

Pyrrolizidine and Piperidine Alkaloids

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Pyrrolizidine Alkaloids

Pyrrolizidine alkaloids

Occurrence

- In 288 species, 40 genera, **about 60 medicinal plants** (WHO, 1988).
- **Asteraceae, Boraginaceae, Fabaceae**, Apocynaceae, Euforbiaceae, Poaceae, Ranunculaceae, Scrophulariaceae

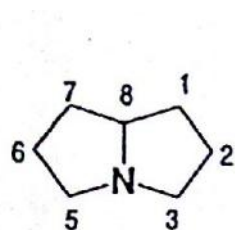
General structure of the alkaloids

Vast majority of these alkaloids are **esters** of **aminoalcohols** and of one or two **aliphatic carboxylic acids**.

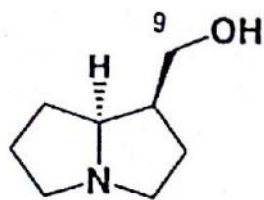
Pyrrolizidine alkaloids

Aminoalcohols (necins):

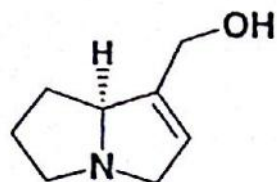
- They are **derivatives of pyrrolizidine**.
- The **configuration at C8** varies, and is most often H-8 α .
- The ring is not always **unsaturated at C-1**, but it is always substituted by a **hydroxymethyl group** at this position.
- A second **hydroxyl group** is possible at **C-7**, and in rare cases, a third hydroxyl group at **C-2**, or at **C-6**.
- In some cases, **oxidation at C-8** leads to the opening of the bicyclic structure (otonecin).



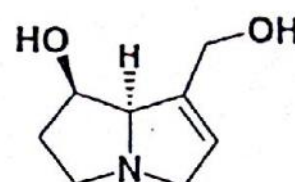
Pyrrolizidine



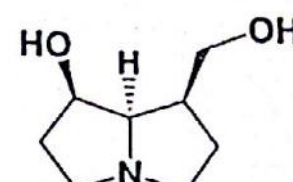
Isoretronecanol



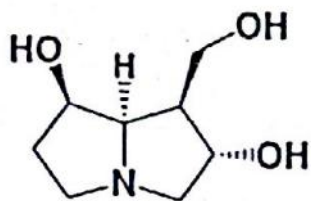
Supinidine



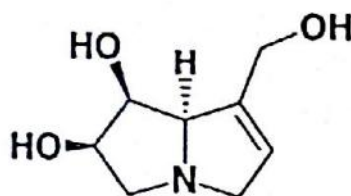
Retronecine



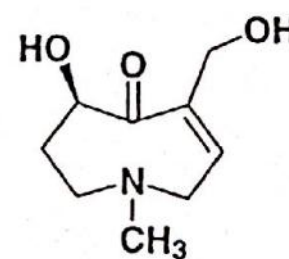
Platynecine



Rosmarinecine



Crotanecine

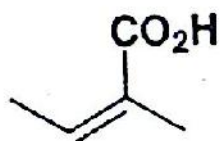


Otonecine

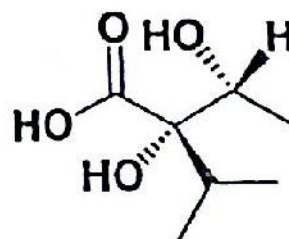
Pyrrolizidine alkaloids

The acids (necic acids) are **C5, C7, C8** or **C10** aliphatic acids,

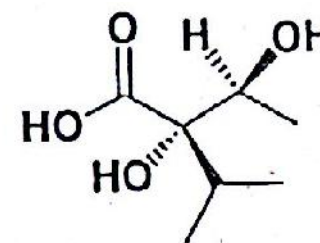
- *sometimes simple*: angelic or tiglic acids with five carbon,
- *most often specific* to this type of alkaloid:
 - C7 hydroxyisopropylbutanoic monocarboxylic acids (lasiocarpic, trachelanthic, viridifloric acids)
 - C8 dicarboxylic acids (monocrotalic acid)
 - C10 dicarboxylic acids (senecic, jacobinecic, retronecic acids)



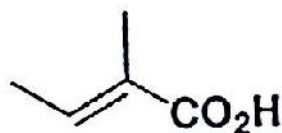
Angelic acid



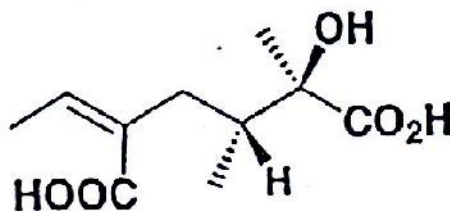
(+)-Trachelanthic acid



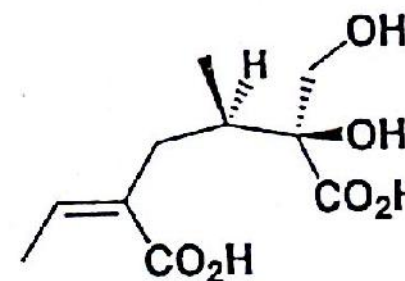
(-)-Viridifloric acid



Tiglic acid



Senecic acid



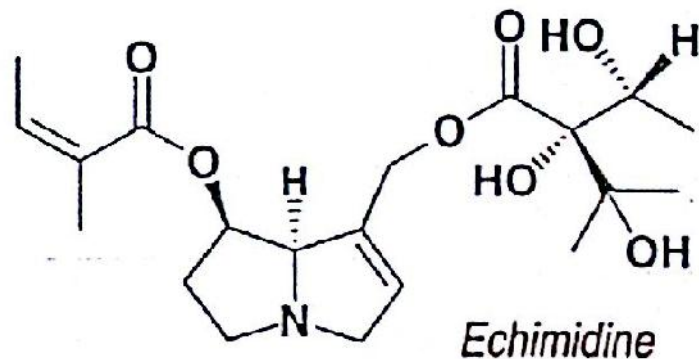
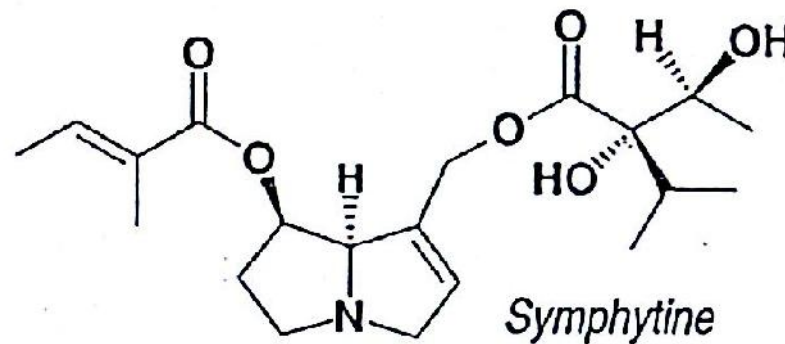
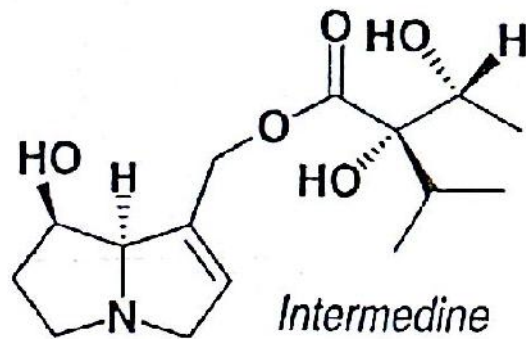
Isatinecic acid

Pyrrolizidine alkaloids

Alkaloids:

Mono- or diesters of monocarboxylic acids (characteristic of the **Boraginaceae**):

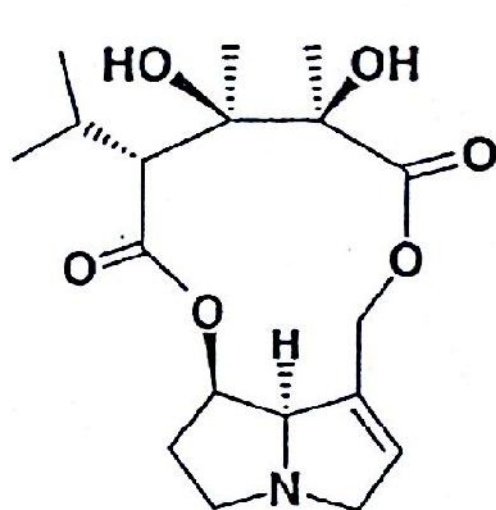
- **C-9 OH** is esterified by a hydroxyisopropylisobutanoic acid (intermedine, lycopsamine)
- **C-7 OH** is esterified by either angelic or tiglic acid (in case of diesters only)



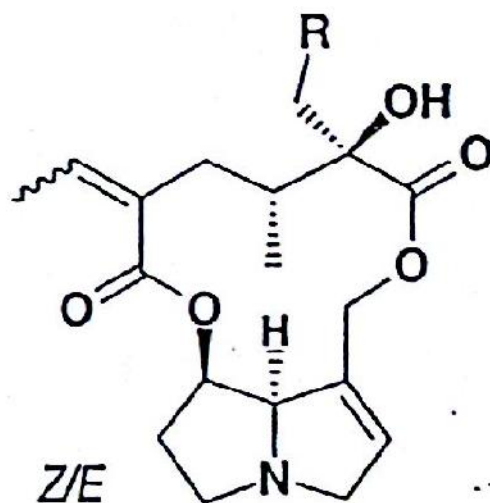
Pyrrolizidine alkaloids

Macrocyclic diesters (mainly in the **Asteraceae**):

The pyrrolizidines that are **7,9-diols** may be esterified by a dicarboxylic acid, which leads to a macrocycle (senecionine, **symphitine**).



Trichodesmine



Z

R = H : *Senecionine*

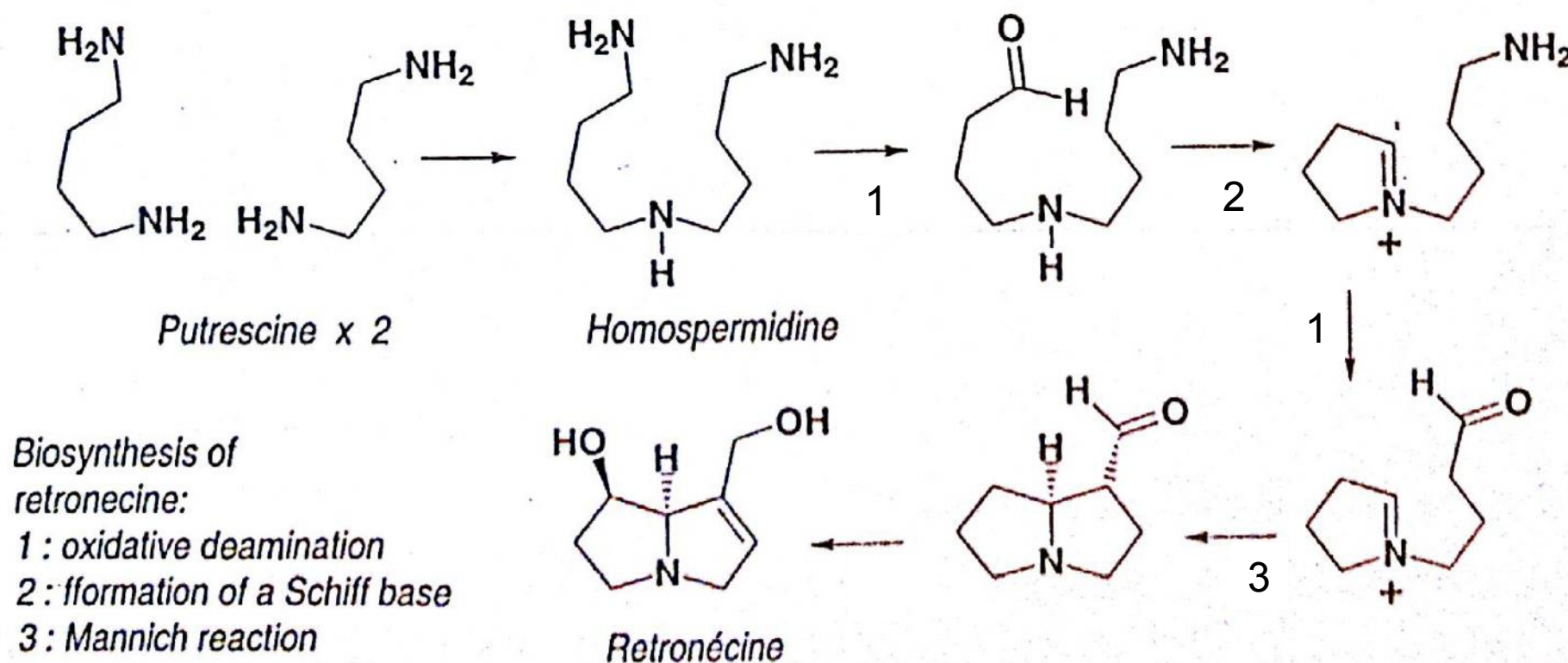
R = OH : *Retrorsine*

Z

R = H : *Seneciphylline*

R = OH : *Ridelline*

Biosynthesis of pyrrolizidine alkaloids



The NAD^+ dependent condensation of two molecules of putrescine (or putrescine + spermidine) yields a symmetrical intermediate, namely homospermidine.

The latter is subsequently cyclized according to a classic sequence: 1, 2, 1, 3.

Pyrrolizidine alkaloids

Toxicity

These alkaloids are **cytostatics**, some of them **mutagenic** and **can cause hepatic tumors**.

A. for Animals:

- Consumption of **feedstuff contaminated** by these toxic plants. Effective treatment do not exists.
- The **toxicity is chiefly hepatic**: swelling of the hepatocytes, centrilobular necrosis, karyomegaly, thrombosis of the hepatic vein, increase in bilirubinaemia ↑, and liver failure.
- Symptoms depends on alkaloid structure, type of intoxication and the animal species.

B. for Humans

Mainly chronic intoxication. Eg.: consumption of grains contaminated by the seeds of *Crotalaria retusa* L. (in Afghanistan, India in the seventies).

Crotalaria retusa L. traditionally used for the flu or pulmonary ailments in the Antilles.

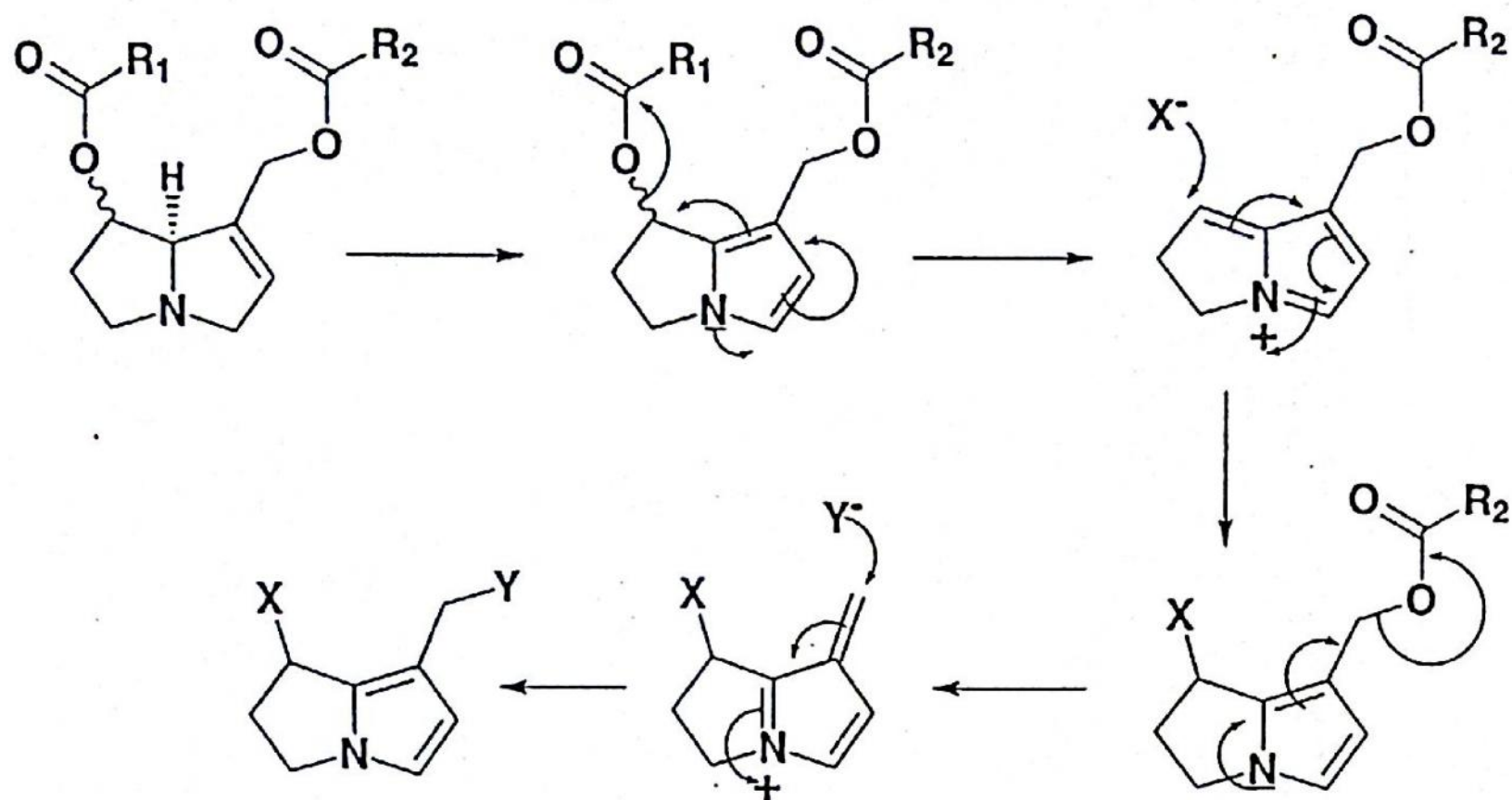
Structure and toxicity:

To be toxic the alkaloid must be **dehydrogenated** at **C-1** and **C-2**, and **at least monoesterified**.

Toxicity: Monoesters < acyclic diesters, < **macrocyclic diesters**.

Pyrrolizidine alkaloids

Pyrrole derivatives resulting from the microsomal oxidation of the pyrrolizidines in the liver, **react as alkylating agents** with **biological nucleophiles** such as nucleic and protein macromolecules.



Oxidation of the pyrrolizidines

Pyrrolizidine alkaloids

Experiments in rats

- **several alkaloids** (retrorsine, **senkirkine**, monocrotaline, lasiocarpine, **symphitine**) and **a number of plants** (*Tussilago farfara* L., *Symphytum officinale* L., *Petasites japonicus* Maxim) **induced hepatic tumors** when administered orally on a regular basis.
- The **mutagenic** and **teratogenic properties** of several alkaloids in this group have also been shown experimentally.

Exceptions

- **Platiphylline** is not toxic and can be considered as an **antispasmodic** and a **mydriatic**.
- **Others**, such as **indicine-N-oxide**, are **anticancer agents** in experimental conditions, but can not be used in humans.

Borage, *Boraginis herba*, *Borago officinalis* L. Boraginaceae

This **annual plant** is indigenous to the Near East and is currently **cultivated to produce seeds** containing unsaturated fatty acids.

It is easy to identify by its **leaves** covered with **rough hairs**, its bright **blue flowers**, with **hairy sepals**, and its connivent stamens and black filaments with a horn-shaped appendix.



Constituents

Stem and leaves: **mucilage**, small quantities of **pyrrolizidine alkaloids**: lycopsamine, intermedine, amabiline, supinine.

Flowers : alkaloids as an **unsaturated derivative**, namely **thesinine**.

- There has been no pharmacological study of this drug.
- It is reputed to be a „sudorific” emollient, and diuretic.

▪Traditionally used

- to treat acute benign bronchial diseases.
- to enhance the renal elimination of water.

Common Confrey, *Symphytum officinale* L., Boraginaceae



Symphytum officinale L.

- A large **perennial plant** (0,5-1 m) with
- voluminous and fleshy rhizome,
- large leaves decurrent on a great part of their length, and
- white, pinkish, or purplish flowers, grouped in scorpioid cymes.
- It is very common in all of Europe.
- Several cytotypes exist ($2n= 24, 48, 40$).

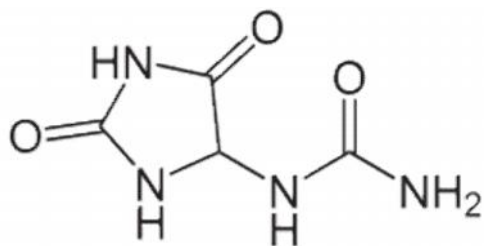


Symphyti radix, Constituents

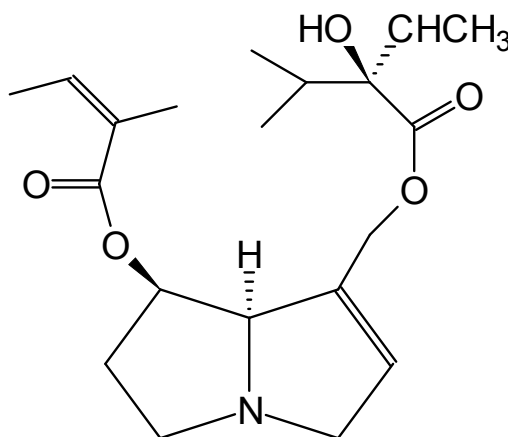
Root

- Fructanes, mucilage,
- **allantoin** (0.6-0.8 %),
- rosmarinic acid, litospermic acid,
- **pyrrolizidine alkaloids** (0.02-0.07%): lycopsamine, **intermediate** and their acetylated derivatives, **symphytine** and echimidine.

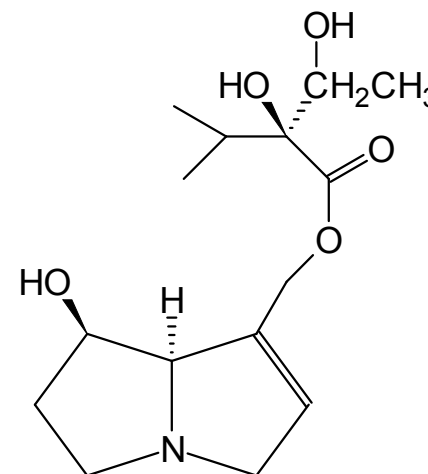
Leaves. **Pyrrolizidine alkaloids (0.003-0.2% !)**



Allantoin
(5-ureidohydantoin)



intermediate



symphytine

Symphyti radix

Effects

Helps tissue regeneration (allantoin, polysaccharides), antiinflammatory, antioedemic.

Uses

- The **root** is an **ingredient of herbal remedies**.
- Indications must be **limited to local use**: emollient, itch-relieving, and trophic protective (cracks, abrasions, chaps).
- It can be applied **only to unbroken skin**, and for maximum **4-6 weeks in a year**.

Toxicity

- When administered **orally to rats** for a long period of time, **the roots and leaves** of comfrey **induce hepatic tumors** in nearly half of the populations, and **so does symphytine**.
- The **percutaneous absorption** of the alkaloids has been studied **in animals**, is **small**, and **the risk seems negligible**.

Coltsfoot, *Tussilago farfara* L., Asteraceae

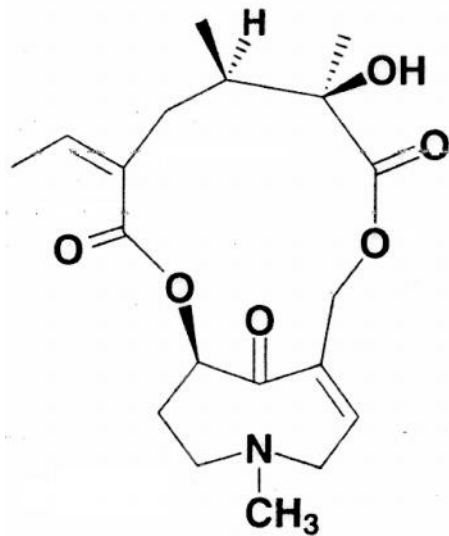
- A small **perennial plant** very common in Europe and in Northern Asia.
- In very early spring, it produces capitulum of **yellow flowers** on a scaly stalk.
- Rosettes of **cordate and coriaceous leaves** that are pubescent on the lower side appear later.



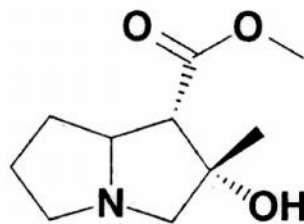
Farfarae folium et flos

Constituents

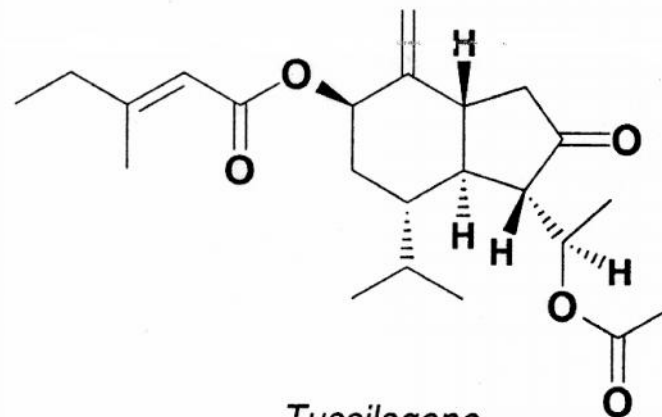
- **pyrrolizidine alkaloids** (few ppm):
 - **senkirkine!**, and artefacts of the extraction with MeOH: **tussilagine**, isotussilagine,
 - the *oriental and North American drugs* contain, in addition, **senecionine**, which is more toxic alkaloid (importance of geographical origin),
- acidic mucilage (~6 %), triterpenes, flavonoids, carotenoids,
- **tussilagon**, a **sesquiterpenoid ester** in the floral buds



Senkirkine Toxic!



Tussilagine



Tussilagone

Farfarae folium et flos

Actions

- **Farfarae folium**. Antitussive, antiinflammatory.
- **Tussilagone** (sesquiterpenoid ester)
 - **respiratory stimulant** (ventilation and arterial blood pressure↑),
 - **inhibits PAF-acether**, a mediator whose role in inflammation and respiratory difficulties is known.

Uses

- Coltsfoot (**infusions, nebulisates**) continues to be used in phytotherapy (**tracheitis, chronic bronchopneumopathy**). It is widely self-administered (**cough teas**).
- The **oriental medicine** use it to treat asthma, bronchitis, and other **respiratory ailments**.
 - **Precautions:** It can be used max. **for 4-6 weeks in a year**.

Toxicity

- Senkirkine: cocarcinogenic, can induce hepatic tumors.
- Contraindications: Pregnancy and lactation.

European ragwort, *Senecio jacobaea* L. , Asteraceae

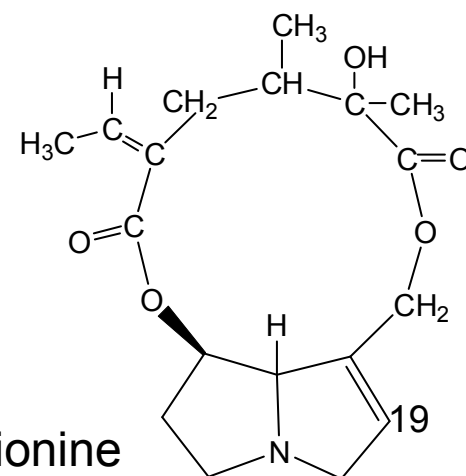
- A **perennial plant**, widespread in neglected meadows and along country roads.
- It is characterized by **very divided leaves** which hug the stem with two jagged little wings.
- The **yellow flowers** are grouped in a **corymb of radiate capitulums**.

Constituents. **Pyrrolizidine alkaloids**, esters of retronecine: seneciphylline, **senecionine**, jacobine, jacozone, and closely related products.



Intoxications. Mainly in **horses**, who lose their appetite, and develop **jaundice**, edema, ascites, and finally, an encephalopathy, which includes **gait anomalies**.

Accidents occur following the **repeated ingestion of preserved fodder**. (Often fatal, but quite rare intoxication in Europe).



Senecionine

Common groundsel, *Senecio vulgaris* L., Asteraceae

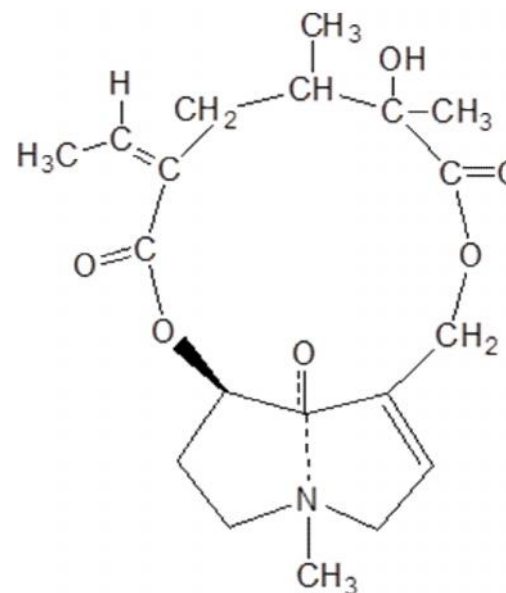
Constituents

Pyrrolizidine alkaloids (0,05-0,1%): seneciphylline, **senecionine**, retrorsine, spartioidine, usaramine, integerrimine.

Uses, *Senecionis herba*

- It is presented, without any pharmacological evidence , as capable of improving *venouos circulation*.
- As such – despite the presence of toxic pyrrolizidine diesters –it still finds some uses (*compound herb teas, extracts*).

Senecionine
Toxic pyrrolizidine alkaloid!



Quinolizidine Alkaloids

Scotch Broom, *Cytisus scoparius* (L) Link., Fabaceae



This plant also known as *Sarothamus scoparius* (L.) Wimmer ex Koch is a **bushy shrub** (50-150 cm) fond of siliceous soils and **very common in all of Europe**.

It is characterized by erect, angular, and glabrous branches,

at the apex of which are inserted **simple and sessile leaves**, whereas **at their base** the leaves are **petiolate and trifoliate** .

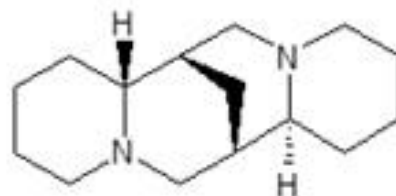
The flower's **zygomorphous corolla** with vexillar prefloration is **typical of the Fabaceae**. It has a short, bilabiate, and scarious calyx, and a coiled style.

The fruit is a *hairy and flattened pod* which turns black when ripe.

Sarothamni scoparii herba

Constituents

- **Quinolizidine alkaloids** : (-) **sparteine** (0.5-1%), **lupanine**, 17-oxosparteine, 4-hydroxylupanine, 13-hydroxylupanine.
- **Sparteine** (chief alkaloid in the brances, 60%), a tetracyclic alkaloid without oxygen atoms and **with two *trans*-fused *cis*-quinolizidine nuclei** (6*R*,7*S*,9*S*,11*S* isomer).
- **Flavonoids**: isoflavones (genistein) and flavones C-glycosides (**scoparozide**).
- **Amines**: (especially in the flowers, up to 2%) **tyramine**, **dopamine**, epinine.



(-) Sparteine

Sarothamni scoparii herba

Pharmacological Action, **Sparteine**

- A **mild ganglioplegic** blocking conduction and preventing the depolarization of the post-synaptic membrane.
 - In the **heart**, after a transient phase of ganglionic excitation,
 - it **shields the myocardium from central neurovegetative regulation**, and
 - *decreases* excitability, conductivity, and the frequency and amplitude of the *contractions*.
- An **oxytocic** causing a moderate increase in the tone and strength of the contractions of the uterus.

Sarothamni scoparii herba

Uses

- The **branches** are used **to extract sparteine**.
- Proprietary products based on **sparteine sulphate** are indicated
 - for sinus tachycardia of neurotonic origin and cardiac erethism,
 - in obstetrics, as an oxytocic during labor.
- Phytopharmaceuticals based on **broom flowers** may be (traditionally) used
 - to enhance renal and digestive elimination functions and
 - to enhance the renal excretion of water (watching out for possible drug interactions with MAO inhibitors).

Piperidine Alkaloids

Indian Tobacco, *Lobelia inflata* L., Campanulaceae



Indian tobacco grows wild in the Appalachian Mountains, **North America**.

It is a small **annual herb** (20-50 cm) with erect and ramnified stems.

The **leaves** are sessile and the blades have a **dentate margin**.

The **flowers** are pale **blue** with foliaceous bracts, and are gathered in **terminal racemes**; their inflated calyces become vesiculose after the floration.

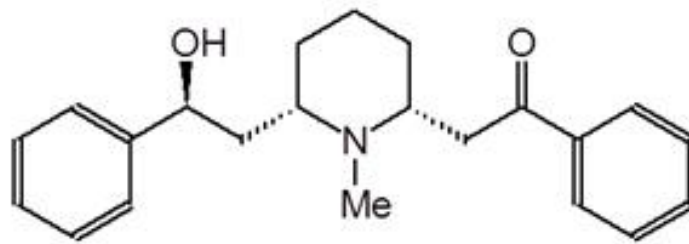


The commercial drug consists of 50-60 % **stems** which are **angular, hollow**, covered with **rough hairs** and mixed with broken leaves.

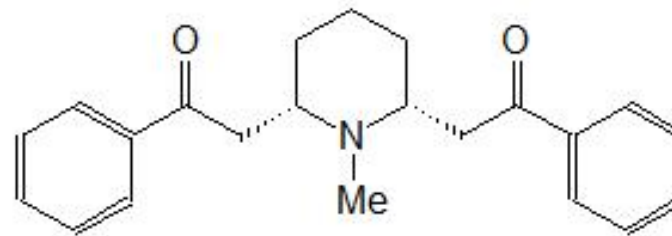
Lobeliae herba

Constituents

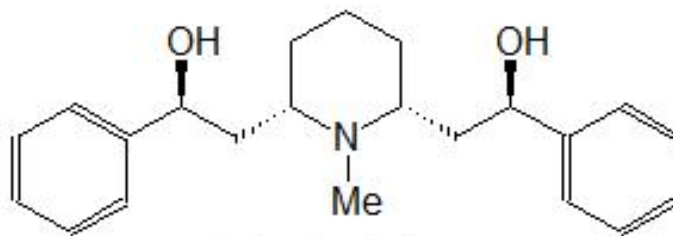
- 0.2-0.5 % alkaloids (> 50): piperidines [(-) lobeline (chief constituent), *meso*-lobelanine, *meso*-lobelanidine, lobinine] and piperideines.
- chelidonic acid, lobelic acid.
- Inflantint (fitoszterin)



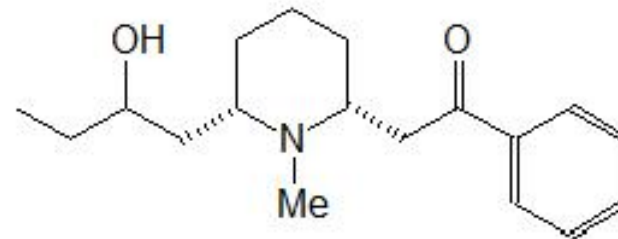
(2R,6S,8S)-(-)-lobeline



lobelanine



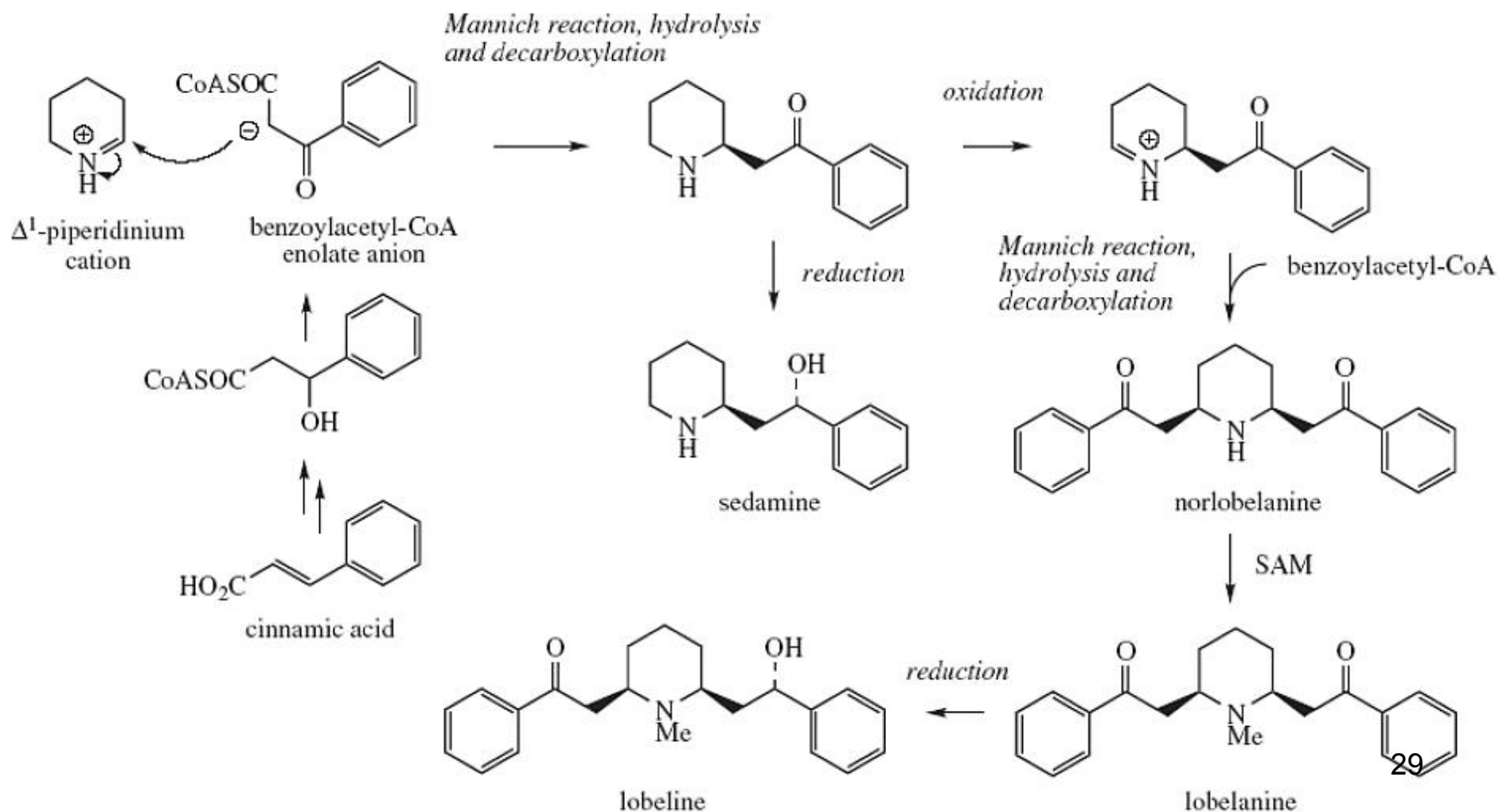
lobelanidine



lobinine

Biosynthesis of lobelia alkaloids

Biosynthetically, these alkaloids may be formed by a double Mannich reaction between two molecules of phenylalanine (*via* cinnamic acid and benzoylacetyl-coenzyme A) and one Δ^1 -piperidinium cation arising from lysine via cadaverine.



Lobeliae herba, Pharmacological activity

Lobeline

- It is a **respiratory stimulant** which enhances and accelerates the respiratory movements by
 - improving the reactivity of the **brain stem centers** to carbon dioxide and also,
 - acting by a reflex mechanism involving the **carotid chemoreceptors**.
- Secondly, it is a **ganglionic stimulant** and a **β -adrenergic bronchodilator**.
- It showed positive effects in the treatment of multidrug-resistant tumor cells [*in vitro*](#).
- Lobeline can be modified to lobelane which decreased methamphetamine self-administration in rats.
- It therefore opens a perspective in methamphetamine dependency treatment.
- The North American Indians smoked lobelia rather like tobacco (*Nicotiana tabacum*).
- **Lobeline stimulates nicotinic acetylcholine receptor sites in a similar way to nicotine, but with a weaker effect.**

Lobeliae herba, Uses

Lobeline

- **Formerly used** (IM or SC) *for resuscitation after asphyxia*, particularly to treat apnea in new borns,
- lobeline is **no longer used** because of its **substantial side effects** and **poor therapeutic index**.
- Several studies show that lobeline (in smoking cessation preparations) is ineffective in helping people to quit smoking.

Galenicals

- prepared from indian tobacco (**extract** and **tincture**) are ingredients of a few specialized medications designed **for the symptomatic treatment of various bronchopulmonary ailments**.

Piperine Amids:Piperaceae

Black Pepper, *Piperis nigri fructus*, *Piper nigrum* L., Piperaceae



- Pepper is one of the most ancient spices.
- It is a **perennial plant** originally from the south-west of **India** (Malabar Coast), and now **cultivated** in India, Indonesia, Malaysia, Sri Lanka, and South America (Brazil).
- Black pepper is **a flowering vine** with ligneous voluble stem affixed to their support by secondary branches.
- The **leaves** have an **oval acute blade** and are alternate.
- The **sessile flowers** have **no perianth** and are grouped by 20 to 20 units into **dangling spikes**.
- The **fruit** is a **berry** of 4-8 mm in diameter, which turns from green to **red as ripens**.

Piperis nigri fructus

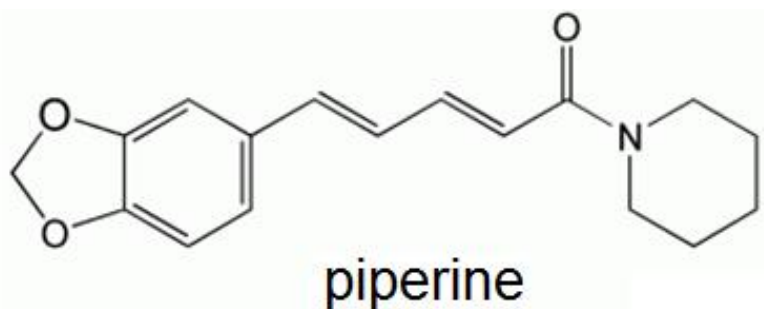
Different kinds of pepper are well recognized.

- **Green pepper:** the **whole fresh berries**, generally **conserved** in acidic aqueous solution (or frozen, or pasteurized). Highly aromatic.
- **White pepper:** the **fruits** collected **at full maturity**, dried after removing fruit pericarp and the external layer of mesocarp.
- **Black pepper:** **collected** immediately **after the first berries turn red**, dried than separated from the stalks. The **dried fruits** are **spherical** (3-6 mm) and particularly **hard**. Their surface is **brownish black** and **extremly wrinkled**.



Piperis nigri fructus

- The pepper *odor* is due to 1 to 3.5 % of an **essential oil** rich in terpenoid hydrocarbons, and
- the *pungent taste* to **amides** (5-10 %).
 - The chief constituent is **piperine**, an amide of piperidine and of piperic acid.
 - The other amides are **piperidines** (piperanine, piperettine), **pyrrolidines** (piperyline) or **isobutylamines**; The **acid** which is part of their structure **has a side chain of variable length** (5 to 10 carbon atoms).
- **Piperine** is a **CNS depressant** and an **anticonvulsant** in rats. Some of its **synthetic derivatives** have been **used in china** as **anti-epileptics**.



Piperidine Alkaloids
not from the Metabolism of Lysine

Poison Hemlock, *Conii fructus*, *Conium maculatum* L., Apiaceae



- A **large biennial herb** indigenous to Europe and naturalized in North and South America.
- This plant can be differentiated from most other members of the Umbelliferae /Apiaceae by its tall (1-2m), **smooth, purple-spotted stems**.
- The **sheathing leaves** have a **tripinnatisect blade** with acute lobes.
- The umbel has an involucre and involucels consisting of two to six short curved bracts.
- When crushed the whole plant releases an unpleasant „**mouse**” odor.

Poison hemlock, Constituents

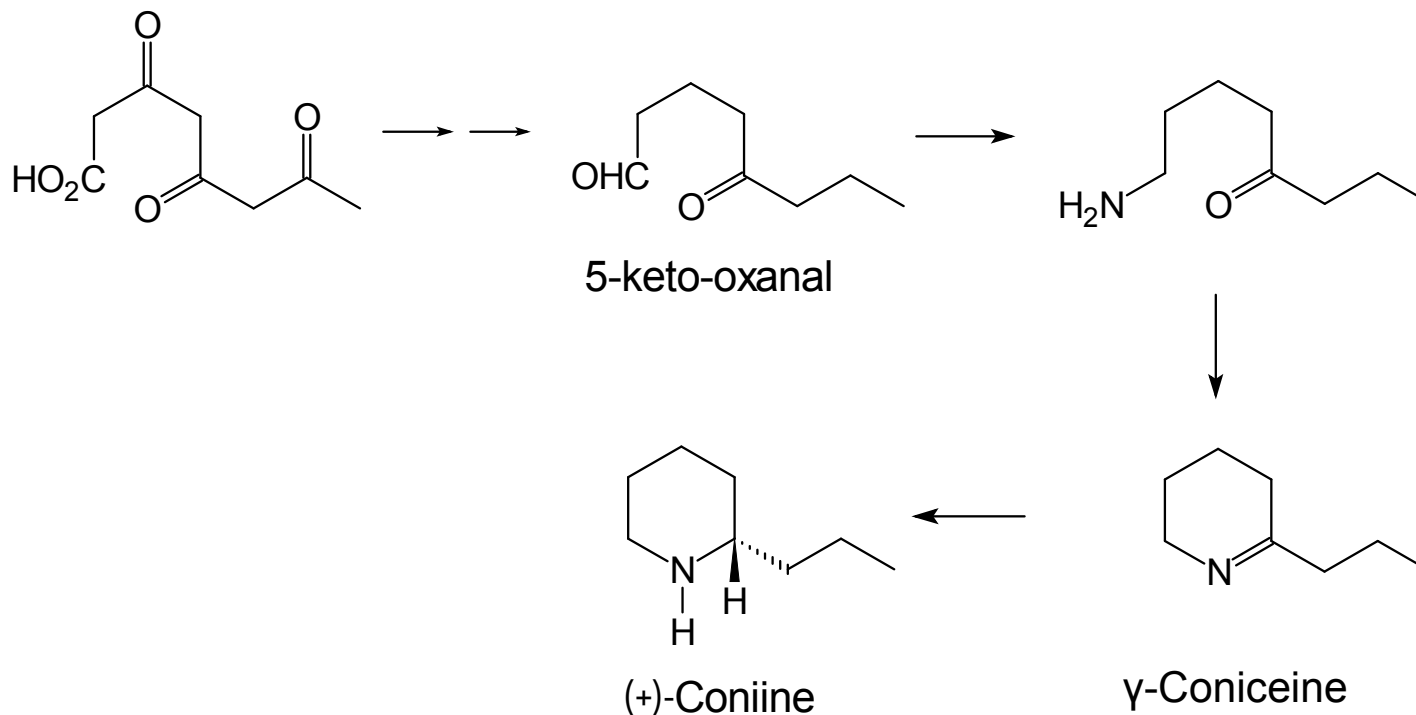
- The **chief alkaloids** found in the plant are **coniine** (volatile alkaloid that can be distilled), γ -coniceine, conhydrine, *N*-methylconiine, *N*-methylconhydrine, pseudoconhydrine, and conhydrinone.
- The **ripe fruit** can contain more than **1.5 % alkaloids** located in the epicarp and endocarp, and **mostly** represented by **coniine**.
- In the **vegetative parts**, **coniceine** is the chief constituent , especially at the beginning of the growth phase (furthermore, it is six to eight times **more toxic**).



Poison hemlock, Biosynthesis of the Alkaloids

These alkaloids are **elaborated from a polyacetate unit which incorporates a nitrogen atom**:

- in case of coniceine, there is a **transamination** between alanine and 5-keto-octanal formed from capric acid.
- Subsequent transformations are **imine formation giving the heterocyclic ring of γ -coniceine**, reduction to **coniine**, then methylation to **N-methylconiine**.



Poison hemlock

The fruit of hemlock was used for two millennia for its antineuralgic properties, but have no medicinal use now.

Toxicity

- **Coniine blocks neurotransmission in ganglions and neuromuscular junctions.**
- All parts of the plant are poisonous due to the alkaloid content.
- The ancient Greeks are said to have executed condemned prisoners, including Socrates, using poison hemlock.
- **Symptoms of the intoxication:** decrease in mobility and sensitivity, progressive paralysis of the muscles, progressive cooling of the extremities, dizziness and mydriasis. The **gradual muscular paralysis is followed by convulsions and death from respiratory paralysis.**
- Human intoxication by poison hemlock, which is sometimes confused with chervil, require rushing the victims to a hospital emergency room.
- **All animals can be intoxicated** by the plant , but their susceptibility varies with the species. Poison hemlock **can induce congenital malformations** in pregnant females.

Alkaloids Derived from Nicotinic Acid

Tobaccos, *Nicotiana tabacum* L., *N. rustica* L., Solanaceae



- These tobaccos and their multiple cultivars are grown for the **production of leaves for smoking**.

N. tabacum is an **annual plant** reaching 2m in height.

- Characterized by **very large** (50-70 x 30-45 cm) alternate, sessile or sheathing **leaves**, and
- panicles of flowers with a **tubulose flared corolla**, ranging in color from pinkish to ruby red.



Dohány



Dohánylevelek



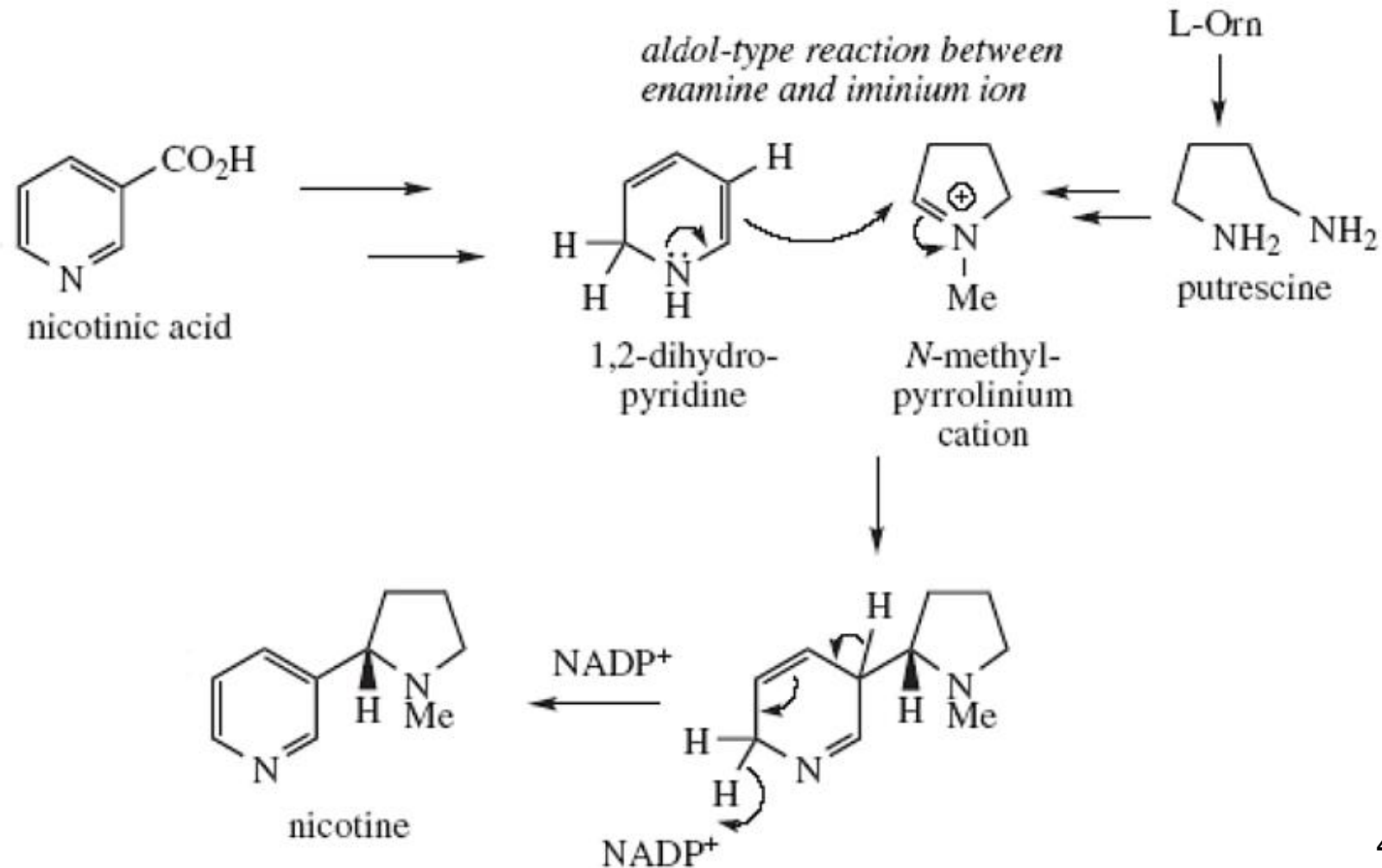
Nicotianae folium

Chemical Composition

- Green tobacco leaves are rich in **sugars** (40%; starch, pectin, cellulose, soluble sugars), proteins and organic acids (15-20%).
- The **alkaloid concentration** varies greatly depending on the cultivation practices and the variety (**2-10%**, more than 15% in some cultivars of *N. rustica*).
- The chief alkaloid is **(S)-(-)-nicotine**.
- The other alkaloids are very close structurally and are **anabasine**, **nornicotine**, the *N*-oxidized derivatives of nicotine, *N*-acetylnornicotines, nicotirine, and **myosmine**; they also include anabaseine and **anatabine**.
- Nicotine is a strong volatile base.

Biosynthesis of Nicotine

The formation of nicotine proceeds through the condensation of the *N*-methylpyrrolinium cation with a 1,2-dihydropyridine (enamine). The resulting product undergoes oxidation which regenerates the pyridine ring.



Biosynthesis of Anabesine

The formation of **anabesine** and other **piperidine analogs** involves **nicotinic acid** and **lysine**.

Nicotianae folium, Pharmacological activity

Nicotine is readily absorbed through the mucosas and through the lungs.

By transient stimulation followed by persistent depression of all automatic ganglia, it acts:

—on the **CNS**, which

- it **stimulates** up to the point of **causing** ,if the dose is sufficient, **tremors** and **convulsion**;
- it also **stimulates** the **respiratory** and **vomiting centers** (at high doses, respiratory paralysis occurs);

—on the **smooth muscle of the intestine**, by increasing tone and motor activity;

—on the **neuromuscular junction**; the initial phase of the stimulation is brief and soon followed by a blockade phase;

—on the **cardiovascular system**, by inducing, through a complex mechanism, a vasoconstriction and an increase in arterial blood pressure.

Nicotianae folium, Toxicity

- The **immediate toxicity** of tobacco is linked to the presence of **nicotine**.
- Combustion products, especially the **nitrosamins** are responsible for the **genesis of cancer**.
- In the long run, nicotine is responsible for the genesis of **cardiovascular** and **pulmonary diseases** other than tumors.
- Nicotine absorption can alter the activity of certain drugs: it **induces enzymes** , therefore the blood levels of drug decrease.

Nicotianae folium

Uses

The only medicinal use of **nicotine** is to relieve the corresponding symptoms during smoking cessation programs.

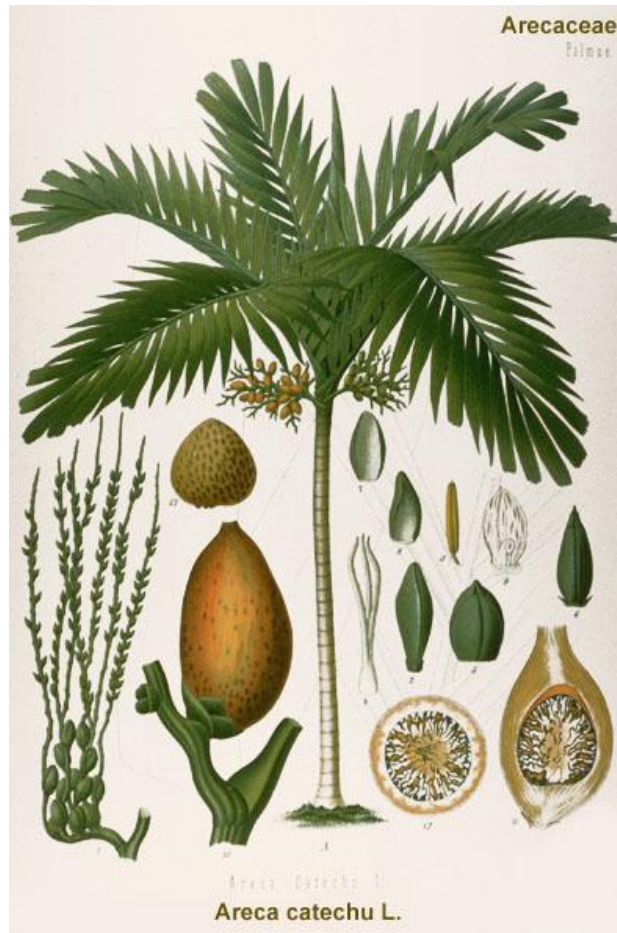
Nicotine based products:

- **chewing gum** (2-4 mg nicotine),
- **transdermal nicotine system** (patch) releasing 5-7 to 15-21 mg/24h of nicotine.

These products (being considered to be highly toxic) can be useful

- **as adjuncts in highly dependent patients**, but
- they are no substitutes for a strong motivation to quit smoking and long-term psychological support.

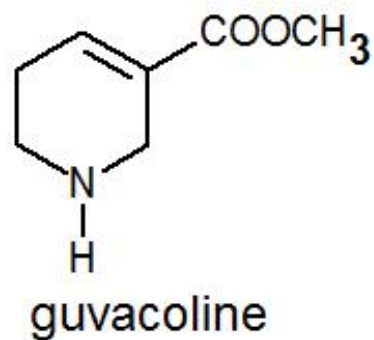
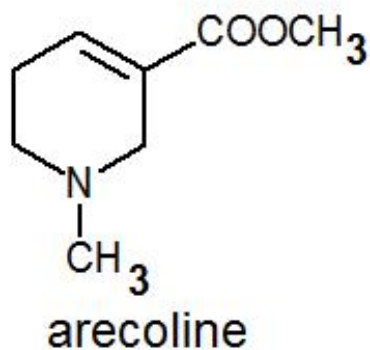
Betel (Nut) Palm, *Arecae semen, nuces,* *Areca catechu* L., Palmae



- The betel palm is a **palm tree** with a slender stipe ending with a bunch of feathered leaves.
- The **fruit** is a **fibrous drupe**, red when ripe, and it contains only **one seed**.
- The tree is **widely cultivated**, from India and Sri Lanka to south of China and the Philippines , in Malaysia and in Indonesia; it is also found in Africa (Tanzania).

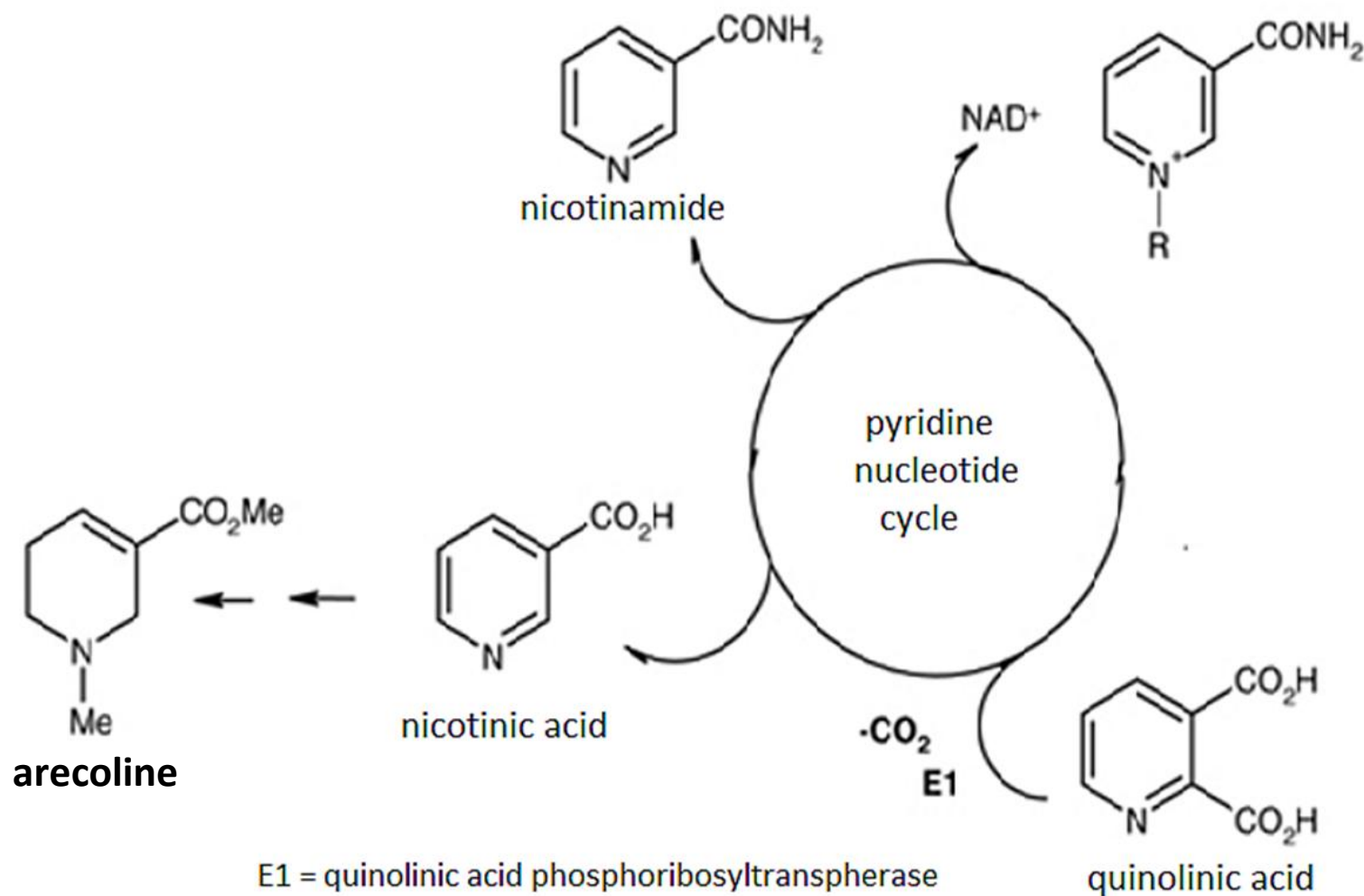
Arecae semen, nuces

- Areca nut (betel-nut), the seed of *Areca catechu*, is a hard ovoid mass (2 cm in diameter) the color of cinnamon.
- Constituents: 50-60 % sugars, 15 % lipids, 15 % **condensed tannins**, and 0.2-0.5 % **alkaloids**.
- Alkaloids: **Arecoline**, arecaidine, guvacine (tetrahydronicotinic acid), and guvacoline.



Arecoline, Biosynthetic Origin

Though **arecoline** is a **piperidine derivative**, its *precursor* is not an amino acid but *tetrahydronicotinic acid*. Therefore, it is a **pseudoalkaloid** of pyridine nucleotide origin.



Arecae semen

Effects

- Arecoline is a **parasympathomimetic** which acts on the **muscarinic receptors**, and at high doses , on the nicotinic receptors.
- This results in **multiple actions**:
 - vasodilation, hypotension, and
 - reflex of tachycardia at low doses,
 - stimulation of intestinal tone and peristalsis,
 - increase in secretions (hypersalivation and sweating),
 - myosis, and
 - bladder contraction.
- The mechanism of the **psychostimulant effects** of the drug has not been explained.

Traditional use

- The drug has been used as a **taenicide** *in humans* and also *in veterinary medicine*.
- Betel is widely used as a **masticatory** in all of southeast Asia; its consumption is a very ancient social, religious, and cultural practice.

Betel masticatory

- The masticatory known as betel is a concoction at times complex:
- the cut up **betel nut**, mixed with **lime** (charred shells or corals, vegetable ashes), is **rolled in betel leaf**; depending on the area, **spices** (nutmeg, cardamom, clove), tobacco, gambír, or saffron are added to the preparation.
- It is **chewed** for its **stimulant effect**, and subsequent **feeling of well-being** and **mild intoxication**.
- The chewers spit frequently, and their saliva is colored red due to the oxidation of polyphenols contained in the drug.
- Betel is suspected of inducing **buccal cancers** due to the **cytotoxic and teratogenic N-nitrosamines** formed from the alkaloids of the betel nut, particularly 3-(N-nitroso-methylamino)-propionaldehyde (=NMPA).



Figure 1: Leaf of betel (Piper betle).



Figure 2: Sliced areca nut, one of the major constituents of betel quid (paan), can also be chewed on its own.



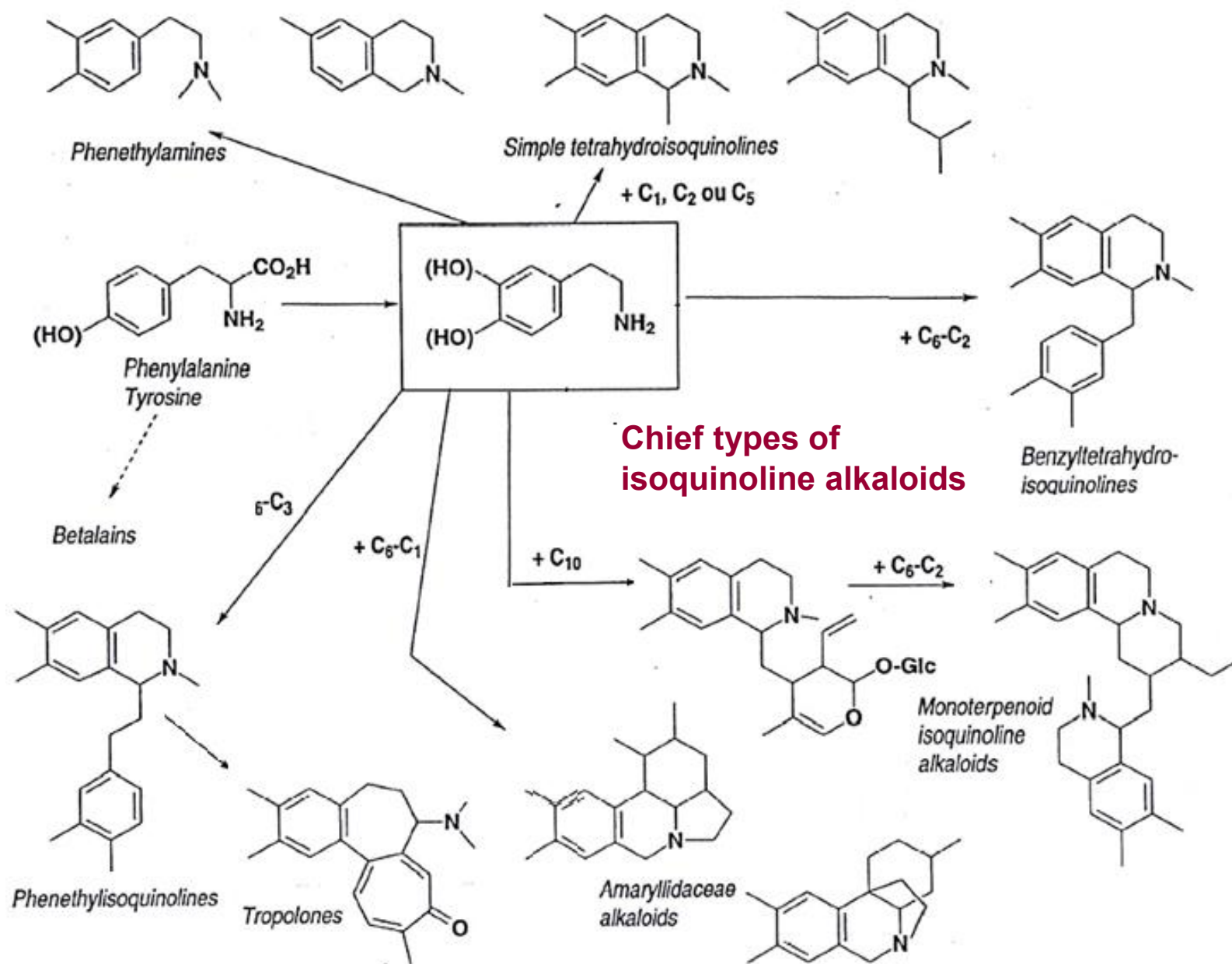
Figure 3: Sweeteners are added to children's paan.



Figure 4: Once the ingredients have been placed on the betel leaf, the leaf is folded and the paan is ready to chew or suck.

Alkaloids Derived from Phenylalanine and Tyrosine

- **Phenylethylamines and simple tetrahydroisoquinoline alkaloids**
- **Benzyltetrahydroisoquinoline alkaloids**
- **Phenethylisoquinoline alkaloids**
- **Terpenoid tetrahydroisoquinoline alkaloids**
- **Amaryllidaceae alkaloids**

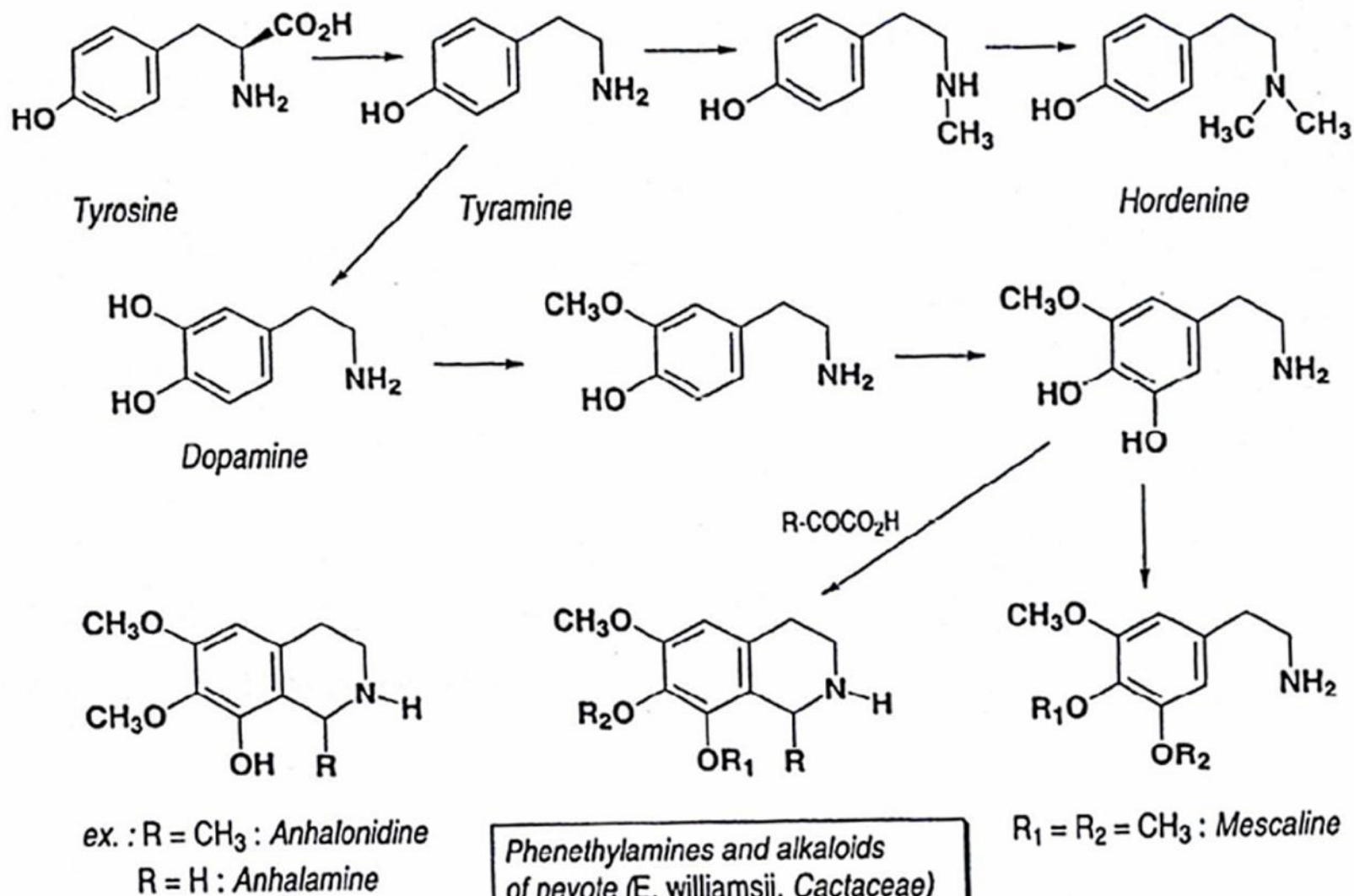


For the sake of clarity, the substituents have been omitted purposely (H or CH_3 on the nitrogen atom; OH, OCH_3 , $\text{O-CH}_2\text{-O}$, or H on the aromatic carbon atom).

Phenethylamines

Phenethylamines

Phenethylamine derivatives are derived via **dopamine**, the decarboxylation product from L-DOPA.



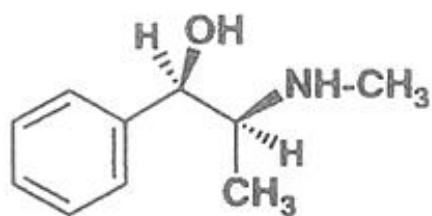
Ephedras, *Ephedra* spp. Ephedraceae

- Ephedras are **dioecious subshrubs**
 - with slender, angular, and striated branches, and
 - with **leaves reduced to membranous scales**.
 - The **female flowers** are *reduced to the ovule* and **surrounded by bracts** that are red and fleshy at maturity.
 - The **male flowers** are grouped in yellowish catkins.
- The **species** that contain substantial quantities of alkaloids are mostly Asian
 - ***E. equisetina*** Bunge and ***E. sinica*** Stapf **from China**,
 - ***E. intermedia*** Schrenk and C A Meyer, and ***E. gerardiana*** Wall ex Stapf **from India and Pakistan**
- The genus is represented in Europe by species with very few alkaloids, for example ***E. distachya*** L. of the Atlantic coast (shrubby horsetail).

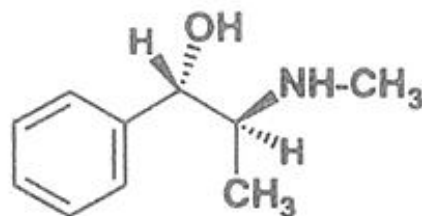
Ephedras

Chemical Composition

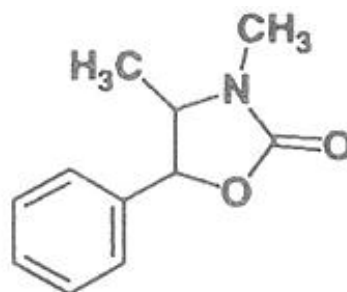
- Flavonoids and proanthocyanidins.
- **Protoalkaloids**. These are phenethylamine-type derivatives and their concentration can exceed 2%.
 - The chief constituent is almost always **(–)-ephedrine** [= (1*R*,2*S*)- 1 -phenyl-2-methylaminopropan–1–ol], which represents from 40 to 90% of the total alkaloids.
 - It occurs alongside **(+)-pseudoephedrine** (1*S*,2*S* config.) and the corresponding *nor* and *N,N*-dimethyl derivatives.
- Traces of cyclic compounds: **5-phenyloxazolidines** and ephedroxane (a 3,4-dimethyl-5-phenyloxazolidone).



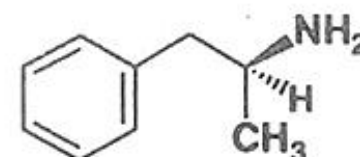
(–)-Ephedrine



(+)-Pseudoephedrine



Ephedroxane



D-Amphetamine

Ephedras, Pharmacological Activity

Ephedrine is an **indirect sympathomimetic**, a *CNS stimulant similar to amphetamine*.

- 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 a **bronchodilator**;
- it decreases the contractility of the bladder.
- **CNS**. Releasing mediators centrally, has a **stimulating psychic effect**:
 - stimulation of the attention and of the ability to concentrate,
 - decrease in the sensation of fatigue and the need for sleep, and so forth (qualitatively, amphetamine like activity);
- **Side effects** include anguish, tremors, and insomnia.

Ephedroxane and **(+)-pseudoephedrine** are experimental **anti-inflammatory agents**.

Uses of Ephedrine

Ephedrine hydrochloride

- to *treat the acute attack of asthma* (as a **bronchodilator** and **analeptic**).
 - Its **multiple activities**,
 - **numerous contraindications** (coronary insufficiency, arterial hypertension, closed angle glaucoma, hyperthyroidism),
 - **drug interactions** (MAO inhibitors, tricyclic antidepressants),
 - the **required precautions** (prostatic hypertrophy, cardiac insufficiency, diabetes),
 - **potential adverse effects** (tachycardia, headaches, sweating, agitation, insomnia, anxiety),
 - as well as the fact that the effects wear out if the doses are repeated in close time proximity (**tachyphylaxis**) have led to its **infrequent use**.
- for its **vasoconstrictive properties**,
 - in nasal sprays/drops (still available), for the antiseptic and vasoconstrictive **treatment of** the acute congestion of **rhinitis, sinusitis, and rhinopharyngitis**.
 - **Contraindications**: childrens under three years of age (risk of central excitation symptoms); closed angle glaucoma and treatment with MAO inhibitors.
 - **Precautions**. For hypertensive and coronary patients, Limiting the use of these solutions to a short time is crucial, because they can induce iatrogenic rhinitis.
- for the symptomatic **treatment of non-productive coughs** (in sirups and other formulations).
- for the topical **treatment of ear inflammations**.

Ephedrine is a **banned stimulant in sports** (positive doping control test).

Uses of Pseudoephedrine

Pseudoephedrine hydrochloride/sulphate

- Alone or in combination (with chlorphenamine, ibuprofen, paracetamol, or triprolidine), *for the symptomatic treatment of nasal congestion and rhinorrhea (coryza).*
- **Contraindicated** in children, in pregnant or breast-feeding women and in patients taking MAO inhibitors.
- They must be **used with caution** in case of hypertension or urination difficulties.
- Pseudoephedrine has a **low toxicity**, but it can cause dryness of the mouth, insomnia, sweating, and anxiety. The onset of tachycardia requires discontinuing the treatment.
- A **banned stimulant in sport** (a risk of positive doping control test).

KHAT, *Catha edulis* Forsk., Celastraceae

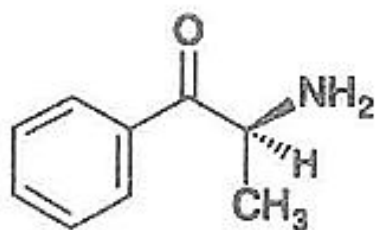
- A **shrub** of modest size in arid areas (1-2 m), but reaching 10 m in the tropics.
- **Leaves:** highly polymorphic, indeciduous.
- Also known as **Abyssinian tea**, it is native to the horn of Africa (but some think that it originated in Yemen).
- It is cultivated in the south-east of the Arabian peninsula (Ta'izz, Yemen), in Somalia, Sudan, Ethiopia (Harrar), and as far as Kenya (Meru district) and Madagascar.
- The leaves are harvested from the tip of the branches in the morning and carefully wrapped (banana leaves, damp paper, plastic) for protection against drying and wilting.



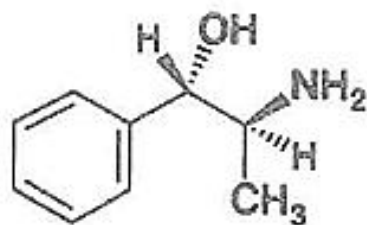
KHAT, Chemical Constituents of Leaves

- Flavonoids, some essential oil,
- **Cathedulines**: complex polyesters of polyhydroxylated dihydroagarofurans (sesquiterpenes). Mw : 600 -1200.
- **Khatamines : arylalkylamines** responsible for the activity of the drug.
 - *In the fresh and young leaves*, the chief constituent is **cathinone** = (S)- α -aminopropiophenone.
 - *In the dried drug and in older leaves*, this (–)-cathinone has been converted to an 80-20 mixture of (S,S)-(+)-**norpseudoephedrine** and (R,S)-(–)-**norephedrine**.
 - Fresh drug from northern Kenya also contains the **C6-C4 homologs** of these phenylpropylamines: (R,S)-(+)-**merucathine**, (S)-(+)-merucathinone, and (S,S)-(–)-pseudomerucathine.
 - The **phenylpropylamine content** is maximal in the **young shoots** and appears to depend on the **geographical origin**.
 - A wide range of variation has been observed for the level of cathinone (9-300 mg/100 g) and of norephedrine and norpseudoephedrine.

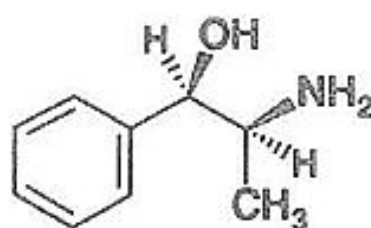
KHAT, Chemical Constituents II.



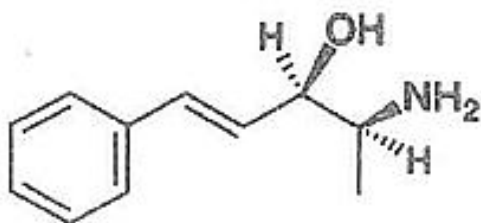
(-)-Cathinone



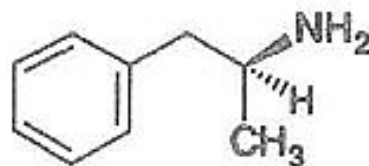
(+)-Norpseudoephedrine



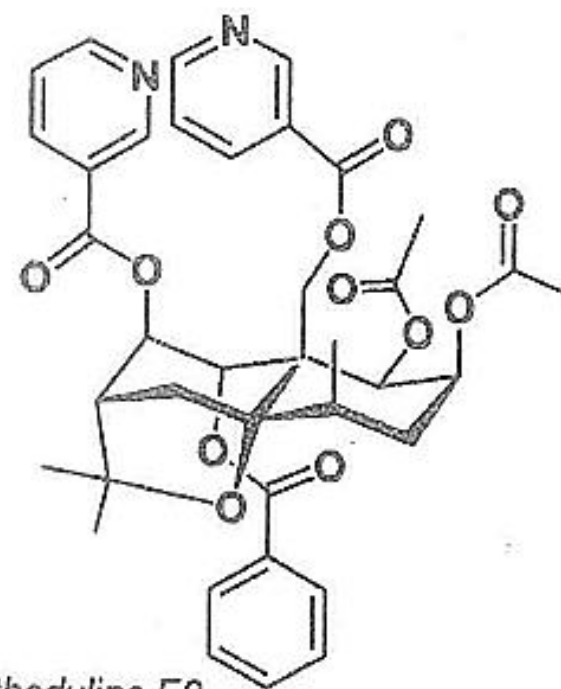
(-)-Norephedrine



Merucathine



D-Amphetamine



Catheduline E2

KHAT, Pharmacological Activity - Toxicity

- The activity of (—)-cathinone is qualitatively quite comparable to that of D-amphetamine:
- it causes anorexia, hyperthermia, respiratory stimulation, mydriasis, arrhythmia, and hypertension.
- This amine *induces the release of catecholamines from storage*.
- Its effects on the **CNS** depend in part on the subject's environment; they are characterized by a subjective and euphoric *sensation of increased energy*, well-being, *self-confidence*, mental acuity, and *ease in thought formation*.
- Objectively, **slight euphoria** can be observed in a **talkative** and sometimes **hyperactive subject**.
- Later on, **undesired effects** can appear: **insomnia**, **nervousness**, and **nightmares**; toxic psychosis in rare cases. **Depression** is then observed, and even schizophreniform or paranoid symptoms.
- **Psychic dependence**: *moderate*, but common—the use becomes compulsive; *no physical dependence or tolerance*; withdrawal syndrome in heavy abusers only.
- The tannins in the drug can cause constipation in regular users.

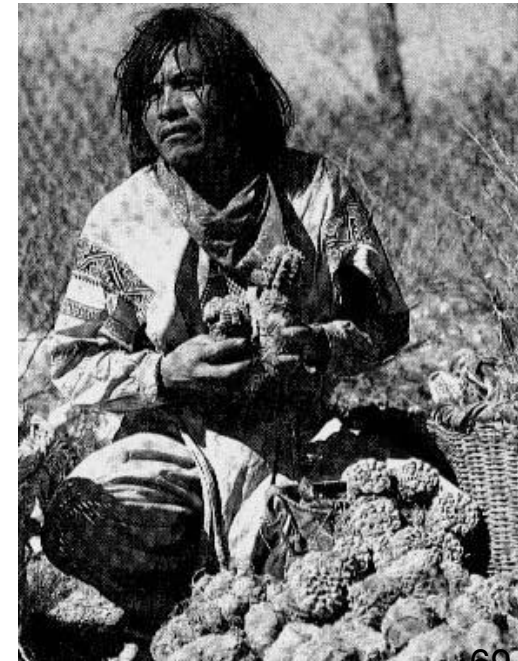
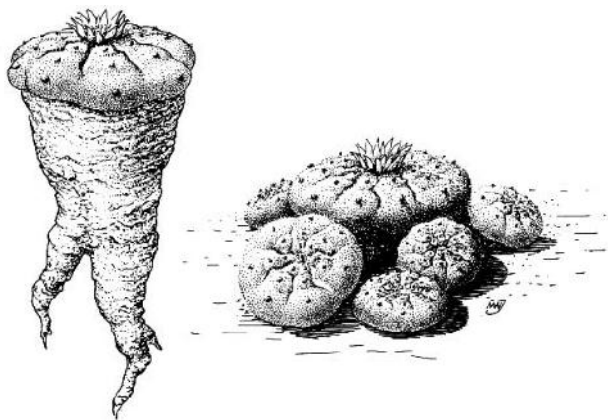
Use of Khat

- The fresh leaves, sold within 24 hours of harvest, constitute a masticatory known for its stimulating properties.
 - In some countries (Yemen), khat use is **an ancient custom** and it is **practiced at social events**, thereby strengthening social bonds.
 - In other countries, khat is used mainly **to seek the pharmacological effects** of the alkaloids (to suppress the appetite and to combat fatigue).
 - Traditionally, the leaves (50-200 g) are **chewed** one by one, **kept in the mouth** for a while, then most often **spit out**.
- In the early 1990s, **the number of daily users** was estimated to be *between two and eight million* (northeast Africa, Yemen).
- **Khat use** is officially **forbidden in** some countries (*Saudi Arabia, Sudan, Somalia*) and more or less **tolerated in** other countries (*Yemen, Ethiopia*).
- The use of the drug is at the origin of **serious socio-economic problems** *linked to* the possible *malnutrition, drug-seeking behaviors* and *its negative impact on agriculture*.
- **Cathinone** is on the list of substances whose **production, marketing and use are prohibited**.

Symple Tetrahydroisoquinolines

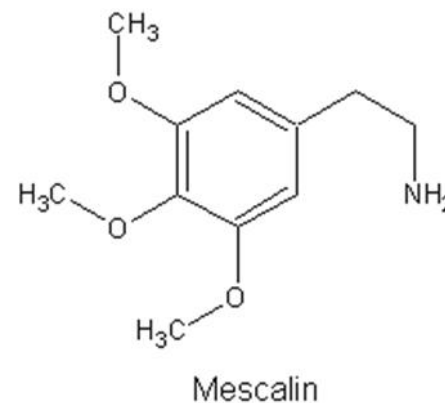
Peyote, *Lophophora williamsii*, Cactaceae

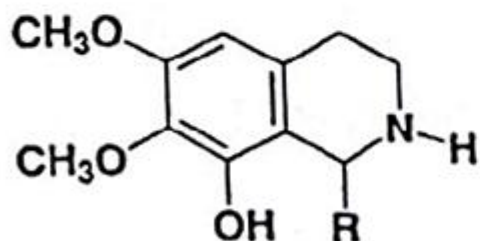
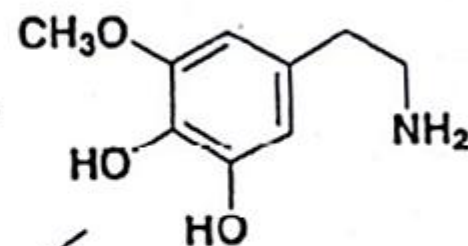
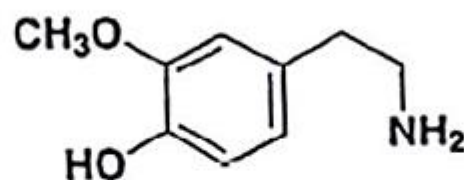
- Peyote is a **globular cactus, fleshy, composed of rounded lobes** and spineless, reaching a maximum of 20 cm in height and 5-10 cm in diameter.
- The **fleshy stem** is divided into 5-14 prominent **ribs**, themselves further divided into „**tubercles**“.
- The **solitary flower** is pink, white or yellow.
- Peyote **grows from the north of Mexico to Texas**, on high limestone plateaus.
- Considered a **divine plant** by the Aztecs, this cactus is a **particularly potent hallucinogen**



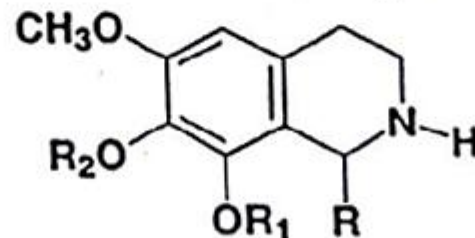
Peyote

- **The drug** consists of **the aerial part**, sliced and dried in the sun.
- **Constituents:**
 - **Phenethylamines:** include **mescaline**, and its *N*-substituted and demethyl derivatives, hordenine, tyramine and its *N*-methylated derivatives and dopamine.
 - **Tetrahydroisoquinolines:** anhalamine, pellotine, lophophorine and others.
 - A large amount of mucilage.

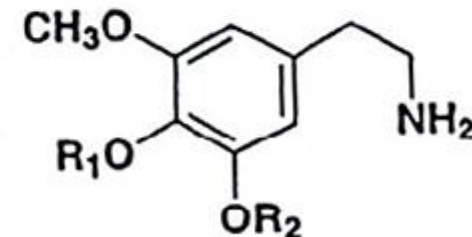




ex. : R = CH₃ : Anhalonidine
R = H : Anhalamine



Phenethylamines and alkaloids of peyote (E. williamsii, Cactaceae)


$$R_1 = R_2 = \text{CH}_3 : \text{Mescaline}$$

Peyote, Mescaline

Peyote causes visual hallucinations, due to the CNS activity of a phenethylamine alkaloid, **mescaline**.

Mescaline has clinical effects resembling those of LSD: **psychic**, **cognitive**, and **physical**.

Main symptoms:

- A distortion of the perception of **shapes**, an intensification of **colors**, auditory **hallucinations**, a slowing in the perception of **time**.
- The nature of the effects are highly dependent on the **environment** and the **intellect of the subject**.

Physical symptoms:

- mydriasis, tachycardia, bradypnea, a sensation of change in temperature, nausea, and possibly agitation and anxiety.
- At high doses:** memory loss, hypertensive encephalopathy and intracranial hemorrhage may be observed.

The use of peyote and mescaline is disallowed by antidrug law in the USA.