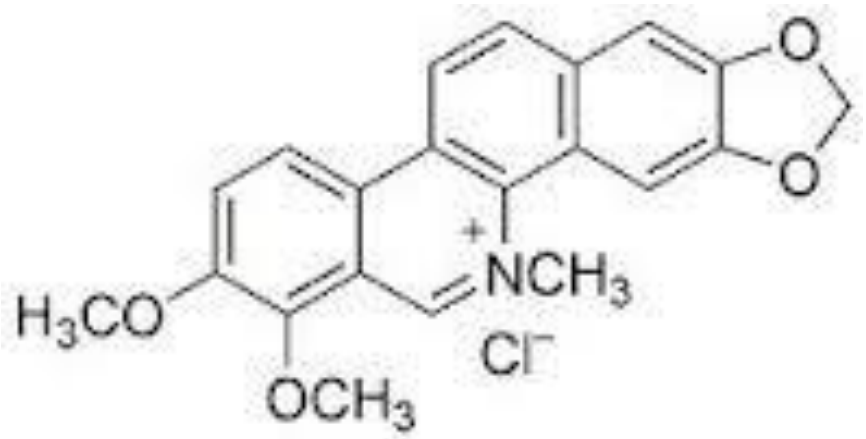
Papaveraceae

Bloodroot is a perennial herb producing a red latex, common in North America. The alkaloids, which occur in all of the parts of the plant, are mostly concentrated in the rhizome (4-7%). The chief constituent (50%) is a benzophenanthridine, namely sanguinarine (red colored) which occurs alongside other derivatives of the same type : chelerythrine (25%), sanguirubine, chelirubine.

Sanguinarine has antimicrobial, antifungal, and anti-inflammatory properties. Sanguinarine chloride is used in mouthwashes and toothpastes.



sanguinarine



chelerythrine

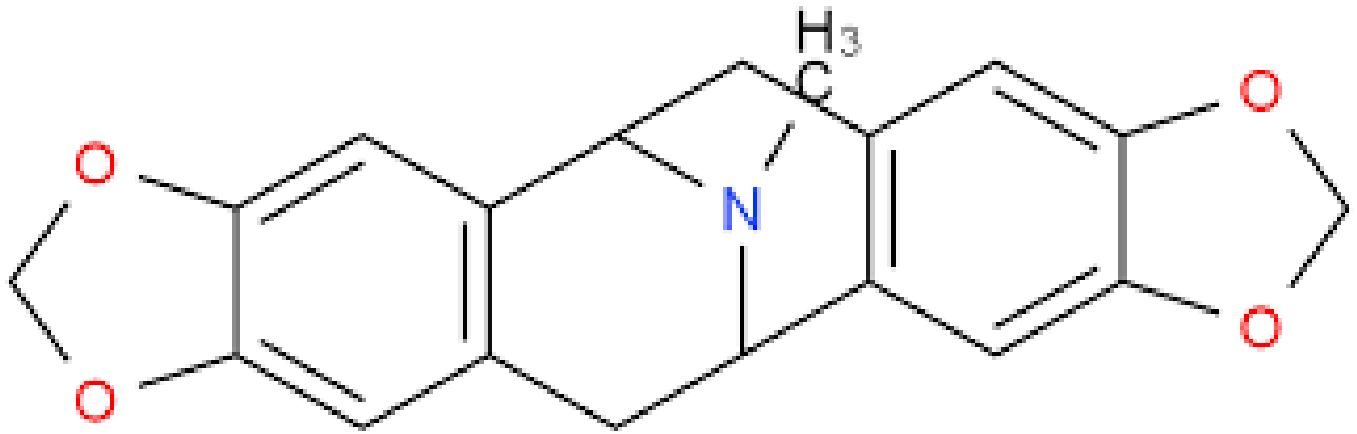
California poppy

Eschscholtziae californicae herba

Eschscholtzia californica

Papaveraceae

Chemical Composition : The composition of the drug is fairly well known, at least as far as the alkaloids are concerned. Besides the pavines, which predominate and characteristic of the genus (eschscholtzine, californidine), protopine and aporphines (N-methyllaurotetanine) have been isolated.



eschscholtzine

HCl

Pharmacological Activity and Uses: The drug is a light spasmolytic. It has also light sedative activity. The phytopharmaceuticals containing the drug may claim the following indication : traditionally used in the symptomatic treatment of neurotoxic disorders in adults and children, especially for minor sleeplessness.

Corn poppy

Gelincik

Papaveris rhoeas flos

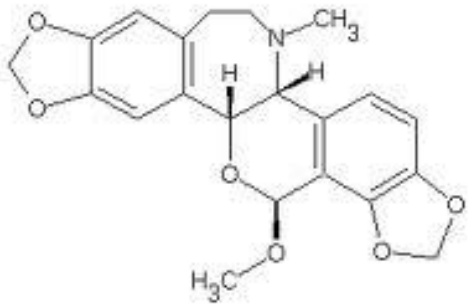
Papaver rhoeas

Papaveraceae

Widespread in Turkey and Cyprus

The petals of this herbaceous plant common along country roads and on neglected lands all over Europe enjoy a reputation as mild sedative and antitussive. They are known to contain anthocyanins and a small amount of alkaloids (0.07%). The chief alkaloid is a tatrahydrobenzazepine, namely rhoeadine.

rhoeadine

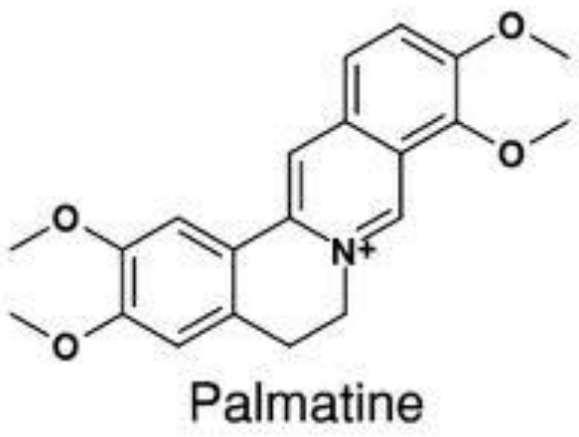


Officially corn poppy petals may be «traditionall» used in 1. the treatment of cardiac rhythm abnormalities in adults (normal heart) 2. the symptomatic treatment of neurotoxic disorders in adults and children especially for minor sleeplessness 3. the symptomatic treatment of cough.

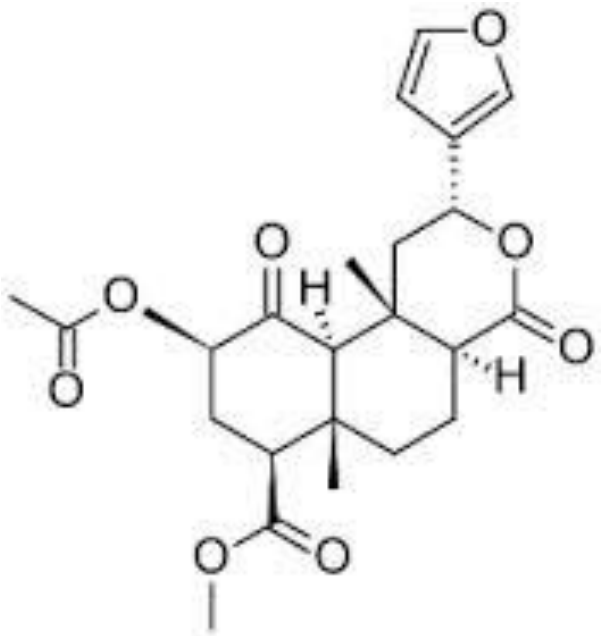
Calumba root **Güvercin kökü** **Calumbae radix = Colombo radix**

Jateorhiza palmata **Menispermaceae**

The roots of this climbing herbaceous plant from the eastern coast of Africa contain 2-3% total alkaloids, chiefly protoberberins (palmatine, jatrorrhizine, columbamine), as well as furanoditerpenoid lactones which impart to it a very bitter taste (columbin, palmarin). The drug was formerly used as a bitter tonic.



Palmatine

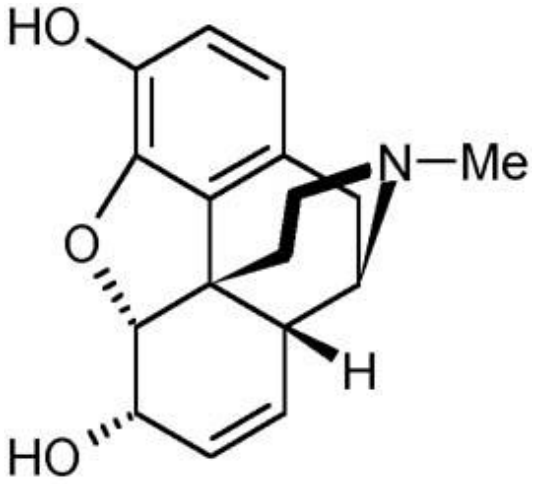


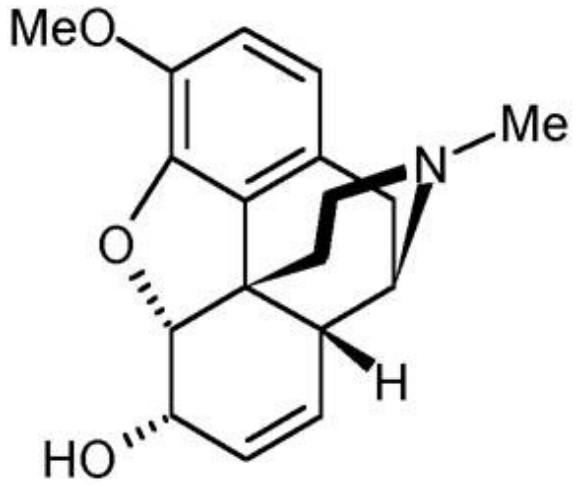
columbin

Morphinanes

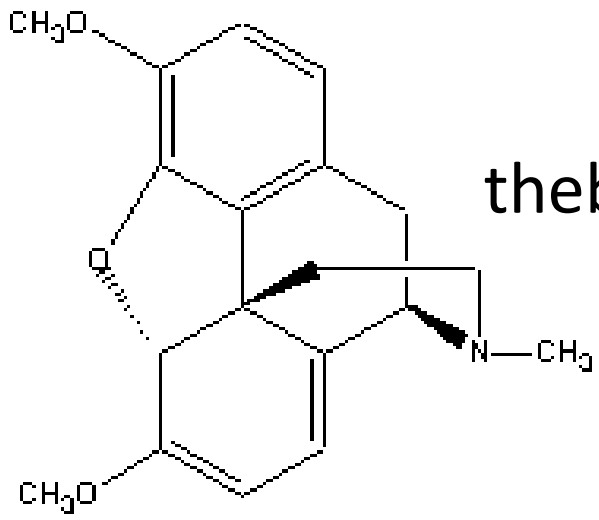
In contrast to isoquinoline alkaloids, which occur particularly frequently in the Papaveraceae (*Argemone, Chelidonium, Eschscholtzia, Glaucium, Papaver, Roemeria,* and more), morphinane alkaloids are specific to *Papaver*. However that out of more than one hundred species in this genus of complex taxonomy, only about ten biosynthesize thebaine (*P. bracteatum, P. orientale*) and that morphine is only elaborated in *P. somniferum* and *P. setigerum.*

morphine





codeine



thebaine

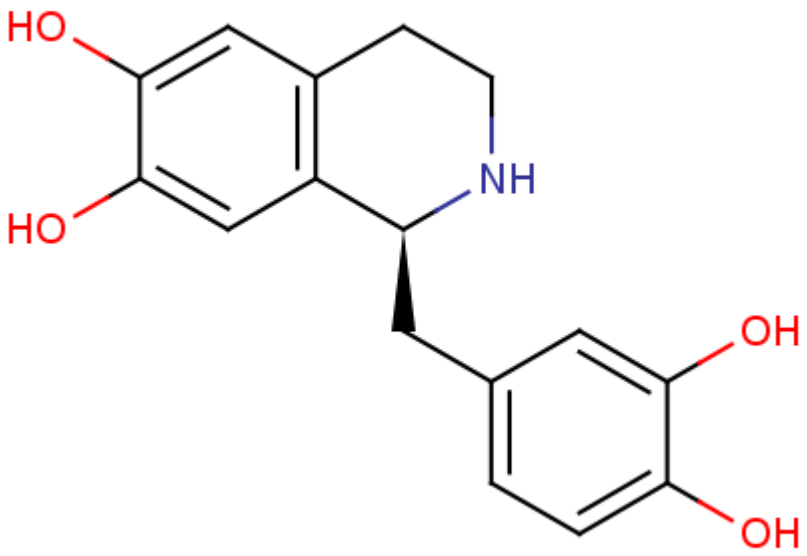
Papaver somniferum
Haşhaş

Papaver setigerum (Papaver somniferum ssp. setigerum)

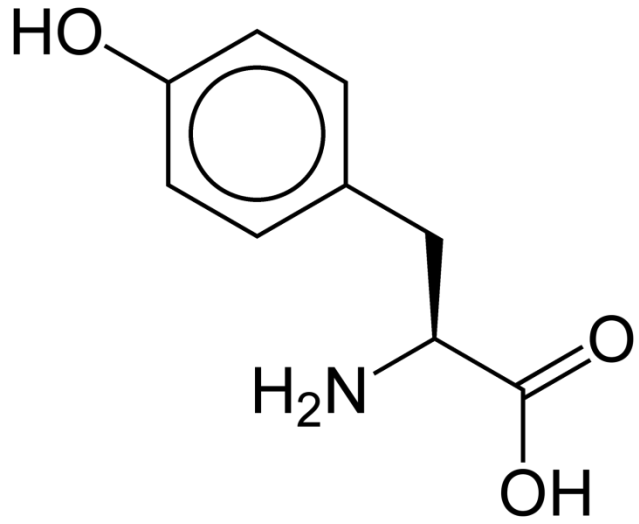
Papaver bracteatum

Papaver orientale

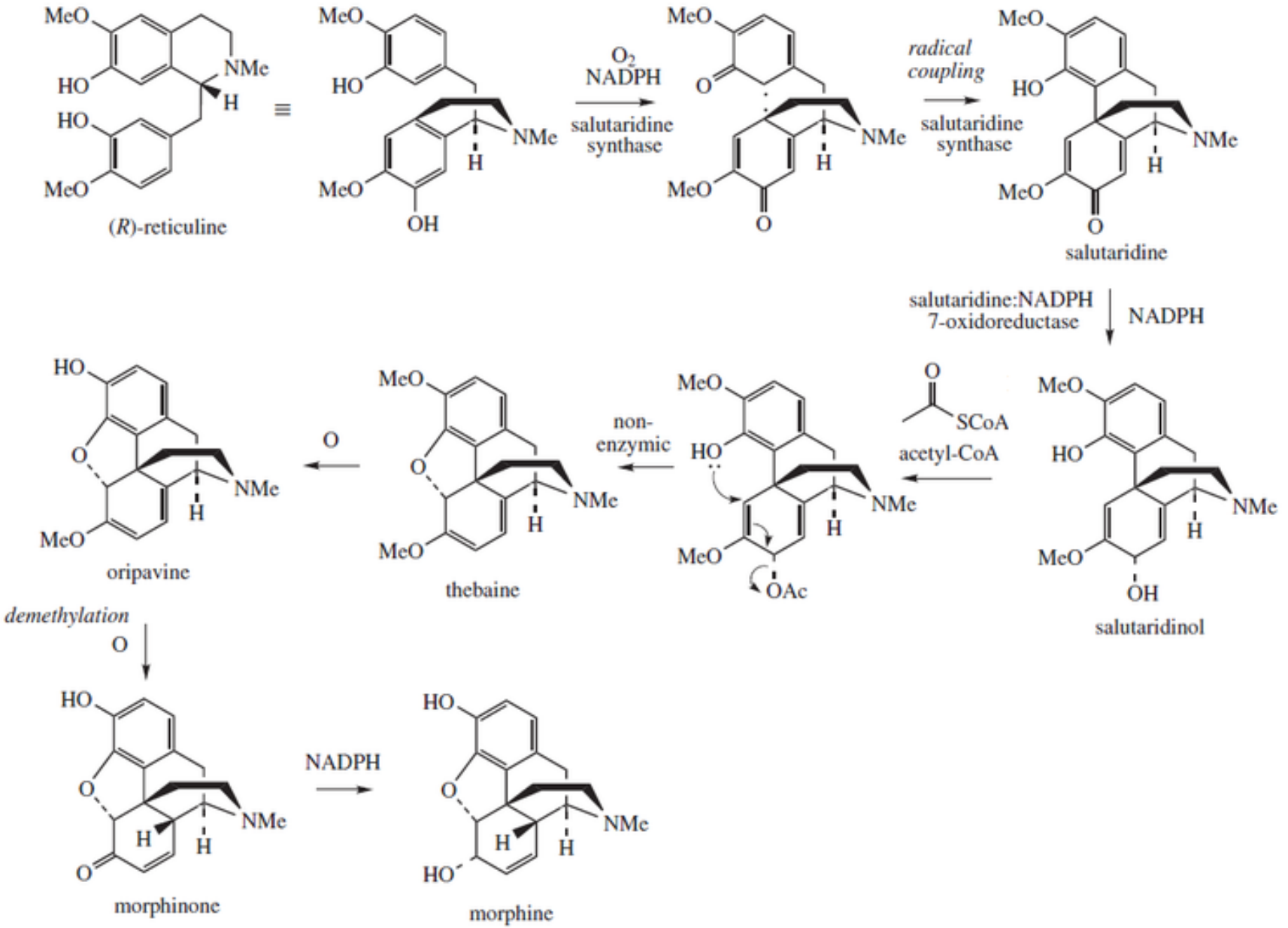
The biosynthesis of the morphinan alkaloids only appears as if it should be complex. Various labelling experiments prove unambiguously that morphine is formed from norlaudanosoline which arises from the metabolism of tyrosine.



norlaudanosoline



tyrosine

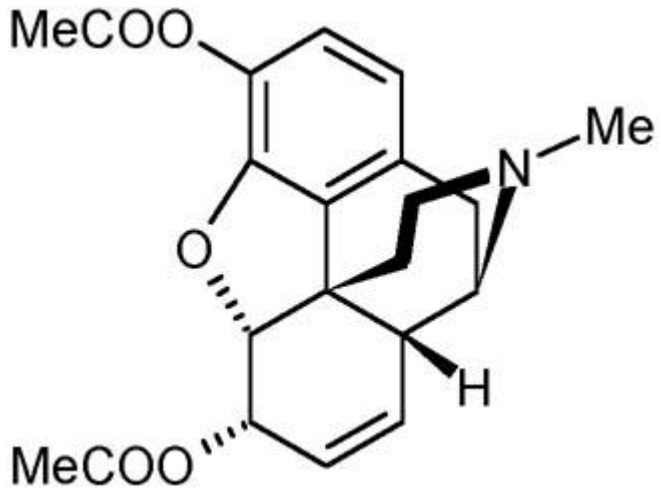


Biosynthesis of morphine

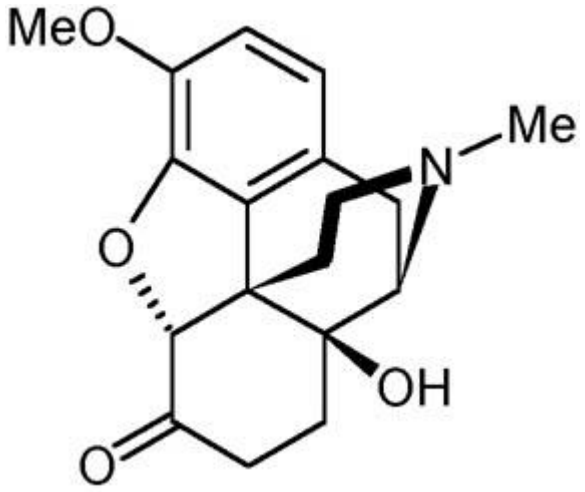
OPIUM POPPY : OPIUM AFYON

Raw opium is the air-dried latex obtained by incision from the unripe capsules of *Papaver somniferum.*

Opium contains not less than 10.0 % of morphine and not less than 2.0 % codeine.The poppy straw concentrate, opium, morphine, morphine derivatives with a pentavalent nitrogen atom, thebaine, most of their semisynthetic derivatives (heroin, hydromorphone, oxycodone), and structurally synthetic derivatives are controlled narcotics.

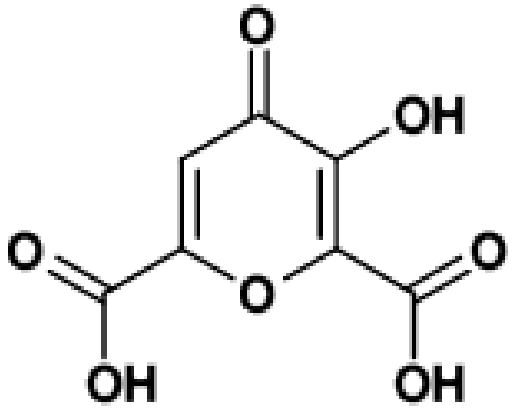


heroin = diacetylmorphine



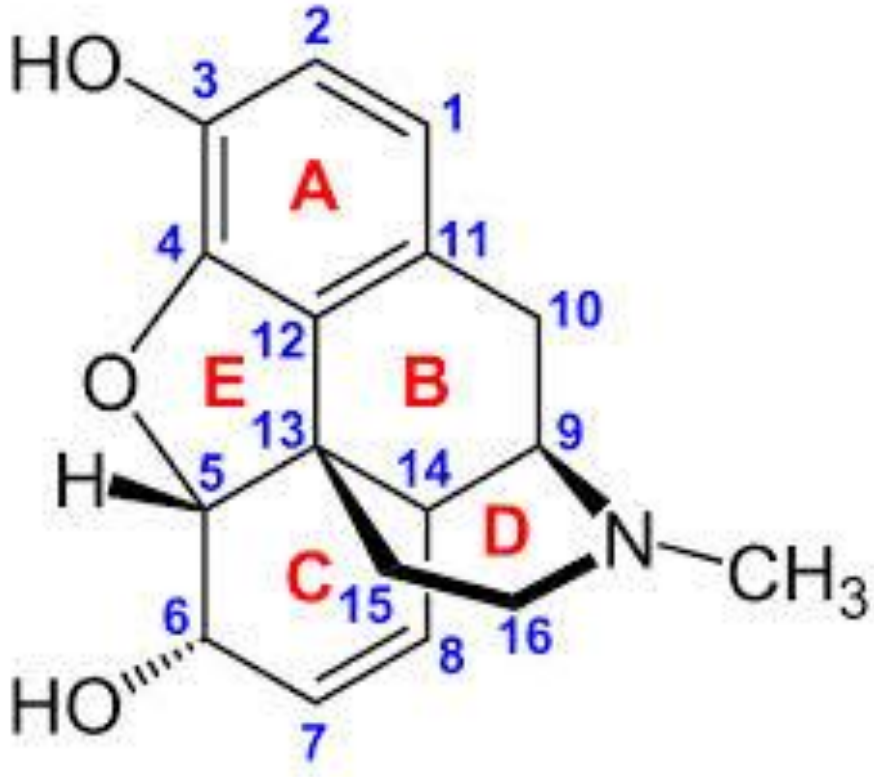
oxycodone

Chemical Composition : Opium can contain besides alkaloids, a lot of organic acids : lactic, fumaric, and oxaloacetic acid, and most of all meconic acid (over 5%). The latter, a dicarboxylic pyrone, only occurs in a limited number of poppies and can be used as an identification marker. The active principles are represented by 10 to 20% alkaloids.



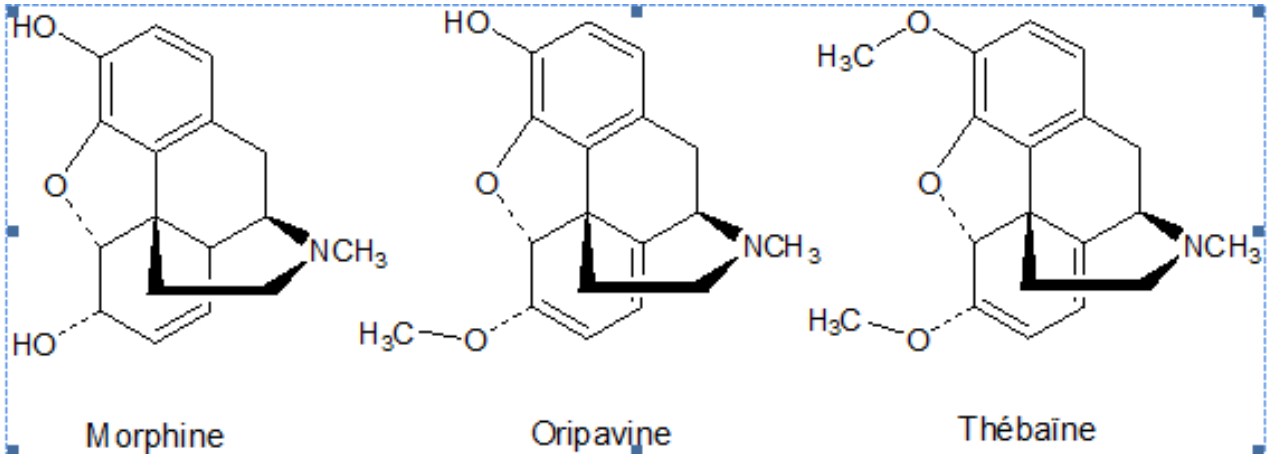
Meconic Acid

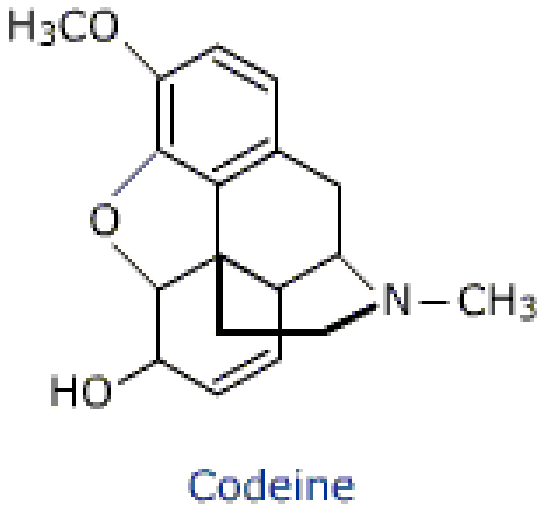
Morphinan Alkaloids : Morphine, the major alkaloid of the morphinan group, is also the most abundant alkaloid in opium (10-12%). It is a pentacyclic molecule with five asymmetric centers : only the naturally occuring enantiomer (levorotatory, 5R,6S,9R,13S,14R) is active.



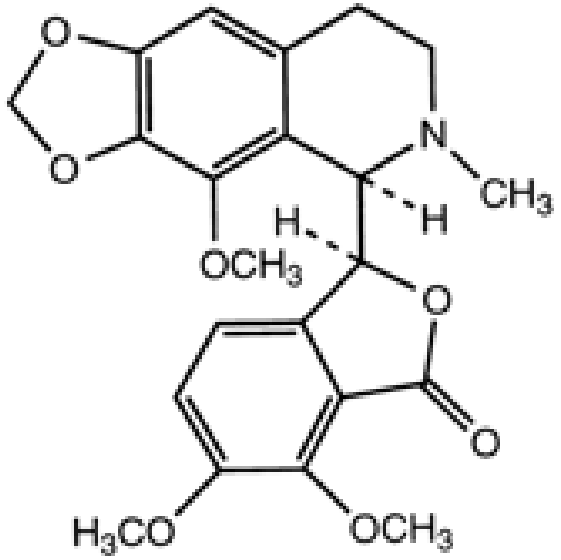
The other morphinan alkaloids occur in opium in variable quantities, and include codeine (2-2.5%), the 3-methyl ether of morphine, thebaine (less than 1%), neopine, codeinone and oripavine.

Thebaine is of interest for synthesis.

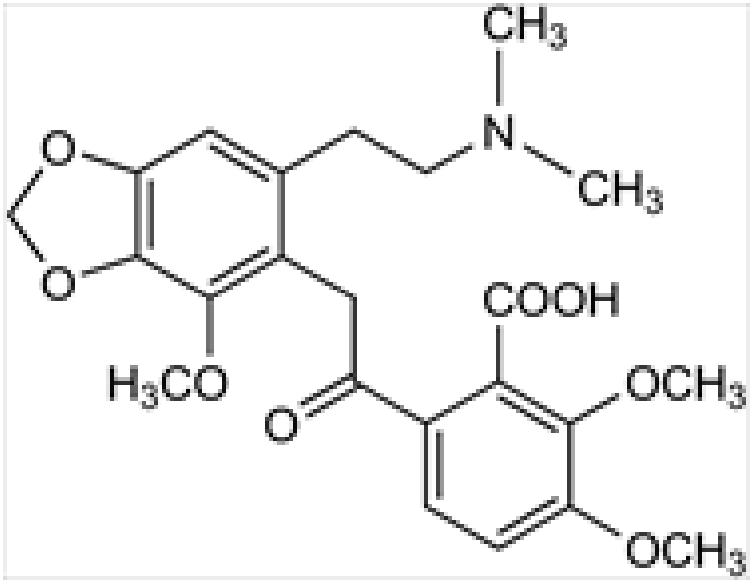




Other alkaloids : Another opium alkaloid which is important by weight is (-)-noscapine (=narcotine) : its level ranges from 2 to 10%. Other derivatives in the same group, which are phtalyltetrahydroisoquinolines, occur in smaller quantities (narcotoline); they occur alongside secophtalylisoquinolines : narceine, nornarceine, and narceinimide.

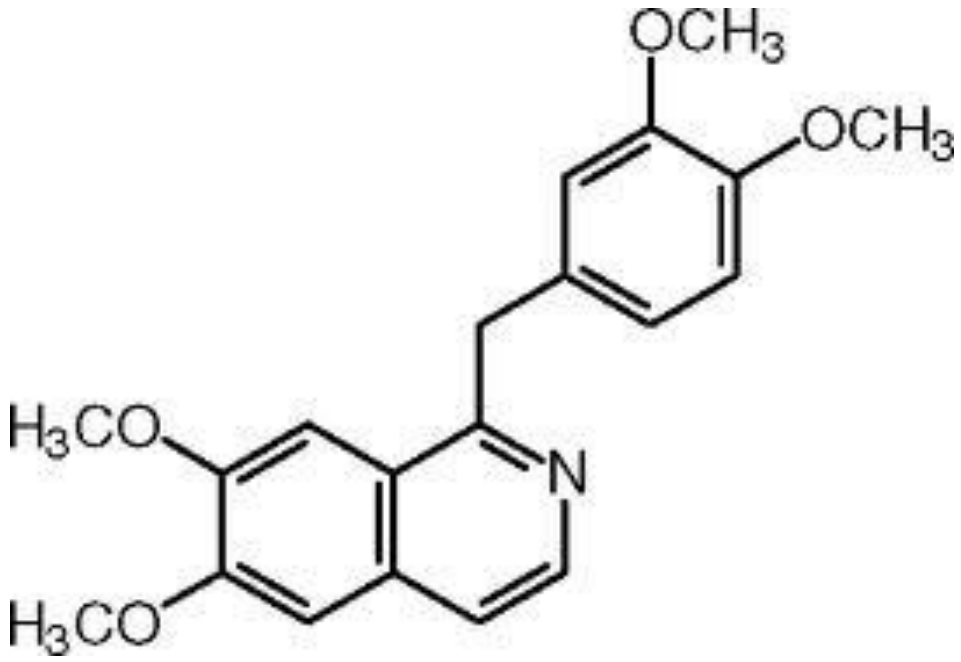


(*S*, *R*)-Noscapine



narceine

Also found in opium are benzyltetrahydroisoquinolines (laudanine, codamine, reticuline) and an isoquinoline derivative , namely papaverine (average concentration : 0.5-1.5%).



papaverine

Tests : The identity of opium can be verified by directly adding ferric chloride to the aqueous extract : a red color develops (characteristic of meconic acid, [Radulescu test]).

Pharmacological Activity

Morphine : Morphine exerts its effects by binding stereospecifically, reversibly, and with a very high affinity, to the specific receptors found mainly at various levels of the CNS. These effects are classically considered to include central and peripheral activities.

CNS Activity

- Analgesic effect : Morpine induces a selective analgesia : it markedly depresses nociceptive perception, and raises the threshold of pain perception. The mind-altering activity of the alkaloid also contributes to the analgesic activity : it induces, in the patient, a certain indifference toward the pain.

- Respiratory effects : Morphine depresses the respiratory centers in the brain stem : the decrease in sensitivity of these centers to carbon dioxide and to hypoxia is proportional to the administered dose; with higher doses, substantial bradypnea and an irregular rhythm appear.

• Other Central Effects : Morphine depresses the cough center. It causes myosis, at least in humans and in animal species that respond to narcotization. This myosis of central origin is an important sign of chronic intoxication.

• Dependence : The psycoactive effects of morphine are substantial. The euphoria and the transient sensation of well-being or sleepiness explain the development of the psychic dependence soon followed by tolerance.

Peripheral Activity : Of note are the digestive effects : vomiting (not in all cases), and activity on smooth muscle fibers.

Codeine : Codeine has an antitussive activity, demonstrated in healthy subjetcs by using cough-inducing aerosols (minimum dose 15 to 20 mg/single dose). This activity is accompanied by a slight depression of the respiratory centers, a slight bronchoconstriction due to a direct effect on smooth muscle, a decrease in secretions, and a release of histamine.

Noscapine (Narcotine): Noscapine is not derived from morphinan and is devoid of addicting effects. It is not an analgesic, nor does it indice respiratory depression. It is a specific antitussive through its central and peripheral activities.

Papaverine : See simple benzylisoquinolines

Extraction of the Alkaloids : The major part of opium is directed toward alkaloid extraction. There are several extraction methods. The traditional procedure begins with an aqueous maceration of opium, which dissolves all of the alkaloids except for noscapine. To the solution of the salts (meconates, lactates, and so forth) is added calcium chloride : the organic acids precipitate as calcium salts and the alkaloids, converted to hydrochlorides, remain in solution. Upon concentrating the aqueous solution, crystals appear, which are a mixture of morphine and codeine hydrochloride. The other alkaloids remain in solution.

Uses : Opium and strow are used for the extraction of the alkaloids. Opium is also still used for the praparation of the following galenicals.

- Opium powder : Contains 10% morphine, maximum dose : 0.2 g/single dose, 0.5 g/day.
- Opium extract : Contains 20% morphine, maximum dose : 0.1 g/single dose, 0.25 g/day.

Morphine : Only a small quantity of extracted morphine is currently used as an analgesic, and the major part of the production is converted to various other compounds (codeine, ethylmorphine, pholcodine, oxycodone, nalorphine, naloxone).

Indications: Morphine is a non specific antalgic for the management of severe acute persistent pain (chronic nociceptive pain), particularly cancer pain. It is used when other antalgics become ineffective in relieving pain (pain level 3 according to the WHO).

Morphine can be used by oral route as morphine sulphate or morphine hydrochloride, by parenteral route, and by epidural and subarachnoid routes.

Contraindications : Morphine has many contraindications : respiratory insufficiency, acute abdominal symtomps of unknown origin, serious hepatocellular insufficiency, trauma of the head and intracranial hypertension, alcohol intoxication, treatment with MAO inhibitors, and must not be used in infants.

The most common side effects are the following :

- Constipation, almost inevitable, and requiring proper menagement
- Nausea and vomiting, which generally subside after 4-5 days of treatment
- Possible neurological and psychic disturbances, which may reflect overdose

Codeine :

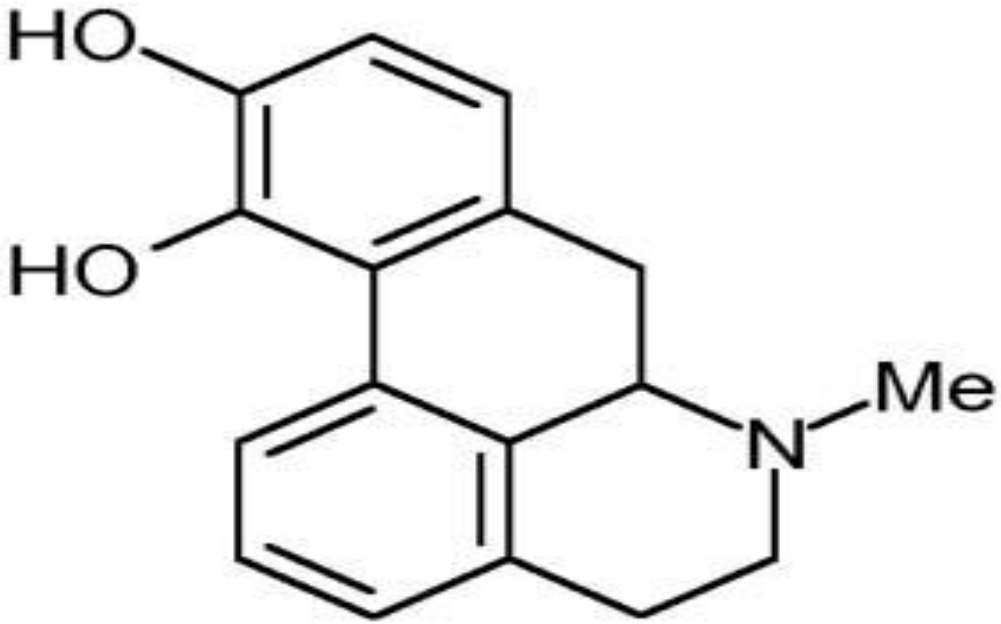
- As an antitussive : Codeine (most often as a salt) is an ingredient of dozens of proprietary drugs indicated or recommended for the symptomatic treatment of difficult, non-productive coughs.
- As an antalgic : Codeine and its combinations are indicated also for the symptomatic treatment of pain in the adults.

Codeine is contraindicated in case of respiratory insufficiency and for asthmatic coughs; to be cautious, its adminstration to nursing mothers and to pregnant women during the first trimester must be avoided.

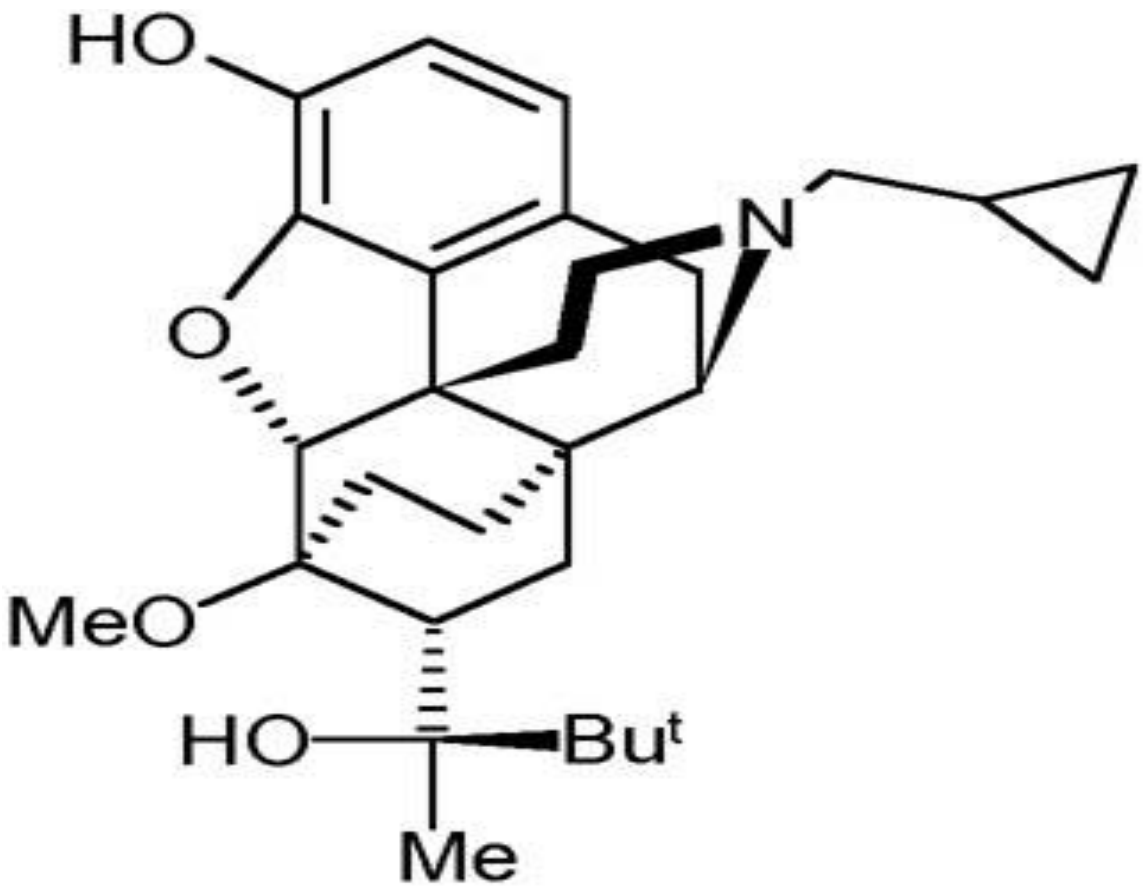
There are many side effects, especially at the higher doses : nausea, vomiting, dizziness, light headedness, constipation, allergic skin reactions; they can appear even after low doses in sensitive subjects. The constumption of alcohol must be avoided during the treatment.

Semisynthetic and Synthetic Derivatives :

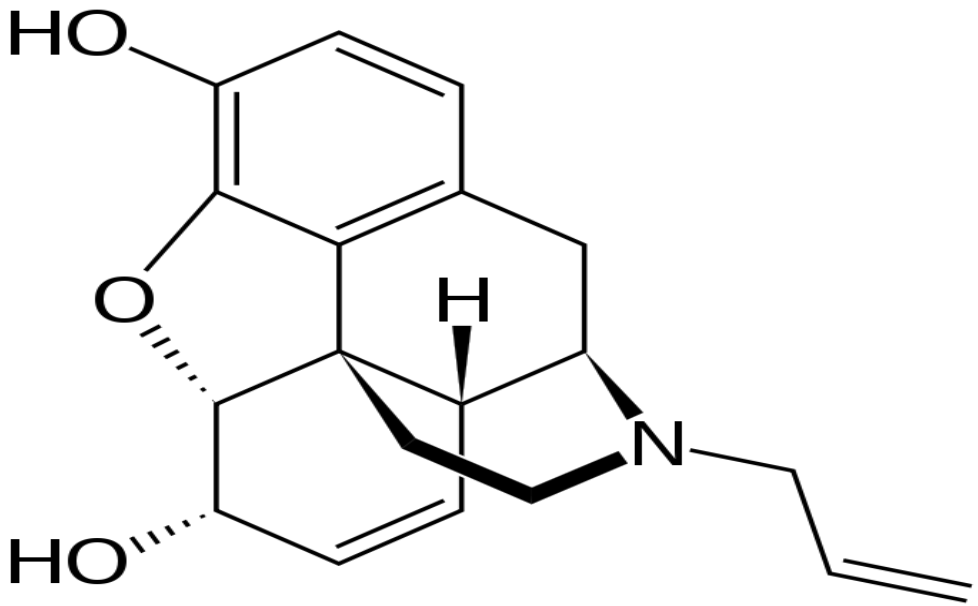
- Ethylmorphine : Antitussive
- Apomorphine : Emetic
- Buprenorphine : Opioid antagonist
- Nalorphine : Narcotic antagonist
- Naloxone : Opioid antagonist
- Oxycodone : Analgesic
- Heroine : This is a very special case, since this compound has no use in therapeutics, but has great abuse potential. The production, marketing and use of heronine are prohibited.



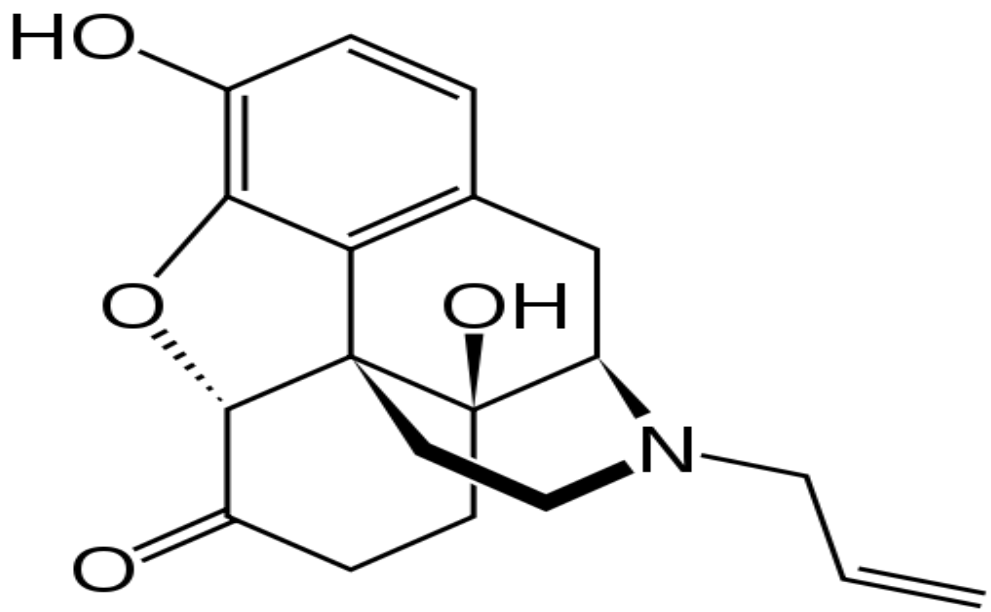
Apomorphine



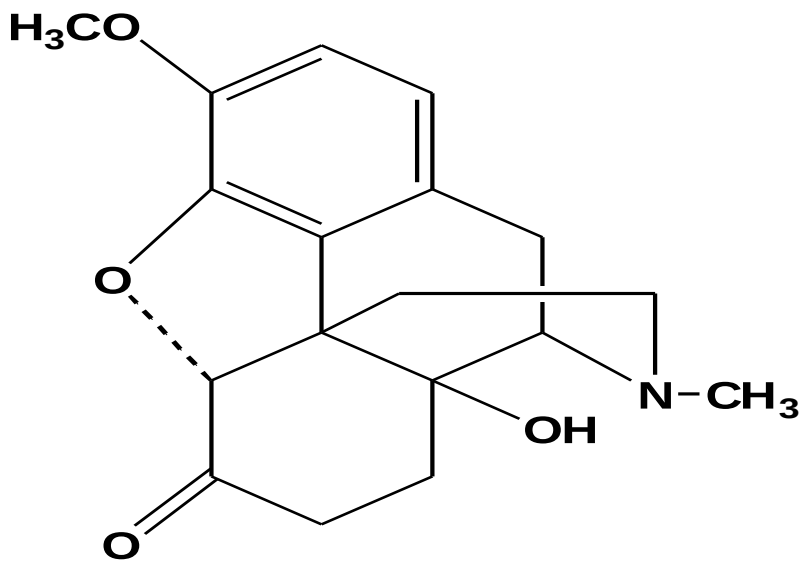
Buprenorphine



Nalorphine



Naloxone



Oxycodone

Papaver somniferum is cultivated in Turkey in some districts under permission

- Afyon
- Amasya
- Ankara (Nallıhan)
- Balıkesir(Balya, Bigadiç, İvrindi, Kepsut, ,)
- Burdur
- Çorum

- Denizli
- Eskişehir
- İsparta
- Karaman (Karatay, Selçuk)
- Konya (Akşehir, Beyşehir, Çumra, Doğanşehir, Ilgın, Kadınhan, Meram)
- Manisa (Merkez, Demirci, Gördes, Köprübaşı, Kula, Sarıgöl, Selendi)
- Tokat
- Uşak

Some important turkish *Papaver* species

Papaver fugax **contains thebaine**

Papaver pseudo-orientale

Papaver dubium

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