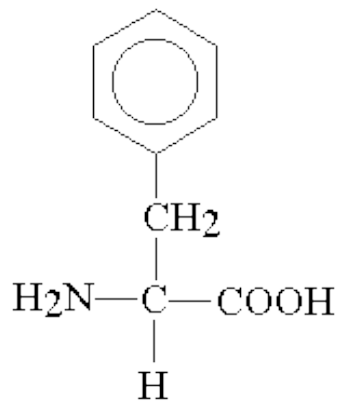
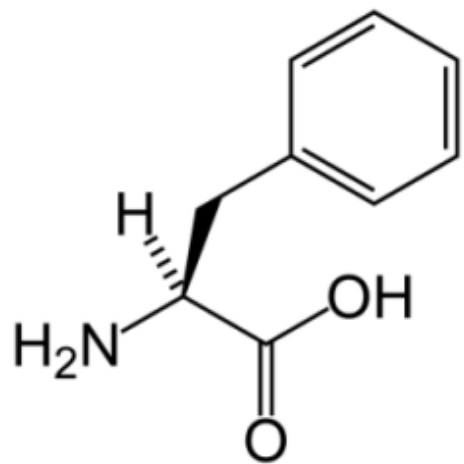
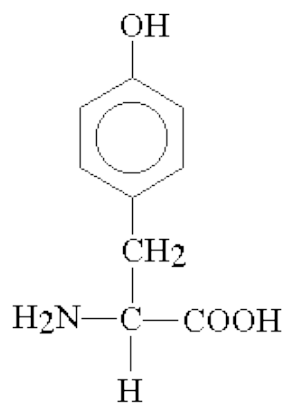
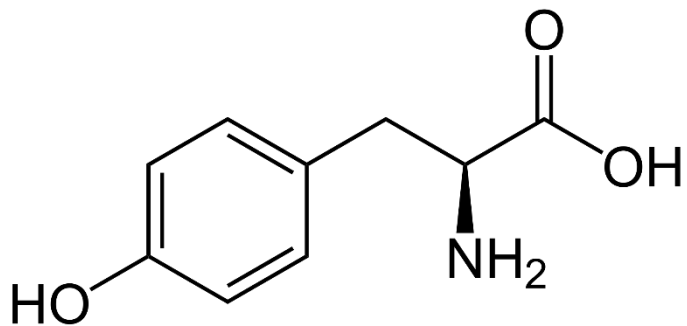
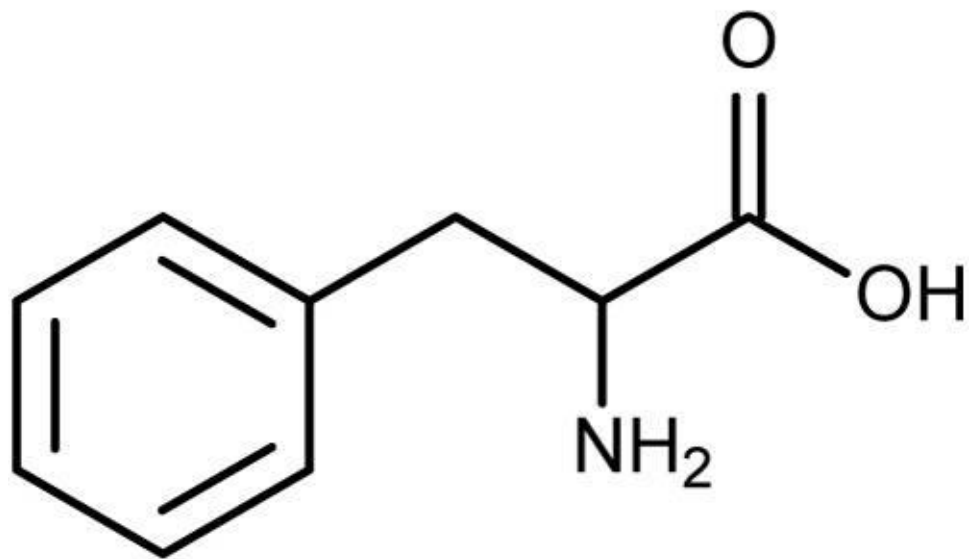


Alkaloids Derived from Phenylalanine and Tyrosine

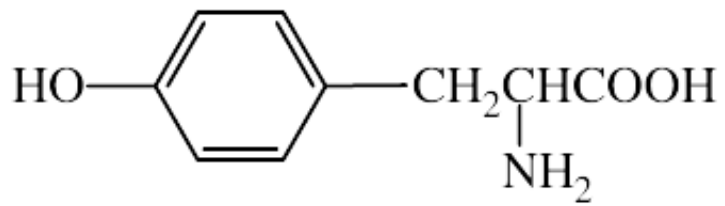
Prof. Dr. Ali Hikmet Meriçli



phenylalanine



tyrosine



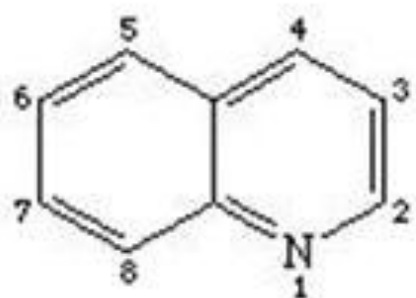
TYROSINE

GENERALITIES : A very large number of alkaloid structures arise from the metabolism of aromatic amino acids (phenylalanine, tyrosine), and at first approximation, these are always **isoquinoline** alkaloids.

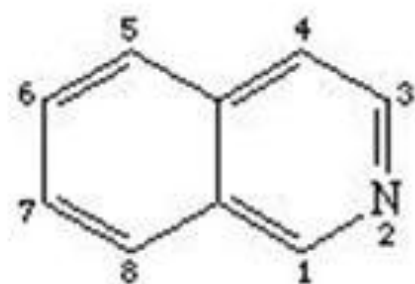
The alkaloids derived from phenylalanine and tyrosine which will retain our attention are compounds in which the basic structural nucleus is isoquinoline, or more often a 1,2,3,4-tetrahydroisoquinoline.

We shall distinguish, besides phenethylamines, five main groups of alkaloids as a function of the nature of the precursor(s) which react(s) with the aromatic amino acid to form the final structure.

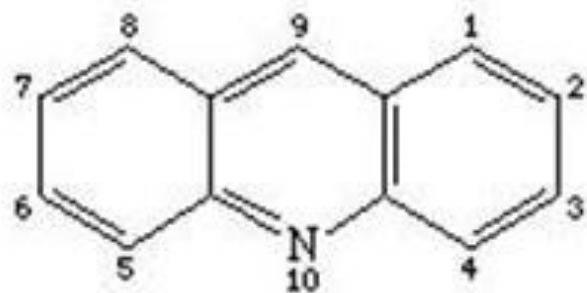
- 1. Simple Tetrahydroisoquinoline Alkaloids**
- 2. Benzyltetrahydroisoquinoline Alkaloids**
- 3. Phenethylisoquinoline Alkaloids**
- 4. Alkaloids of the Amaryllidaceae**
- 5. Monoterpenoid Isoquinoline Alkaloids**



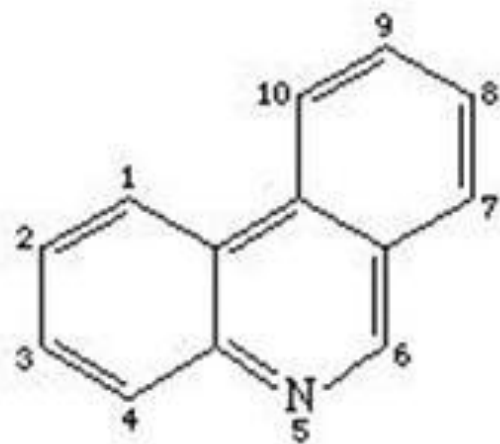
quinoline



isoquinoline



acridine



phenanthridine

Phenethylamines

Phenethylamines occur in many plants. Some are species specific (ephedrine, mescaline, cathinone) and have marked pharmacological properties, others are common products of the metabolism of aromatic amino acids such as tyramine or phenylalanine.

Phenethylamine-containing drugs

Ephedras

Ephedrae herba

efedra

Ephedra ssp. (especially Asian *Ephedra sinica*)

Ephedraceae

In Turkey grow

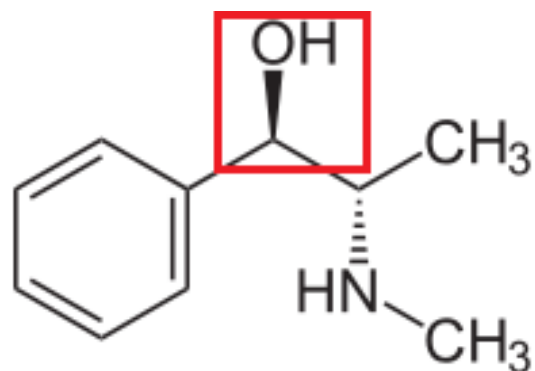
Ephedra major,

E. camphylopoda

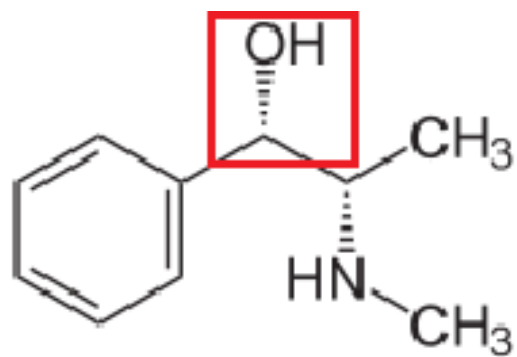
Ephedra fragilis grows in Cyprus

Although ephedrine is the topic of a monograph in the 3rd edition of the European Pharmacopoeia, ephedra has long disappeared from most pharmacopoeias : only synthetic ephedrine still finds some uses.

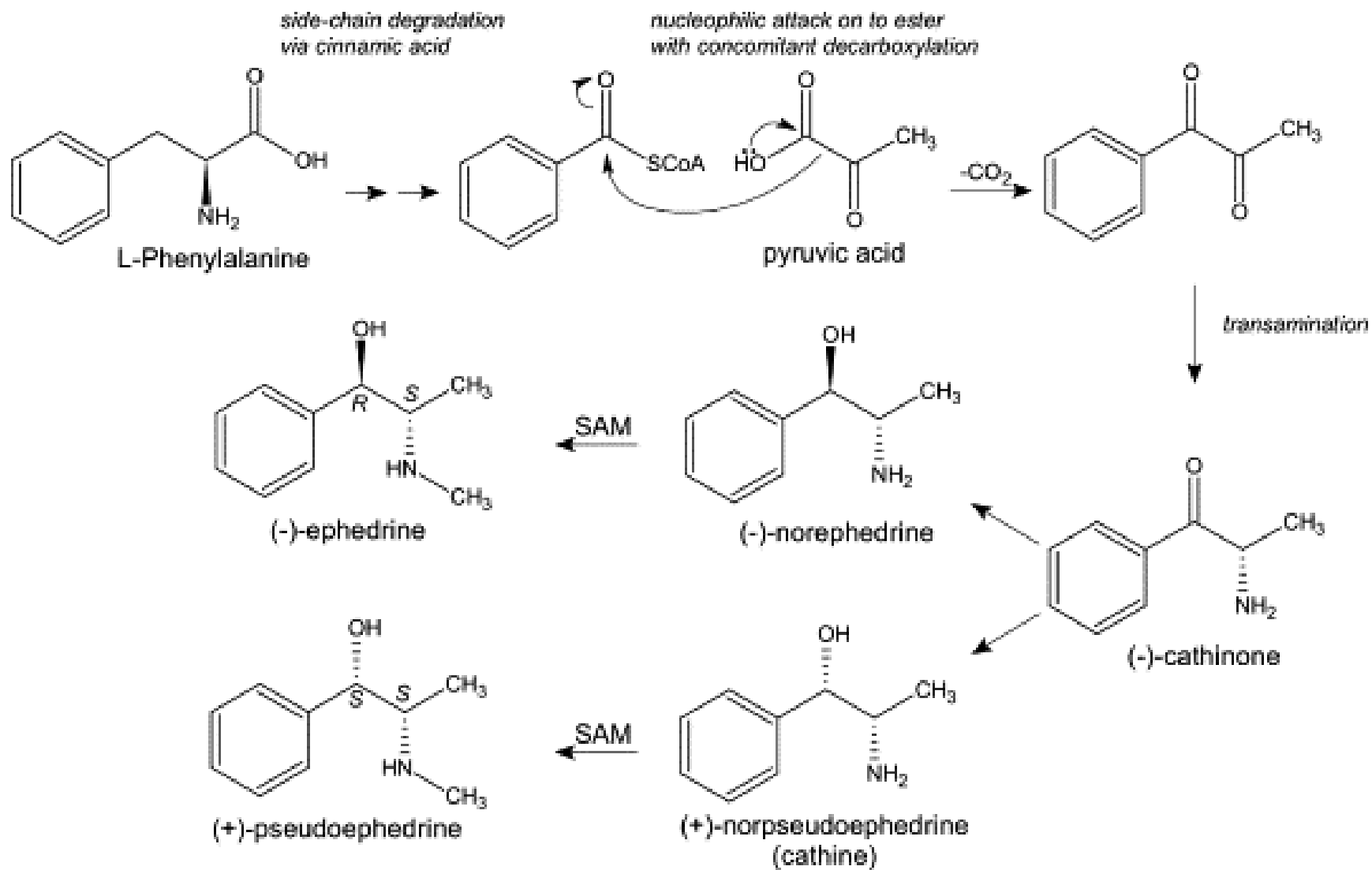
Chemical Composition : Flavonoids and proanthocyanidines have been identified in the drug, but nitrogen-containing substances –**protoalkaloids**- are the focus of attention. These are phenethylamine-type derivatives and their concentration, which varies as a function of the species, can exceed 2%. The chief constituent is almost always (-)-ephedrine, which represents from 40 to 90% of the total alkaloids. The other important alkaloid is (+)-pseudoephedrine.



Ephedrine

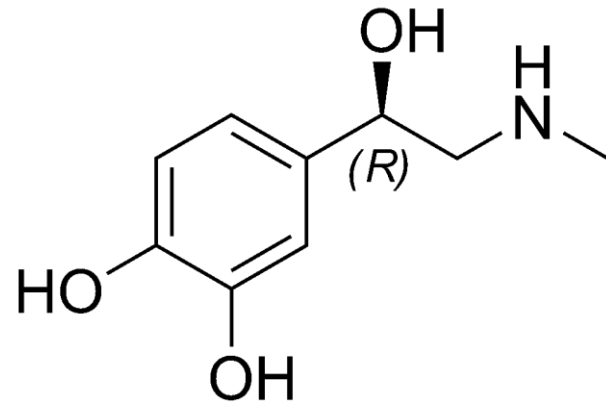


Pseudoephedrine



Biosynthetic pathway of phenethylamines

Pharmacological Activity : Ephedrine is an indirect sympathomimetic. Structurally very close to adrenaline, it triggers the release of endogenous catecholamines from the post-ganglionic sympathetic fibers. It stimulates cardiac automaticity and has a positive inotropic activity; it accelerates respiration and increases its intensity; it is bronchodilator and a stimulant of the brain stem respiration center; it decreases the contractility of the bladder. It is not metabolized much, can be used orally, and its duration of action is longer than that of adrenaline.



adrenaline

Ephedrine is well resorbed and highly lipophilic. High doses can cause headaches, anxiety, tremors, insomnia, and psychotic manifestations; redness of the face, nausea, tachycardia, and precordial pain, sweating, urinary retention and more. (+)-pseudoephedrine is experimental anti-inflammatory agent.

Uses of ephedras : It is believed that in Asia, the drug has been used for about 5 millenia. **Mahuang** consists of the stems of *E. sinica*, *E. intermedia*, and *E. equisetina*, and is officinal in China where it was used as an antiasthmatic, diuretic, and sudorific.

In the United States ephedras and ephedrine have been presented for a few years as potential aids in weight loss.

Uses of ephedrine : Ephedrine hydrochloride has long been used to treat the acute attack of asthma. Ephedrine is also an ingredient of syrups and other formulations designed for the symptomatic treatment of non-productive coughs.

Uses of pseudoephedrine : Pseudoephedrine hydrochloride, alone or in combination (with chlorphenamine, ibuprofen, paracetamol, or triprolidine), is an ingredient of drugs designed for the symptomatic treatment of nasal congestion and rhinorrhea. These products are contraindicated in children and in patients taking MAO inhibitors. Pseudoephedrine has a low toxicity, but it can cause dryness of the mouth, insomnia, sweating and anxiety.

Chat

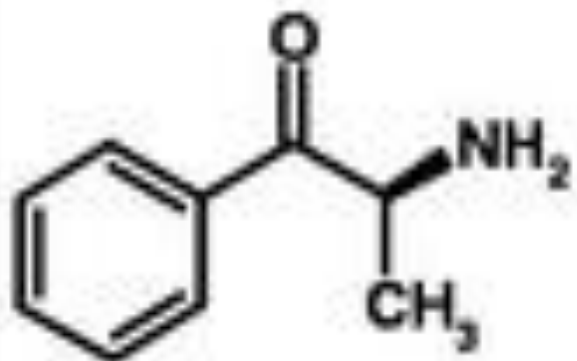
Catha edulis

Chathae folium

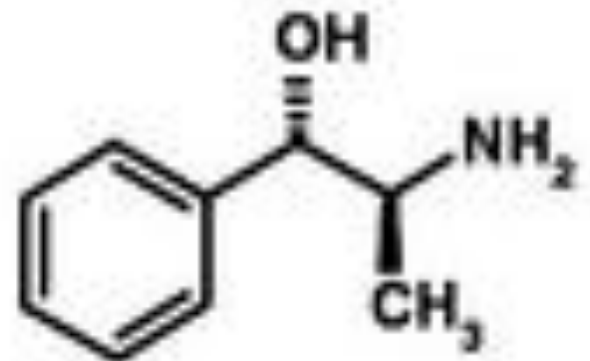
Celastraceae

Khat is a shrub, also known as Abyssinian tea, it is native to the horn of Africa; it is cultivated in the south-east of the Arabian peninsula.

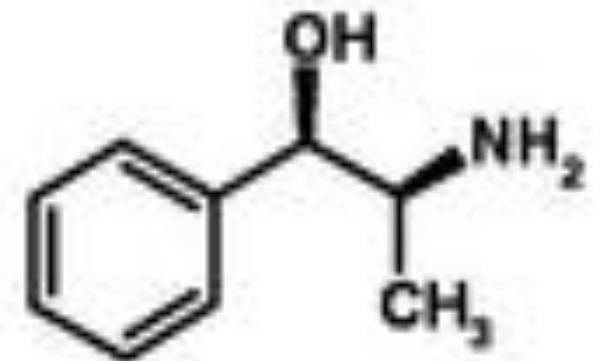
Chemical Composition The leaves contain flavonoids, and arylalkylamines (the khatamines), which are responsible for the activity of the drug. In the fresh and young leaves, the chief constituent is cathinone. In the dried drug and in older leaves, this (-)-cathinone has been converted to an 80-20 mixture of (+)-norpseudoephedrine and (-)-norephedrine.



Cathinone



Norpseudoephedrine
(cathine)



Norephedrine
(phenylephedramine)

Pharmacological Activity, Toxicity : Pharmacologically, the activity of (-)-cathinone is qualitatively quite comparable to that of D-amphetamine : it causes anorexia, hyperthermia, respiratory stimulation, mydriasis, arrhythmia, and hypertension. The effects are characterized by a subjective and euphoric sensation of increased energy, well-being, self-confidence, mental acuity, and ease in thought formation. Later on undesired effects can appear : insomnia, nervousness, and nightmares.

Use of khat : The fresh leaves, sold within 24 hours of harvest, constitute a masticatory known for its stimulating properties. Traditionally, the leaves (50-200 g) are chewed one by one, kept in the mouth for a while then most often spit out.

Isoquinoline Alkaloids

-Simple Tetrahydroisoquinolines-

Peyote

Lophophora williamsii

Peyote

Cactaceae

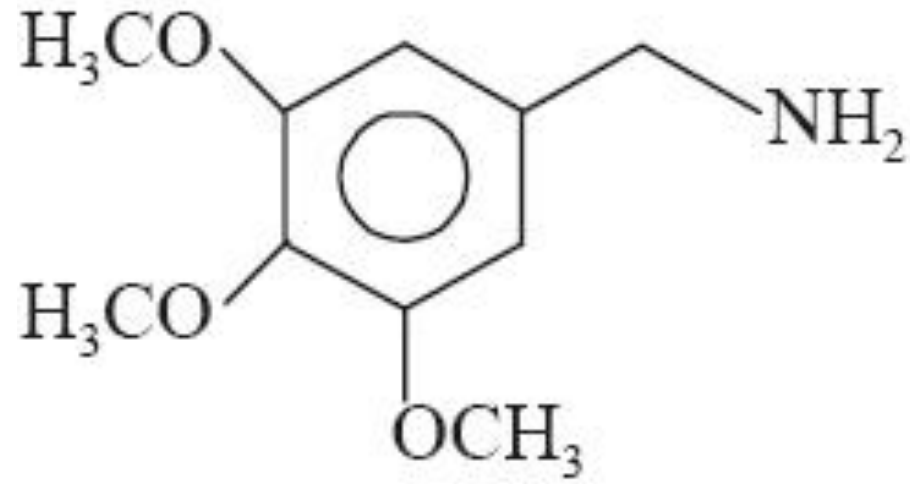
Considered a divine plant by the Aztecs, this cactus is particularly **potent hallucinogen**. This is the «plant that makes the eyes amazed», in other words causes visual hallucinations, due to the CNS activity of a phenethylamine alkaloid, **mescaline**.

The drug consists of the aerial part, sliced and dried in the sun (**mescal buttons**). Its harvest was traditionally the occasion for a complex religious ritual.

The drug contains a large amount of mucilage and about fifty nitrogen-containing compounds : phenethylamines and tetrahydroisoquinolines (fresh plant : 0.5-1%, mescal buttons : 6%).

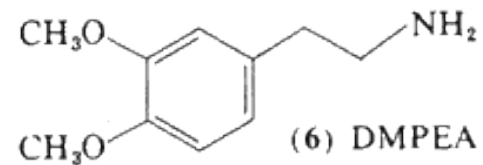
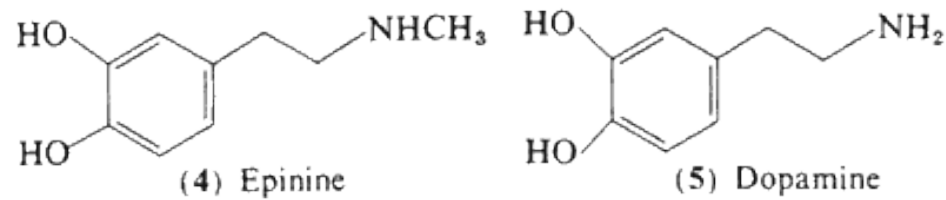
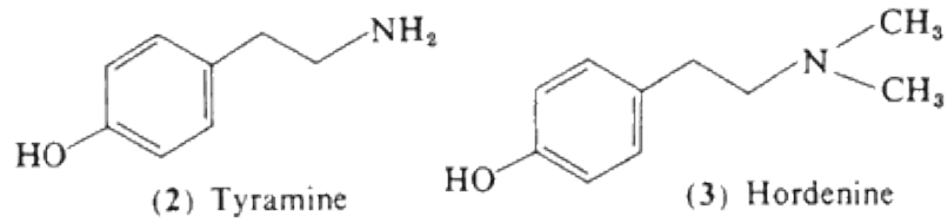
The phenethylamines include mescaline (= 3,4,5-tri-methoxy-phenethylamine), and its derivatives, also hordenine, tyramine and dopamine. The chief tetrahydroisoquinoline alkaloids are anhalamine, anhalonidine, and lophophorine.

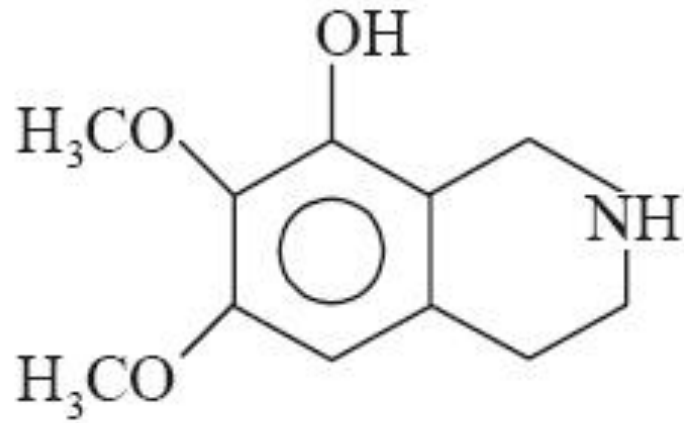
The ingestion of peyote essentially causes psychic effects. Mescaline has clinical effects resembling those of LSD (lysergic acid diethylamide). The physical symptoms that accompany the hallucinations are mydriasis, tachycardia, a sensation of change in temperature, nausea, and anxiety.



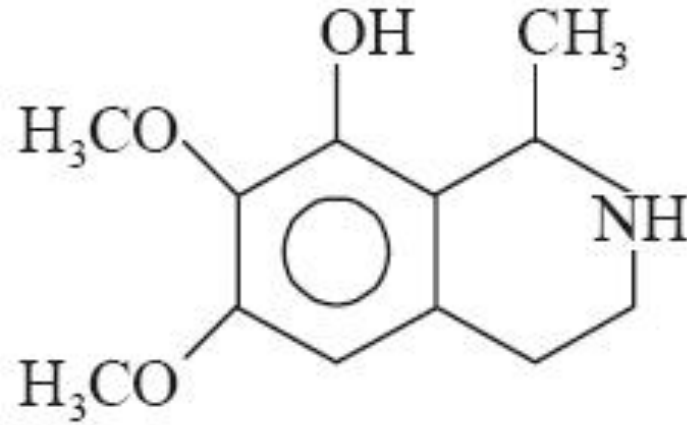
Mescaline

Phenethylamines in Peyote



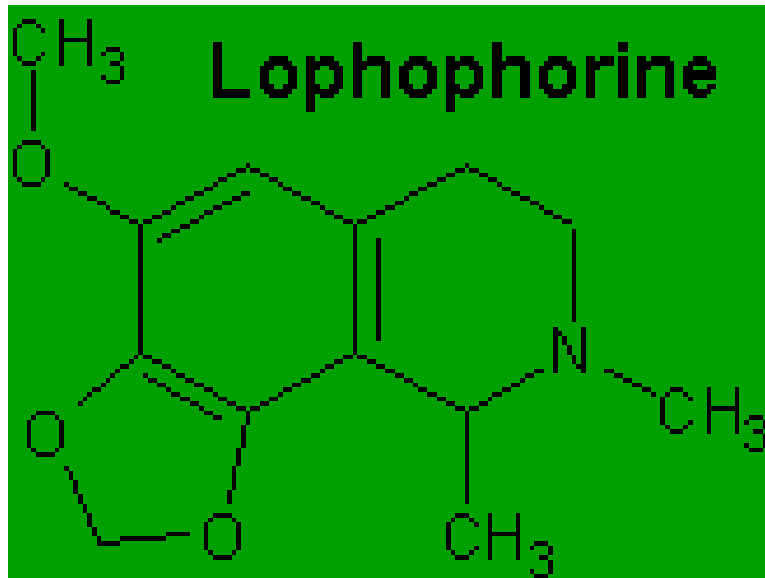


Anhalamine



Anhalonidine

Tetrahydroisoquinolines in
Peyote



Isoquinoline Alkaloids

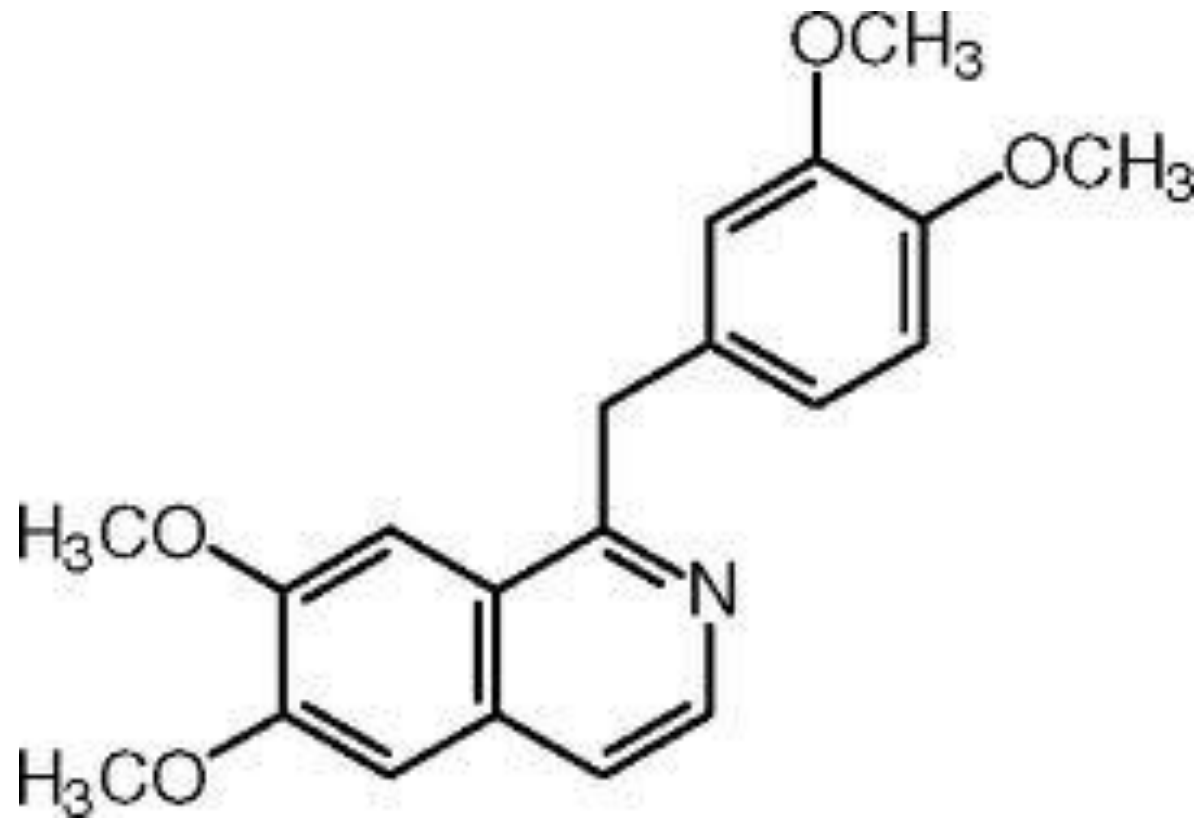
Benzyltetrahydroisoquinolines

Simple Benzylisoquinolines

The quasy totality of these simple compounds are 1,2,3,4-tetrahydro derivatives, in other words benzyltetrahydroisoquinolines. In a few exceptional cases, they are aromatic : one example is **papaverine**.

1. Biosynthetic Origin : Benzyltetrahydroisoquinolines are pivotal intermediates in the metabolism of isoquinoline alkaloids, and are formed by a Mannich-type condensation between two metabolites of phenylalanine.

Only one alkaloid in this group is currently used in therapeutics, namely **papaverine**. Although it is found in **opium** and in the various parts of the opium poppy, this simple alkaloid is, in practice, obtained by total synthesis.



Papaverine

Papaveris fructus

Papaver somniferum

Papaveraceae

Haşhaş

Pharmacological activity : Papaverine is practically devoid of effects on the CNS. It is a musculotropic spasmolytic which relaxes smooth muscle fibers, especially those of cerebral, pulmonary, and systemic peripheral blood vessels, but also those of the bronchia, intestines, ureters, and biliary ducts. The spasmolytic activity is more pronounced in the case of a pre-existing spastic condition. Papaverine has an effect on the heart muscle : it decreases conductivity and excitability, prolongs the refractory period, and increases coronary blood flow.

Uses : **Papaverine is still fairly widely used**. In addition to being indicated as a smooth muscle relaxant (injectable solution at 4%) and for the symptomatic treatment of the intermittent claudication due to chronic occlusive arterial disease of the lower limbs, it is proposed :

1. to improve certain symptoms of senility (e.g. loss of attention and memory); 2. for the symptoms of ischemia in the eye.

Contraindications include intracranial hypertension, parkinsonism, and intracardiac conductivity alterations, but papaverine is not a hypotensive agent and only rarely has side effects (potential tachycardia, constipation, and bilirubinemia). As an antispasmodic, it is a component of proprietary drugs designed to relieve the symptoms of functional colopathy, particularly flatulence and diarrhea.

Reference Books :

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Other Books

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