Alkaloids

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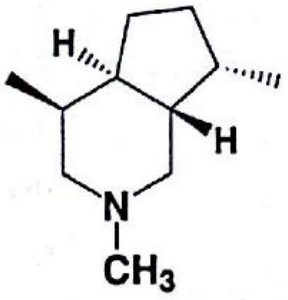
ALKALOIDS

Alkaloid is an organic compound of natural origin,

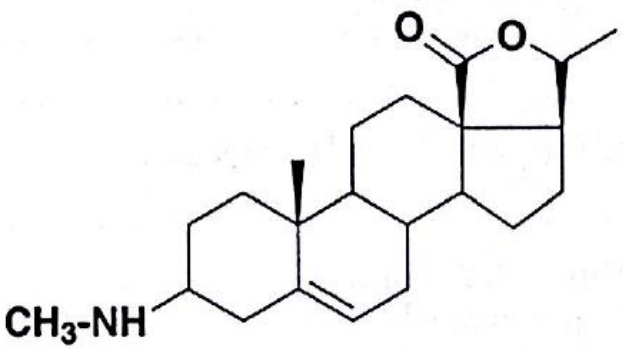
- which contains a *nitrogen atom*, is more or less *basic*,
- is of *limited distribution*, and
- has, at low doses, *marked pharmacological properties*.
- These compounds have in common some reactions of precipitation with the „general reagents for alkaloids”.

ALKALOIDS

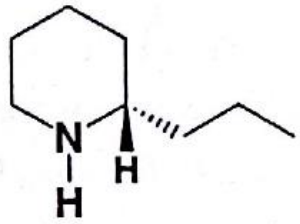
- **Pseudoalkaloids** most often have all of the characteristics of the true alkaloids, but they are **not derived from amino acids**.
  - **Terpenoid alkaloids**: monoterpenoids (e.g., β-skythanine), sesquiterpenoids (from the Nymphaceae), diterpenoids (e.g., aconitine), steroidal alkaloids (e.g., paravallarine).
  - Heterocyclic nitrogen-containing **substances** arising **from the metabolism of acetate** (e.g., coniine, the toxic priciple of hemlock).



β-*Skytanthine*



Paravallarine

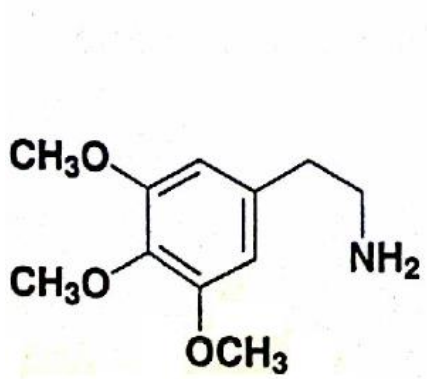


(+)-Coniine

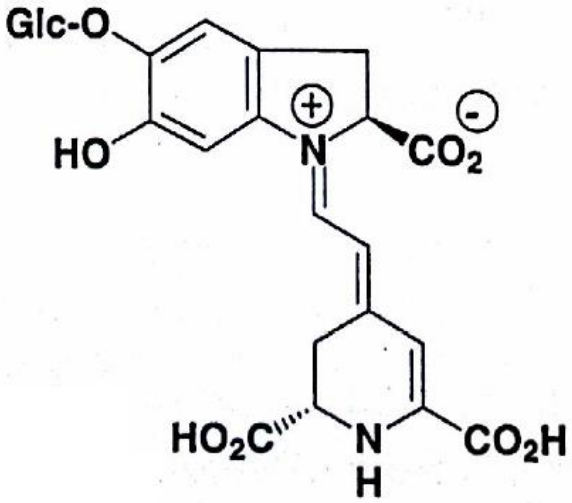
ALKALOIDS

Protoalkaloids are *simple amins* in which **the nitrogen atom is not part of a heterocyclic ring**; they *are basic* and are *elaborated in vivo from amino acids*.

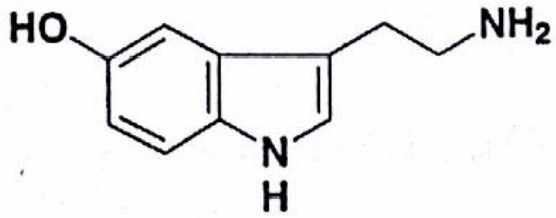
- Various substances fullfil this definition:
  - **Simple amins**, such as serotonin, mescaline from peyote, or cathinone from Abessinian tea,
  - **Betains** (resulting from the quaternization of of the nitrogen atom of amino acids)
  - Some authors include **betalains** („chromoalkaloids") in this group (e.g., Betanin).



Mescaline



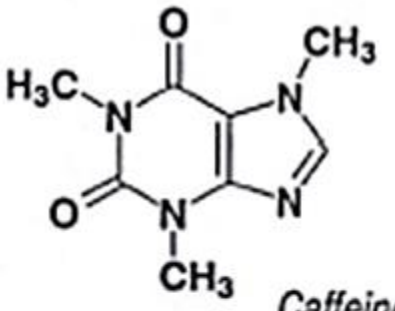
Betanin



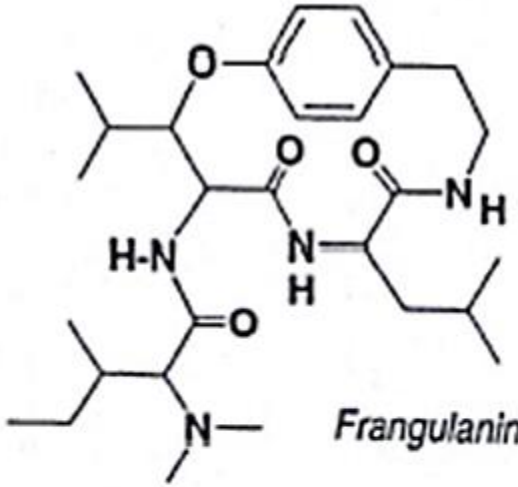
Serotonin

ALKALOIDS

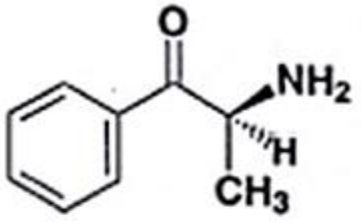
Athough the distinction between true alkaloids , protoalkaloids, and pseudoalkaloids is intellectually appealing, it is not always easy to apply.



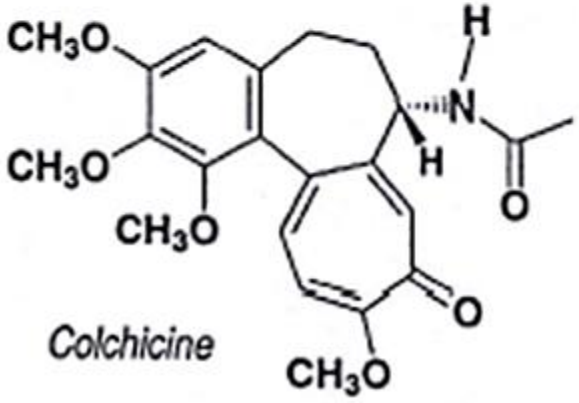
Caffeine



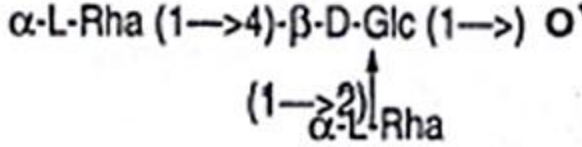
Frangulanine

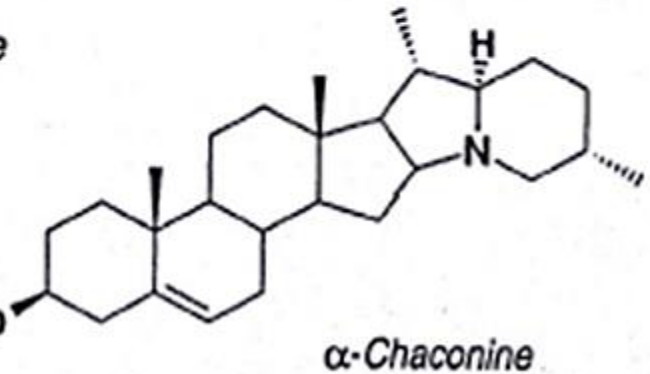


(−)-Cathinone



Colchicine





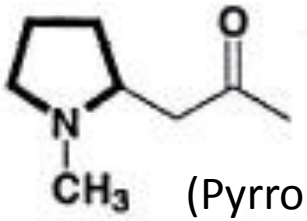
α-Chaconine

In practice, it is widely accepted that the folloving are not alkaloids:

Simple amins, peptides, amino sugars, porphyrins, alkylamins, and arylamins, *at least those that are widely distributed*.

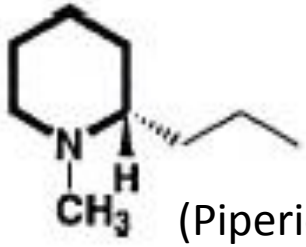
Examples of alkaloid structuters illustrating the chief heterocyclic system encountered.

(The basic heterocyclic system is in boldface.)



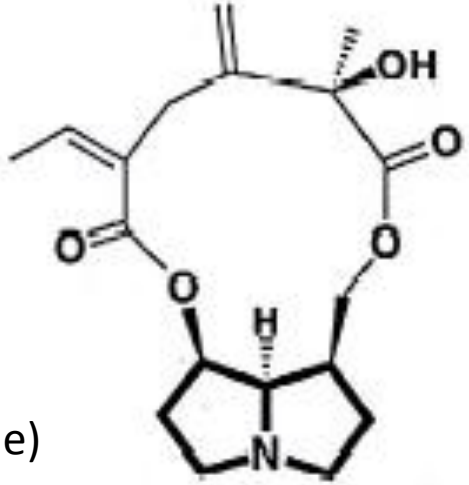
(Pyrrolidine)

Hygrine **A**



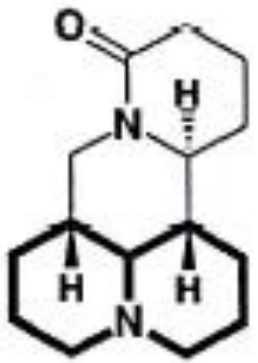
(Piperidine)

N-Methyl coniine **B**



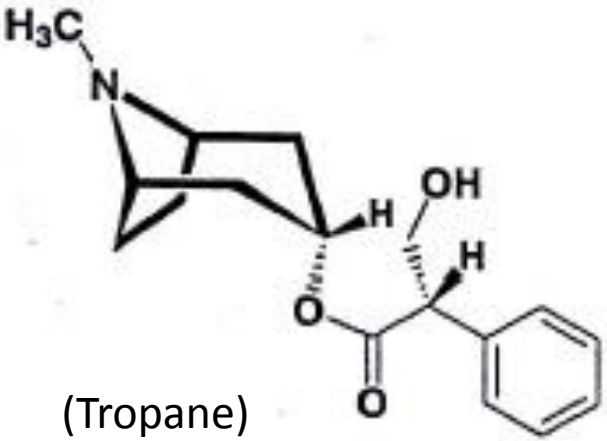
Seneciphylline **C**

(Pyrrolizidine)



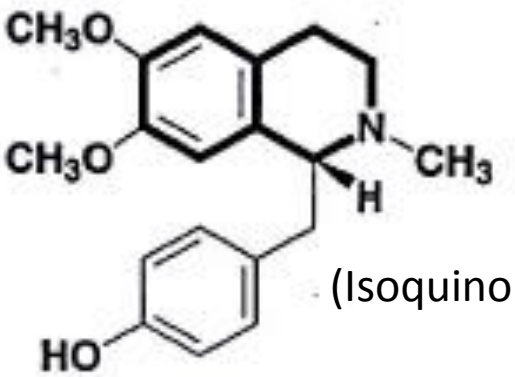
(Quinolizidine)

Matrine **D**



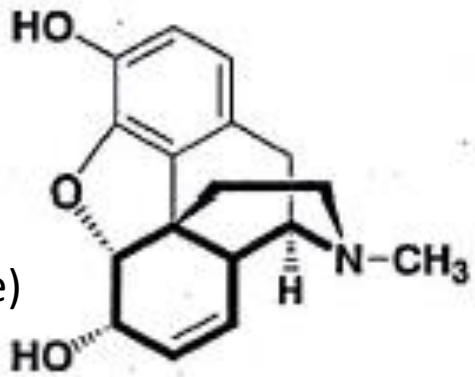
(Tropane)

Hyoscyamine **E**



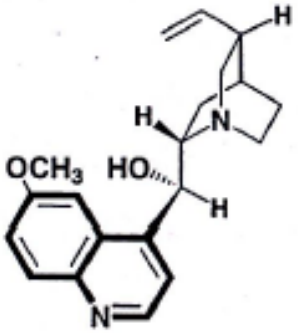
(Isoquinoline)

(–)-Armepavine **F**

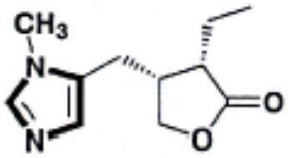


Morphine **F**

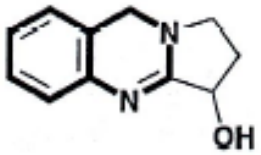
Examples of alkaloid structuters illustrating the chief heterocyclic system encountered.



Quinine J

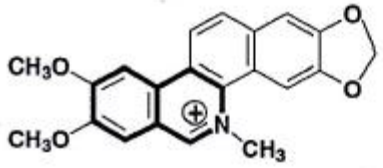


Pilocarpine H

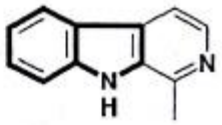


Vasicine I

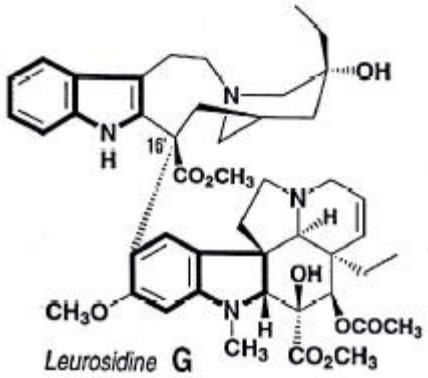
E : Tropane,
F : Isoquinoline,
G : Indole
H : Imidazole,
I : Quinazoline,
J : Quinoline.



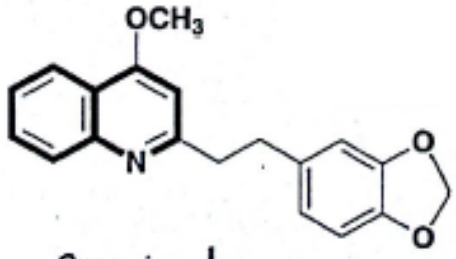
Nitidine F



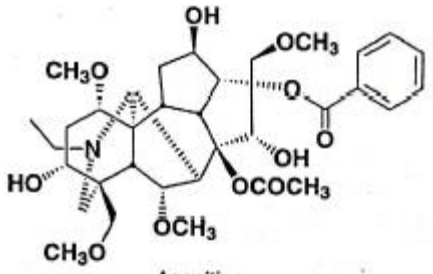
Harmane G



Leurosidine G



Cusparine J



Aconitine

History

Friedrich Wilheim Sertürner

(1783-1841) He was the first to isolate morphine from opium

Pierre Joseph Pelletier

(1788-1842)

Joseph Bienaimé Caventou

(1795-1877)

Isolation of strychnine (1818), brucine (1819), quinine (1820) and caffeine (1821)

Kabay János

(1896-1936)

He earned morphine from the dry poppy-straw. (1925)

Sir Robert Robinson

Nobel Prize in 1947

for his research on plant dyestutts (anthocyanins) and alkaloids

Robert Burns Woodward

Nobel Prize in 1965

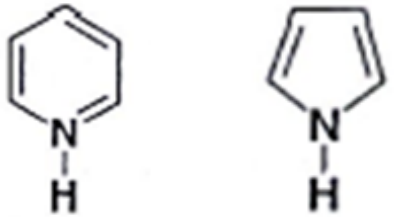
The total synthesis of natural products, e.g. strychnine

ALKALOIDS: PHYSICO-CHEMICAL PROPERTIES

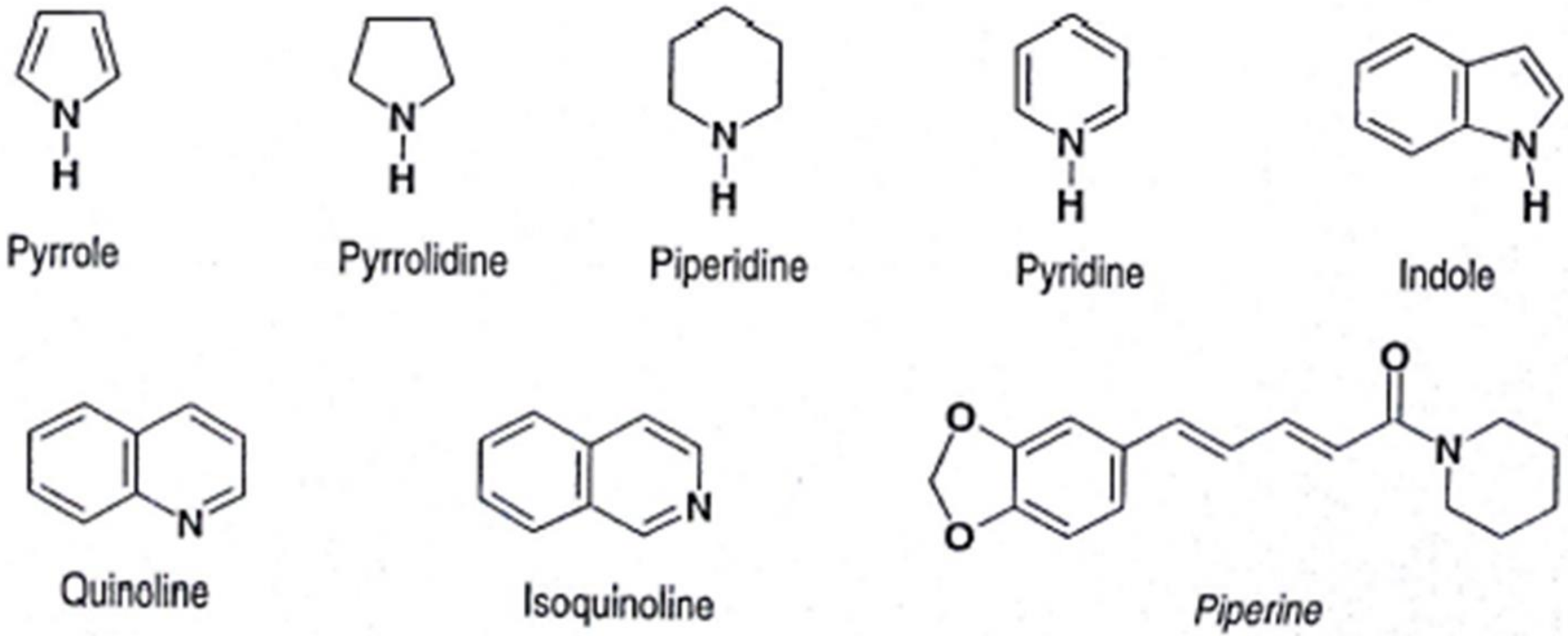
- Alkaloids have **molecular weights** ranging from 100 to 900.
- **Oxigen-free bases** generally are **liquid** at ordinary temperatures (nicotine sparteine, coniine).
- **Bases containing oxygen atoms** are normally **crystallizable solids**, some of them are **colored** (berberine).
- Crystallized bases generally
  - **rotate the plane of polarized light**, and
  - have **sharp melting points**, without decomposition, especially below 200 °C
- ***Solubility.*** As a general rule, **alkaloids as bases** are
  - ***not soluble*** *or are* ***sparingly soluble*** *in water*,
  - **soluble** in apolar or only slightly polar organic solvents, and concentrated hydroalcoholic solutions.

ALKALOIDS, BASICITY

- Basicity varies greatly.
- Depends entirely on the **availability** of the **lone pair of electrons on the nitrogen atom.**
- In close proximity to the nitrogen atom, **electron –withdrawing groups** ↓ , **electron – donating groups** ↑ the basicity . →
- **Colchicine** and **piperine are**, because of the presence of the carbonyl group on the amide, practically **neutral**.
- **The basic character of the heterocyclic ring** itself varies depending on that **the lone pair of electrons on the nitrogen atom is available or plays a role in the aromatic character** (see next slide).
- The basicity is also influenced by **steric constraints.**
- **As bases**
  - in solution they **are sensitive to heat, light, and oxygen**;
  - they **form salts with mineral acids** (hydrochlorides, sulfates, nitrates), **or organic acids** (tartrates, sulfamates, maleates).
- **Alkaloid salts** are generally **soluble in water** and in **dilute alcohols**, and they are, except in rare cases, **not soluble in organic solvents.**



ALKALOIDS, The basic character of the heterocyclic ring



- The basic character of the heterocyclic ring itself varies depending on that **the lone pair of electrons on the nitrogen atom is available or plays a role in the aromatic character.**
- Quinoline, isoquinoline : bases; Pyrrole, indole: acids , Pyrrolidine: saturated, strong bases.

ALKALOIDS: DETECTION AND CHARACTERIZATION I.

General reactions of precipitation :

- Preliminary extraction can be a „classic” alkaloid extraction or alcoholic maceration.
- They are based on the fact that alkaloids form **combinations with metals and metalloids**: bismuth, mercury, tungsten, and iodine.
- The „general reagents for alkaloids” are used:
  - solutions containing iodine and iodide (**Wagner's reagent**), potassium iodide and mercuric chloride (**Mayer’s r.**) ,
  - bismuth nitrate and potassium iodide (**Dragendorff’s r**.).
  - It is also possible to use silicotungstic acid (a mixture of tungsten and silicon oxides), or alkaline solutions of iodoplatinates.
- The specificity of these reagents is not absolute.

ALKALOIDS: DETECTION AND CHARACTERIZATION II.

Color reactions characteristic of subgroups of alkaloids:

- ***p*-dimethylaminobenzaldehyde** for the ergot alkaloids and pyrrolizidine alkaloids;
- **Cerium and ammonium sulfate** , which differenciate indoles (yellow), dihydroindoles (red), b-anilinoacrylates (blue), oxindoles;
- **ninhydrin** for arylalkylamines;
- **the Vitali-Morin reaction** for the esters of tropic acid;
- Reagents containing **ferri chloride** in the presence of ***hydrochloric acid*** (tropolones) or ***perchloric acid*** (*Rauwolfia*).

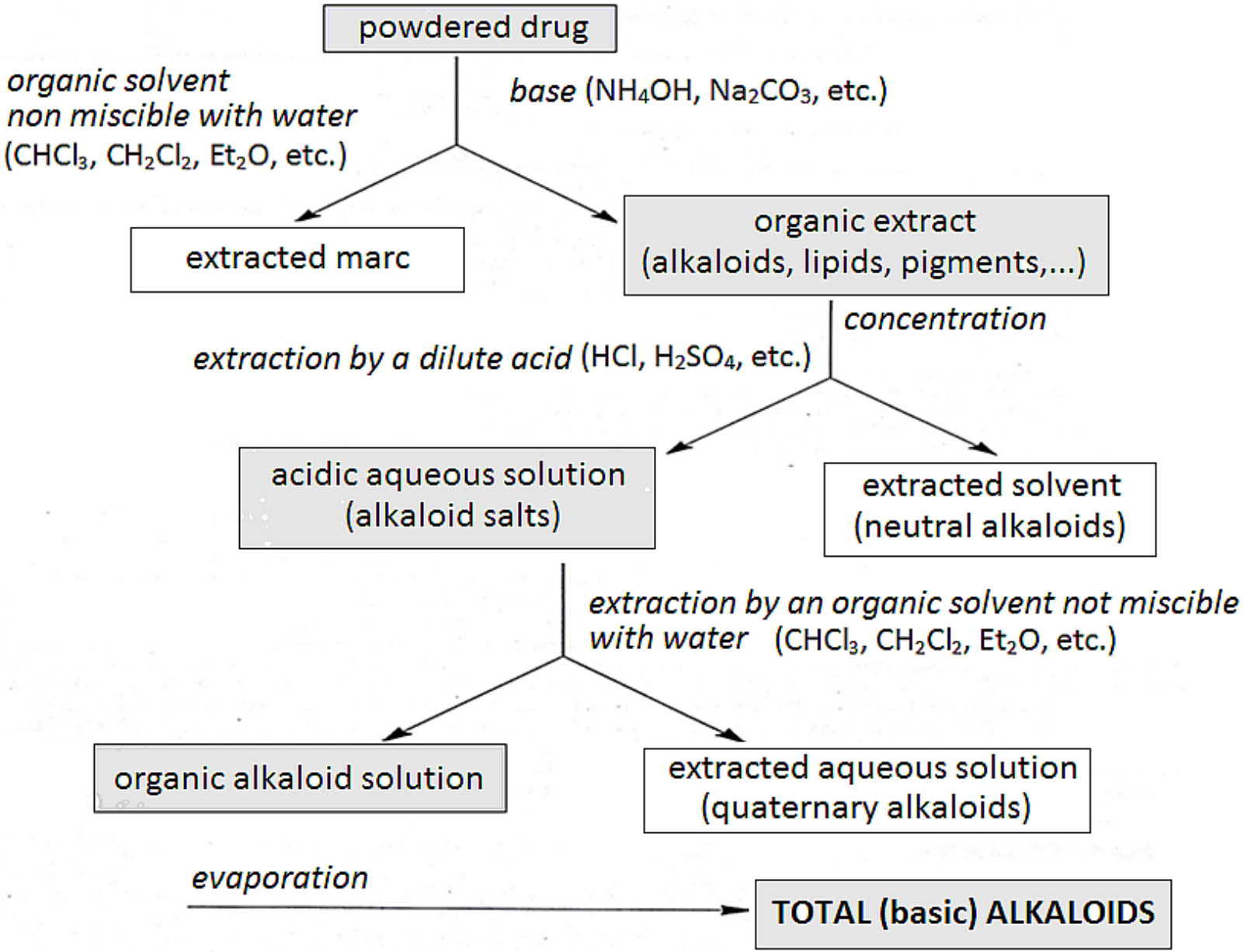
Analysis of alkaloid composition:

- Methods currently used are **TLC, HPLC** on normal or reversed phase, and **LC-MS.**
- Dragendorff's reagent, the iodine-iodide solution, potassium iodoplatinate, or cerium and ammonium sulfate are commonly used to visualize TLC plates.

EXTRACTION OF ALKALOIDS

- It is based, as a general rule,
- on the fact that **alkaloids** normally occur **in the plant as salts**, and
- on the **differential solubility of the bases and salts** **in water and organic solvents**.
- The **plant material often contains** substantial quantities of fats, and also waxes, terpenes, pigments, and other **lipophilic substances**, which may interfere with the extraction procedure, for example, by **causing the formation of emulsion**.
- **Preliminary defatting** of the crushed drug can solve this technical problem.
- **Petroleum ether** and **hexane** are well suited for this step: alkaloids are soluble in these solvents only in exceptional cases, when the medium is neutral.

SOLVENT EXTRACTION IN ALKALINE MEDIUM



EXTRACTION IN ACIDIC MEDIUM

Two approaches are possible: the pulverized drug is extracted with

- a. , acidified water
- b., an acidified alcoholic or hydroalcoholic solution.
- In the latter case, the extraction is followed by a distillation under vacuum which eliminates the alcohol and leaves behind an acidic aqueous solution of alkaloid salts.

In both cases, the result is an **aqueous solution of alkaloid salts requiring purification**. This can be accomplished by

1. alkalinizing the solution and extracting the bases with an immiscible organic solvent, which leads back to the above step;
2. selectively adsorbing the alkaloids contained in the solution on an ion-exchange resin, then eluting them with a strong acid;
3. precipitating the alkaloids as iodomercurates. The resulting complex is recovered by filtration, dissolved in a mixture of water, alcohol, and acetone, and decomposed by passing it through an ion-exchange resin. This technique can be used to extract quaternary ammonium salts.

ALKALOIDS, QUANTITATION (I)

Total alkaloids

- It requires preliminary extraction of the alkaloids using a general method: generally the alkaline medium approach is preferred; at each step the completeness of the extraction must be verified.
- **Gravimetric methods:** are easy to implement, but lack precision.
- **Volumetric methods**. **Acidimetry**: **direct**, or, most often, **back titration** (*p*Ka 5 -10), or **in non-aqueous medium** (weak bases).

Determination of **alkaloid composition**

- The available techniques include **spectrophotometry, colorimetry, fluorimetry, and densitometry**.
- Spectrophotometry: to quantitate quinine- and cinchonine-type alkaloids in Cinchona bark (Ph. Eur.)
- Colorimetry: to the quantitation of the weak bases alkaloids of Ruwolfia.
- Densitometry: TLC isolation of morfine and measurement of the reflectance directly on the plate (laboratory practice).
- **HPLC-UV, LC-MS:** tend to advantageously replace the „classic" methods. HPLC-UV tend to be more and more important technique for the European Pharmacopoeia.

ALKALOIDS, BIOSYNTHETIC ORIGIN I.

The precursor is, for true alkaloids, **an amino acid**: ornithine, lysine, phenylalanine, tyrosine, tryptophan, hisitdine, or anthranilic acid.

The **formation of the alkaloid** may require the involvment of

- only **one molecule of amino acid** (hygrine, cathine), or
- **two molecules of the same amino acid** (quinolizidins, benzylisoquinolines), or,
- less commonly, of **two different amino acids** (tubulosine), or
- else of **several molecules of the same acid** (sparteine).

Mechanism of the formation of the heterocyclic system:

- Generally simple inter- or intramolecular reactions : formation of a **Schiff base**, or, **Mannich reaction**…

ALKALOIDS, BIOSYNTHETIC ORIGIN II.

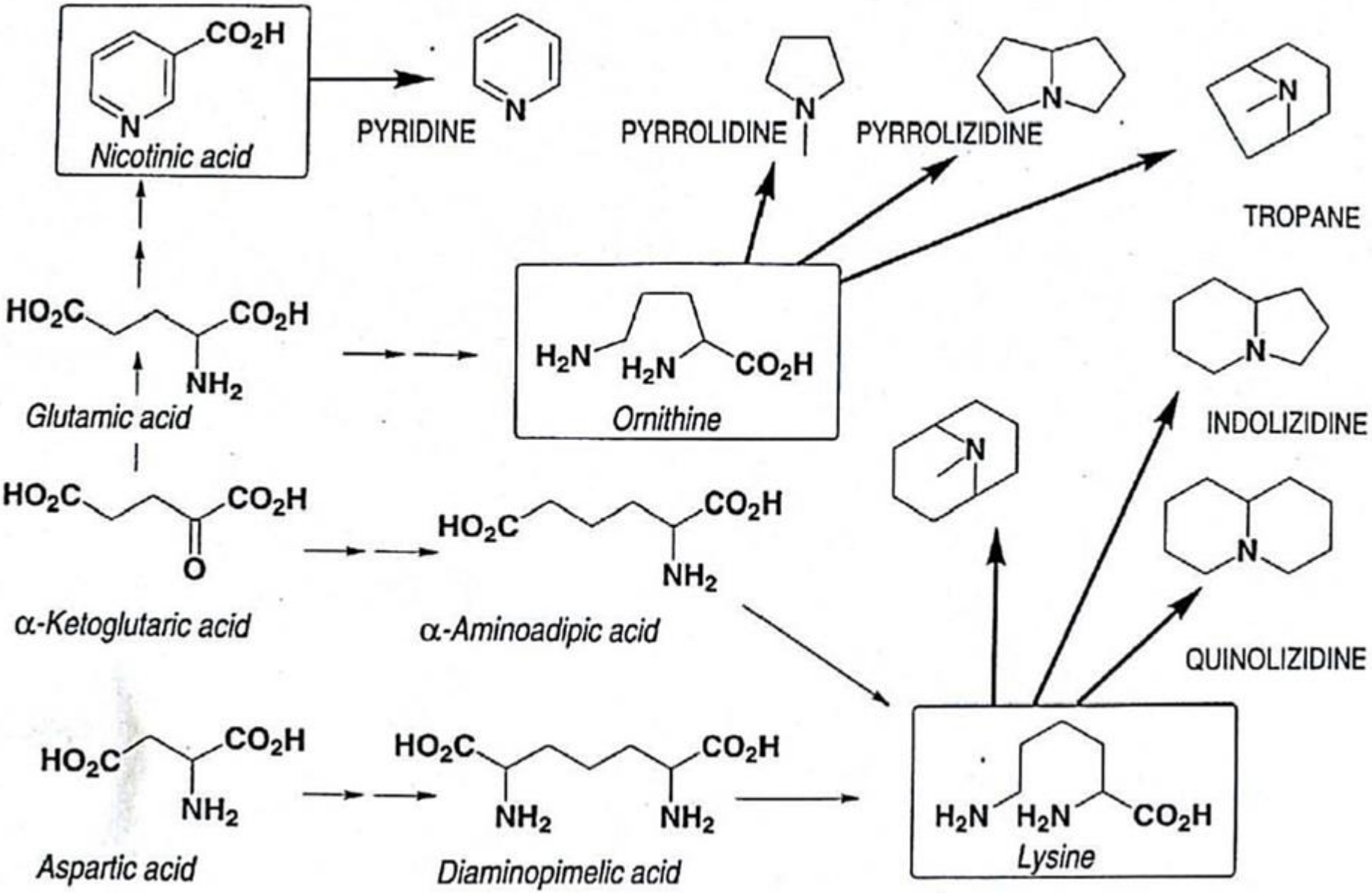
Additional carbon atoms. These come from

- *intermediates that have major role in* other metabolic pathways: **acetate** (tropane), **dimethylallylpyrophosphate** (ergolines, furoquinolines), or
- *intermediates more specific to* a particular group of plants, like **secologanin** **(**monoterpenoid indol alkaloids).

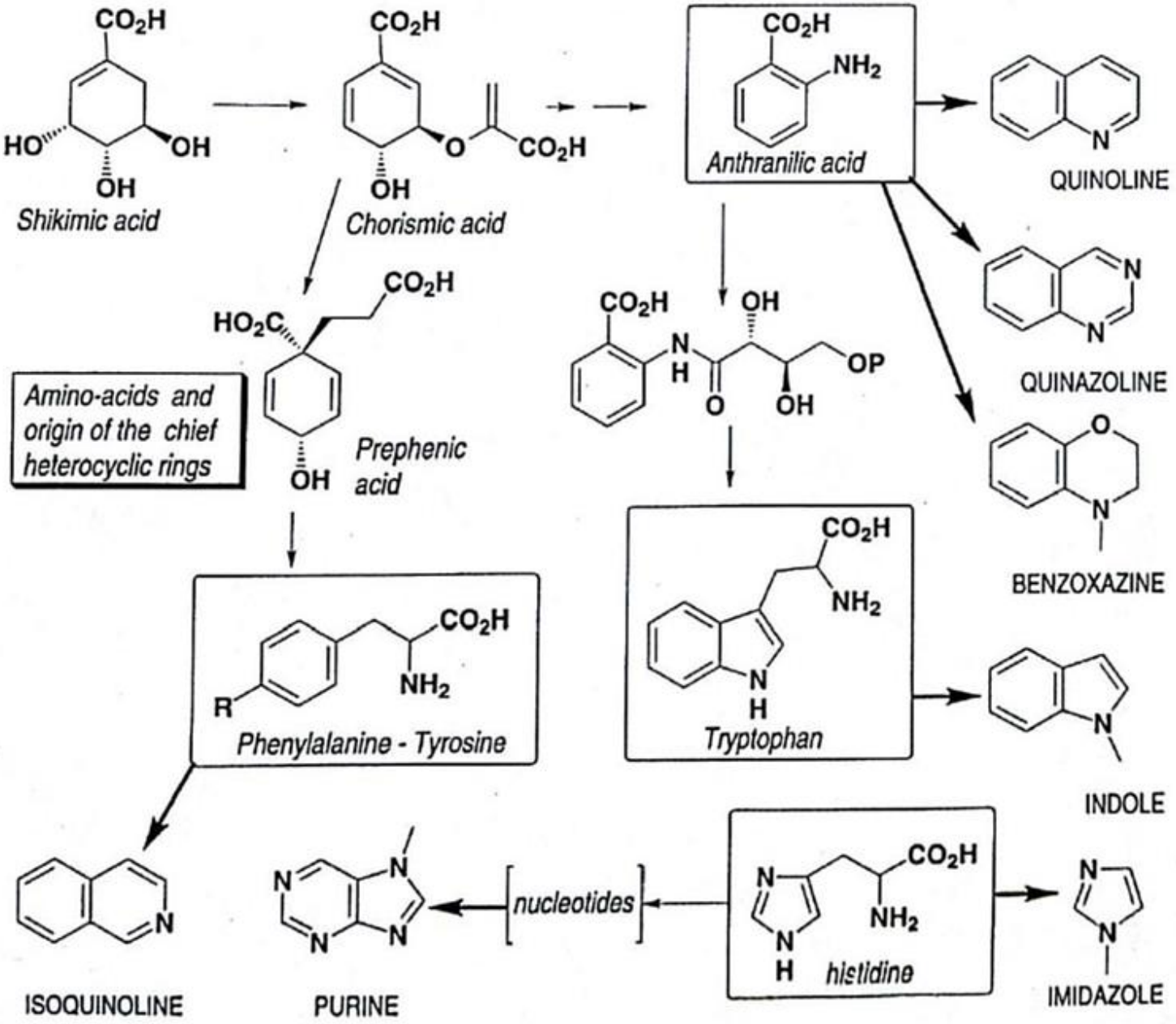
Origin of the wide structural variability: allylic oxidation, oxidative coupling, oxidation of the aromatic rings, esterifications, and etherifications.

Terpenoid alkaloids: the precursors are stricly of terpenoid origin and the formation of an amine function occurs late in the pathway.

Amino acids and origin of the chief heterocyclic rings I.



Amino acids and origin of the chief heterocyclic rings II.



ALKALOIDS, Pharmacological Activity

Alkaloids are particularly interesting substances because of their **multiple pharmacological activities**:

- **on the CNS:** alkaloids are **depressants** (morphine, scopolamine) or **stimulants** (strichnine, caffeine);
- **on the automathic nervous system**:
  - **sympathomymetics** (ephedrine), or
  - **sympatholytics** (yohimbine, certain ergot alkaloids),
  - **parasympathomimetics** (eserine, pilocarpine),
  - **anticholinergic** (atropine,hyoscyamine), or
  - **ganglioplegics** (sparteine, nicotine).
- **In addition**, alkaloids include
  - curare,
  - **local anesthetics** (cocaine),
  - **agents to treat fibrillation** (quinidine),
  - **antitumor agents** (vinblastine, ellipticine),
  - **antimalarials** (quinine),
  - **antibacterials (**berberine), and **amebicides** (emetine).

ALKALOIDS, Uses

These various activities lead to **extensive use of alkaloid-containing drugs**:

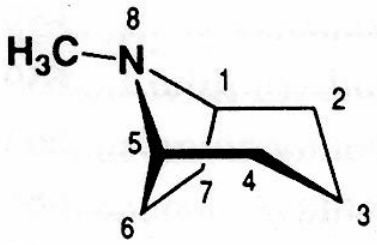
- **as galenicals** (belladonna, datura, hebane)
- **as starting material for industrial extraction**: *morphine* from poppy straw or opium, *scopolamine* from *Duboisia*, *ajmalicine* from *Catharanthus* roots, *vincamine* from periwinkle leaves, and *quinine* from *Cinchona* bark.
- Some of the **extracted alkaloids may undergo transformations**: codeine is produced mostly by methylating morphine, quinine is converted to quinidine, serpentine to ajmalicine, and tabersonine to vincamine; tropane alkaloids are quaternized.
- In a few rare cases, the industry prefers **direct synthesis**: theophylline and papaverine are easily obtained that way.
- The drive to optimize therapeutic efficacy, has sometimes resulted in achieving **deeper transformations**, or even **total syntheses of analogous molecules**, making use or not of starting materials of natural, plant, or fermentation origin
  - (see : derivatives of ergot alkaloids, and binary alkaloids of Catharanthus).

Tropane alkaloids

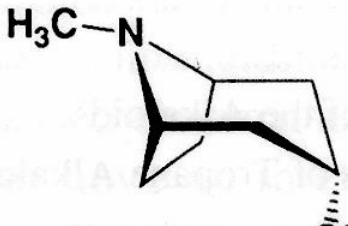
With a few exceptions, tropane alkaloids are *esters of tropane alcohols and of acids of various structures*, either aliphatic or aromatic.

A. TROPANOLS

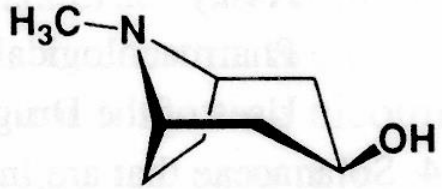
These alcohols fall into two series depending on the orientation of the hydroxyl group at C-3.



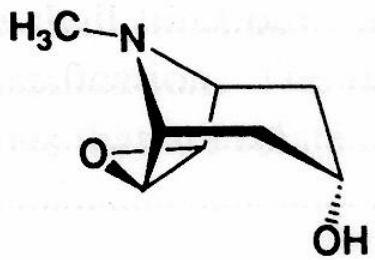
Tropane



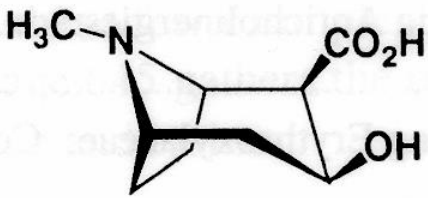
Tropanol
(3α-hydroxytropane)



Pseudo-tropanol
(3β-hydroxytropane)



Scopanol

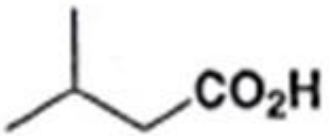


Ecgonine

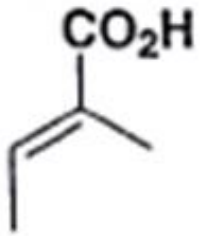
B. ACIDS

The **acids** may be **aliphatic** (acetic, butiric, icovaleric, 2-methylbutyric, tiglic acid, angelic acid) or **aromatic**.

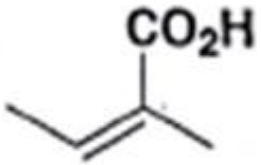
The aromatic acid may be specific like (S)-(-)-tropic acid, or may be more widely distributed in the plant kingdom like benzoic, phenylacetic, cinnamic acid and their derivatives.



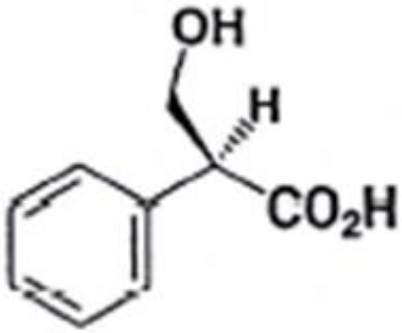
Isovaleric acid



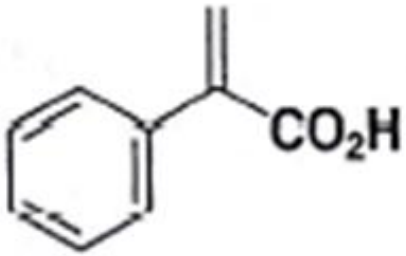
Tiglic acid



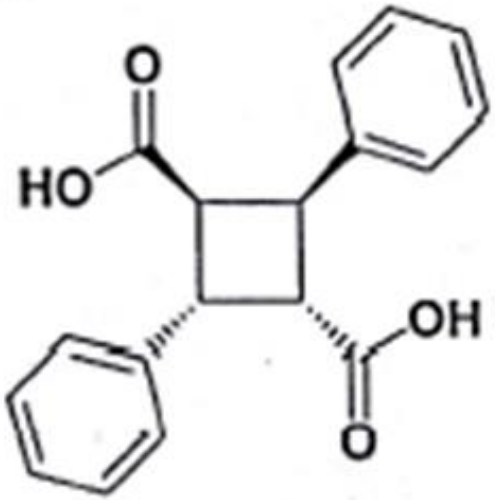
Angelic acid



Tropic acid

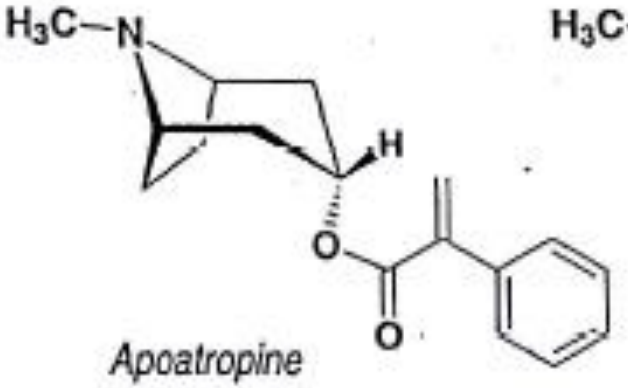


Apotropic acid (atropic acid)

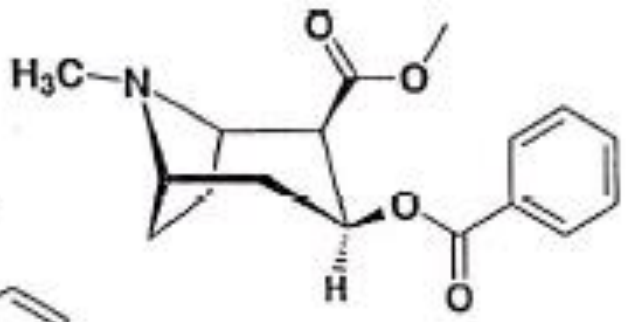


α-Truxillic acid

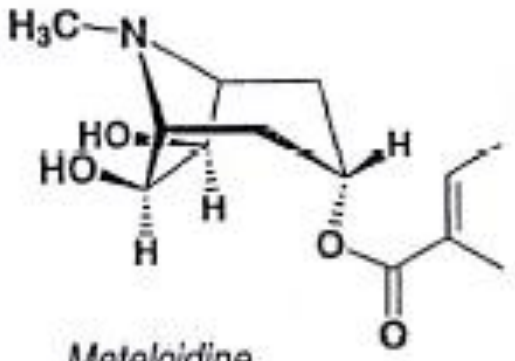
C. ALKALOIDS



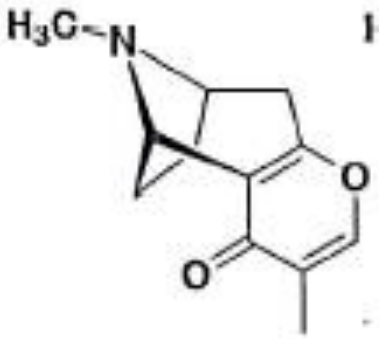
Apoatropine



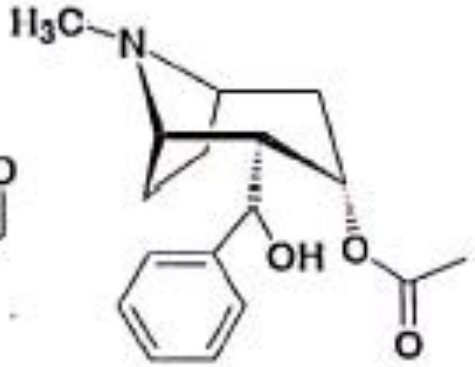
Cocaine



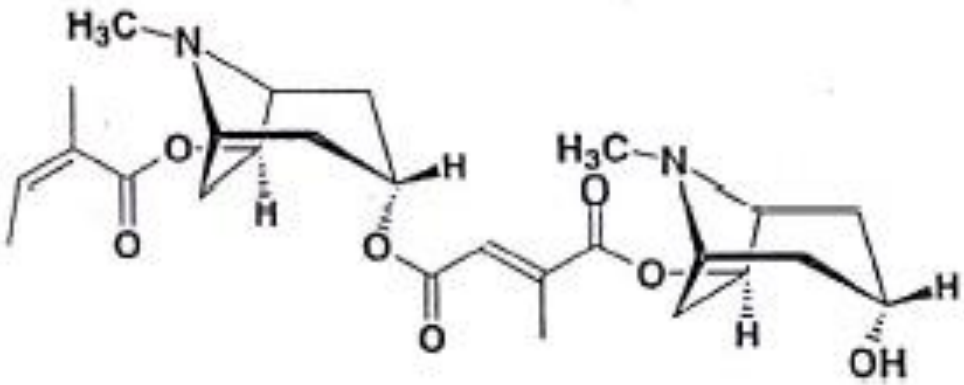
Meteloidine



Bellendine



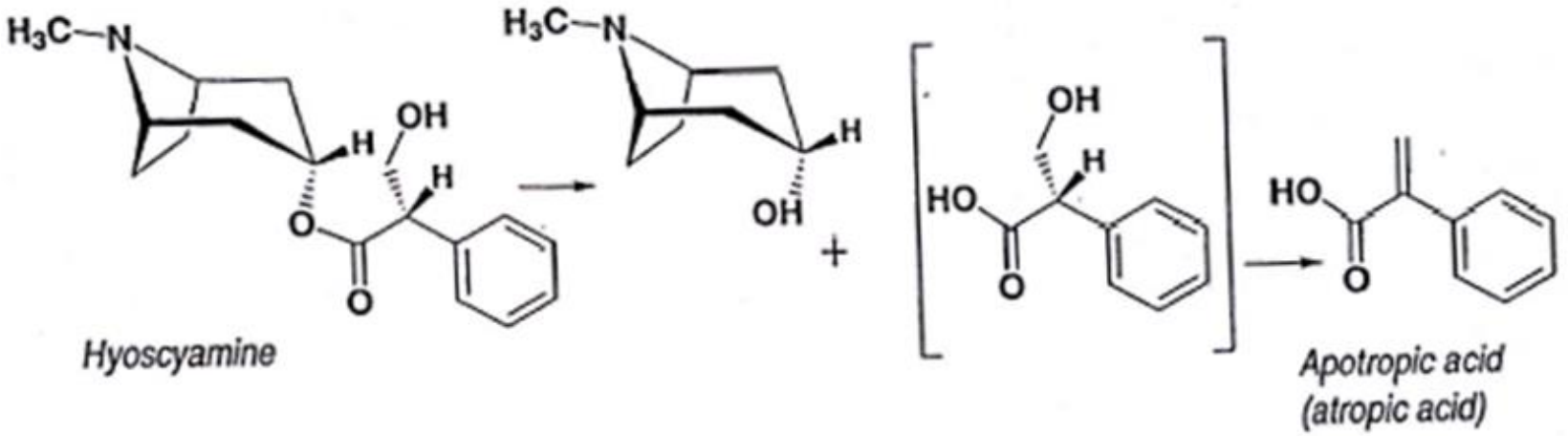
Knightinol

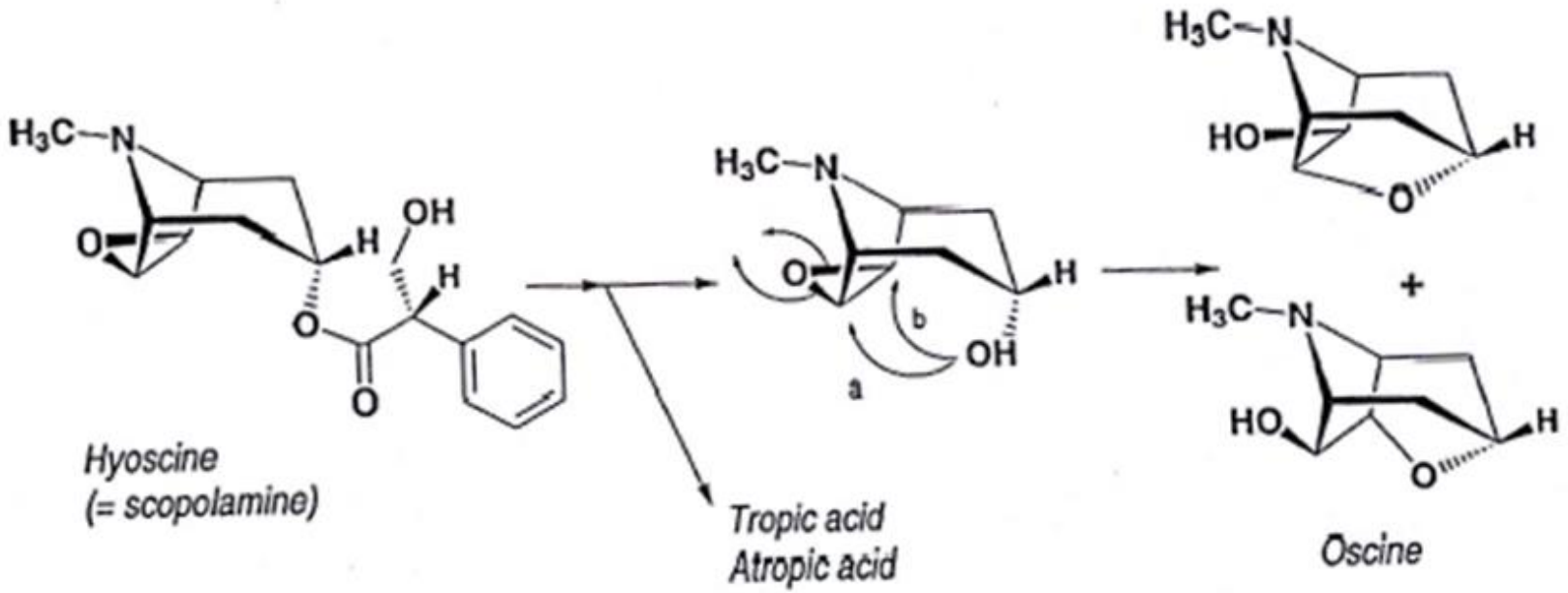


Schizanthine D

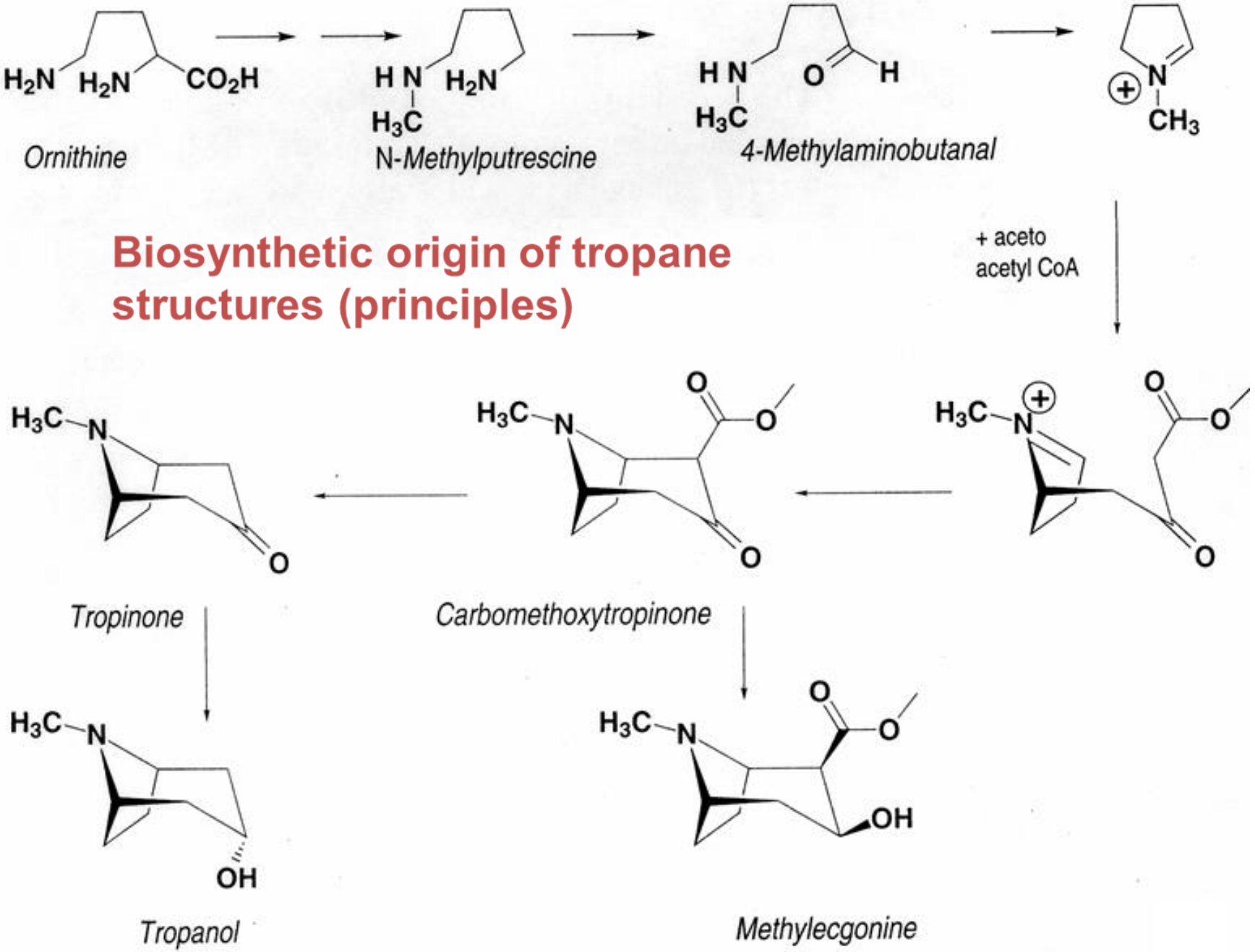
Degradation of tropan ester alkaloids

It occures in acidic as well as basic condition

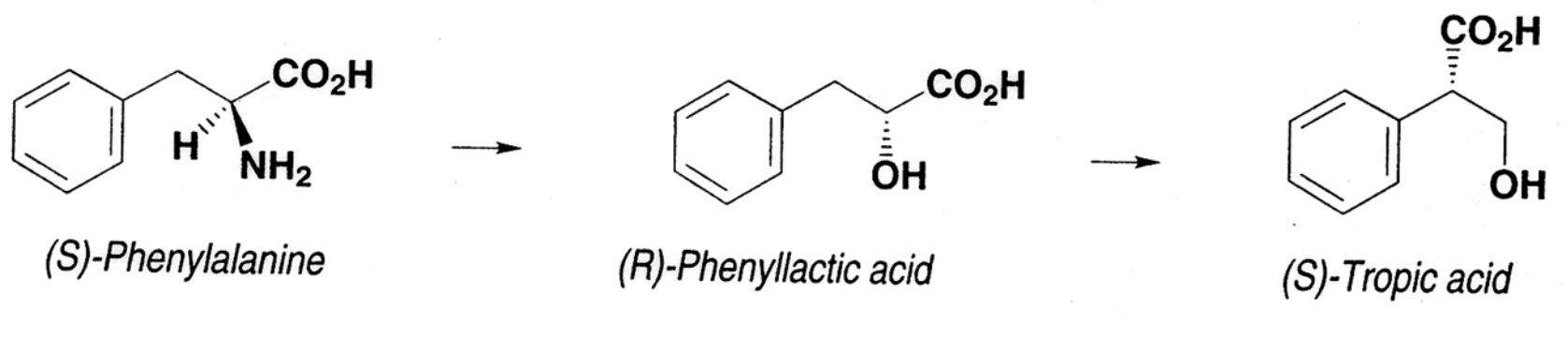




Biosynthetic origin of tropane structures (principles)



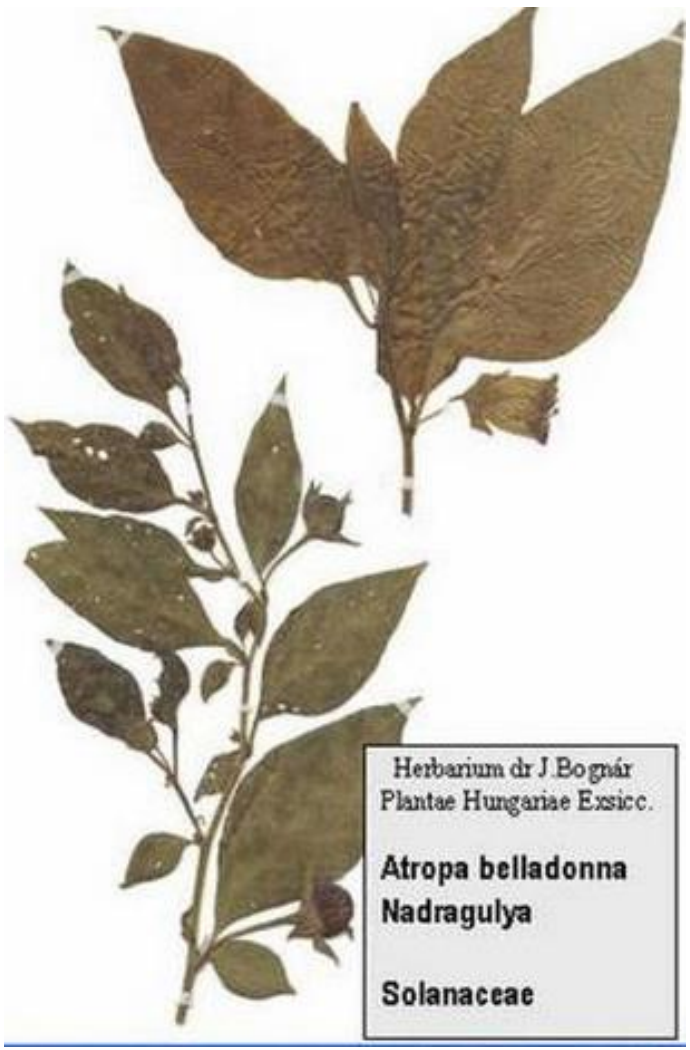
Origin of tropic acid



Deadly Nightshade, *Atropa belladonna* L. (Belladonna), Solanaceae

- Indigenous to western Europe. A perennial plant with a rizoma-like root, erect stems (1-1.5m).
- **Leaves:** alternate on the lower part of the stem , in close pairs near the inflorescence. They are uneven size and not opposite.
- **Flowers:** normally solitary with a **campanulate corolla** with purplish-brown or brownish-yellow lobes.
- **Fruit:** the size of a cherry, shiny black, surraunded at the base by an indeciduous and well-developed calyx.
- (subglobulous bilocular berry)

Belladonnae folium



- **Belladonna leaf** has an elliptic blade, acuminate at the apex, and attenuate at the base (5-25 x 3-12 cm)
- The pubescence of young leaves only remains near at the veins in the older leaves.
- The secondary veins are at 60° and are anastomosed near the margin.

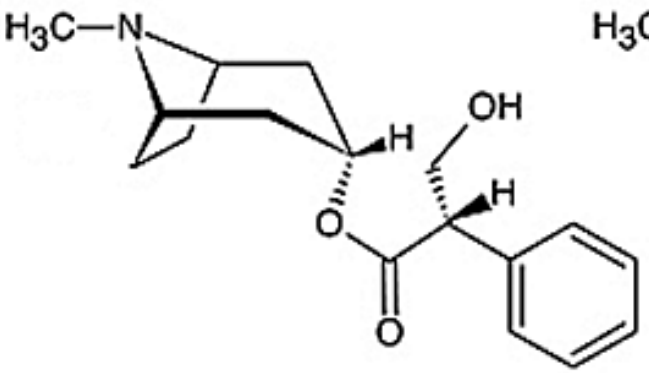
Microscopic characteristic

- Striated cuticle.
- Microsphenoidal crystals in the cells of the parenchymas especially under the palisade layer.
- Trichomes: multicellular, uniseriate, rare covering trichomes.

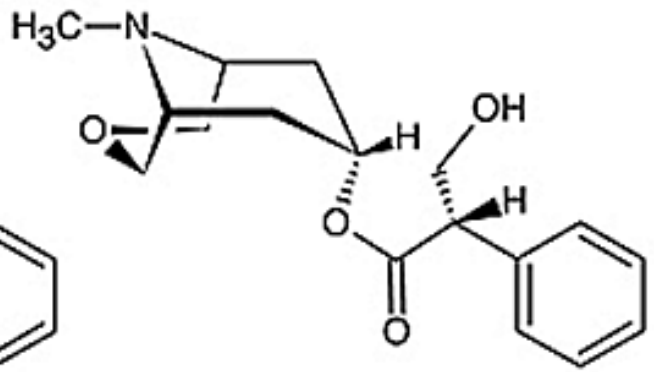
Belladonnae folium

Chemical composition

- Alkaloid content **0.3-0.6 %**.
- **Hyoscyamine as chief constituent** (90 %), occures alongside **scopolamine** (2 %) and their dehydration products (7 %).
- Small quantity of scopoletol (a coumarine).



(-) Hyoscyamine



(-) Hyoscine
[= (-) Scopolamine]

Belladonnae folium, Uses

Galenicals

- **Belladonnae pulvis normatus** (Ph. Eur.): titrated to contain 0.28-0.32 % total alkaloids calculated as hyoscyamine.
- **Belladonnae leaf dry extract, standardised** (Ph. Eur.): 0.95-1.05 % total alkaloids
- **Belladonnae leaf tincture, standardised** (Ph. Eur.): 0.027-0.033 % total alkaloids

Galenicals in various combinations for the symptomatic treatment of

- **unproductive coughs**; sometimes for acute congestion of the throat and larynx.
- as a short term symptomatic treatment for **constipation**,
- the **pain** associated with functional problems of the **gastrointestinal** and **biliary tracts**.
- In rare **antalgic** and **antineuralgic** propietary drugs.
- These combinations have **unfavorable benefit-to-risk ratio** due to their galenicals contents.

Thorn Apple, *Datura stramonium* L., (Stramonium, Jimson weed), Solanaceae

- It grows abundantly in Europe where it most likes neglected country fields and roadsides.
- A hardly annual species , 0.8-1.2m, has a **rounded stem** with **oval acute leaves deeply divaded** in uneven pointy lobes.
- **Flowers:** solitary, large (8-10 cm long), have a **calyx with five sepals** pleated longitudinally, a **tubulous corolla**, pleated, and white.
- **Fruit**: A **bilocular capsule** with a cover that opens. It **covered with tough thorns**.

Stramonii folium

- The blade of the stramonium leaf (8-25 x 7-15 cm) is **acumuminate** and very often **asymmetric at the base**.
- The secondary veins are prominent on the lower side and depressed on the upper side.
- The older leaf is practically glabrous, whereas the veins of the young leaves are tomentose. The **secondary veins** are **at 45°** and **end at the apex of the blade**.

Microscopic characteristics

- Epidermal cells with wavy walls and a smooth cuticle.
- Calcium oxalate **cluster crystals** from 10 to 30 µm.
- Numerous conical covering trichomes, often broken and with verrucose wall .

Stramonii folium (Ph. Eur., Ph. Hg VIII.)

Chemical composition

- Minerals 15-18 %
- Total alkaloid content 0.2-0.5 %.
- At the time of harvest, hyoscyamine and scopolamine represent two-thirds and one-thirds of the total alkaloids, respectively.

Uses

- **Stramonii pulvis normatus (Ph. Eur.):** official stramonium powder titrated to contain 0.23-0.27 % total alkaloids.
- Preparation of galenicals:
  - only one **syrup** proposed **for the symptomatic treatment of unproductive cough**.
  - In the late 1980s, it was still used in cigarettes designed to relive respiratory difficulties.

Henbane, *Hyoscyamus niger* L.

- Hebane can be annual or biennial depending on the variety.
- Originated from Asia, grows all over Europe and North America.
- The **stem** is hairy and viscous, either **simple** (*var. annua*) **or ramnified** (*var. biennis*).
- **Leaves** are petiolate at the base, sessile or sheathing on the stem, with **triangular lobes**, **very hairy**, and pale green.
- The **flowers** grouped into **short racemate** at the base of a larger bract, have **corolla with five lobes incompletly actinomorphic**, and grayish-yelollow with purple or purplish-black veins.
- The **pyxidium** is surrounded by an indeciduous, enlarged, and hardened calyx with thorny teeth.

Hyoscyami folium

- The henbane leaf can be sessile, in which case it is cordate at the base, or on a short petiole, in which case it is acute.
- The blade (25 x 5-7 cm) is highly pubescent and viscous on both sides, especially near the midribs;
- its margin is irregular and divided in wide triangular lobes.
- The secondary veins form **a wide angle with the midrib** and run to the apex of the blade.
- **Microscopic characteristic:** epidermal cells with wavy wall and a smooth cuticule. Calcium oxalate **crytals of prisms** from 5to 20 um. **Trichomes:** very numerous glandular trichomes of several types, often fragmented, and numerous covering trichomes.

Hyoscyami folium

Chemical composition

- Minerals (18-20 %).
- Total alkaloid content: 0.04-0.15%.
- Hyoscyamine is the chief constituent and the percentage of scopolamine can be high (25 % and more).

Uses

- Hebane is not used much more than stramonium.
- It is an ingredient of combinations, for example with buckthorn, aloe (stimulant laxative), belladonna (gastrointestinal pain), or ephedrine (asthma).

Pharmacological activity of the alkaloids I.

Atropine

- Atropine and hyoscyamine are **parasympatholytics.**
- Hyoscyamine has a stronger activity than the racemic atropine, but it is the latter that is commonly prepared and used.
- Atropin is an **inhibitor** of the **muscarinic receptors** of the peripheral organs innervated by the parasympathetic post-ganglionic fibers, and of the central nervous system.
- It acts by competitive and reversible inhibition of acetylcholine binding onto its receptors, and this antagonism leads, in the organs of question, to **sympatomymetic-like effects**.

Autonomic nervous system

- In the **hart** and after temporary bradycardia, atropine **increases the hart rate** by suppressing vagal inhibition.
- The effects on the blood pressure are not marked.
- It **decreases intestinal tone**, the amplitude and frequency of peristaltic contractions, paralyzes the ureters, increases bladder pressure, decreases biliary duct tone, and blocks the bronchoconstricting effect of acetylcholine.
- Saliva, sweat, gastric, pancreatic, bronchial, and lachrymal **secretions are decreased.**
- It induces a passive **mydriasis**, a **paralysis of the accommodation** and **an increases in intra-ocular pressure**.

Pharmacological activity of the alkaloids II.

Atropine

CNS

- **Toxic doses** cause **substantial excitation**: agitation, disorientation, exaggerated reflexes, hallucinations, delirium, mental confusion, and insomnia;
- **at low doses** the action is less clear, and tends to be **depressant** and **sedative.**

Scopolamine

- The parasympatholytic activity of scopolamine is identical to that of atropine, but much less marked, especially on the myocardium.
- Its effects on the **CNS** are clear: **sedative**, **depressant, hypnotic with amnesia**.
- It potentiates neuroleptics, improves parkinsonism, and is „incapacitating” at high doses.

Brugmansia sanguinea Ruiz et Pav (syn. ***Datura sanguinea*****), Solanaceae**

- **Small tree** characterized by **large flowers** (17-25 cm), with a **tubulous corolla**, yellow and orangy with red veins.
- This plant is **cultivated in Equador** in high altitude (3000 m) areas.
- The **leaves**, which contain about **0.8 % alakloids**, **with scopolamine as chief constituent**, are harvested mechanically three times a year.
- ***B. sanguinea*** like other species (***Datura innoxia*** from Mexico, ***B. suaveolens***, ***B. arborea*** from Amazonia and Colombia, among others) is traditionally used for its **hallucinogenic properties**.

Corkwood Tree, Pituri, *Duboisia myoporoides* R.Br., *D. leichardtii* F. Muell. (Solanaceae)

Small trees with

- alternate and **narrow leaves** ,
- panicles of **tubulate white flowers**,
- black **berrie**s.

Both species are **Australian:** *D. myoporoides* is widespread on the **eastern seaboard**, whereas *D. leichardiiis* localized around **Brisbane**.

Both species, as well as and their hybrids, are **rich in alkaloids** **(up to 3%)** and are **cultivated.**

Both species are **exploited for the extraction of alkaloids** , which used to be carried out on site for a long time.

At present, the leaves are exported toward Europe, mainly to Germany for extraction.

Anisodus tanguticus (Maxim.) Pasch

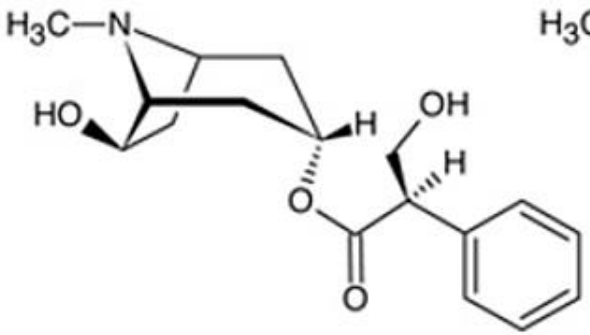
- This Chinese plant is **an ingredient of traditional anesthetic preparations**.

Its **root** contains alkaloids:

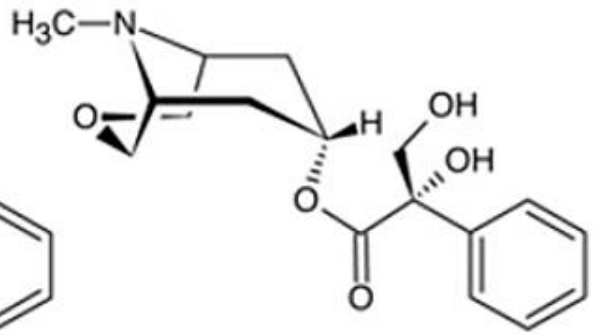
- **Anisodamine**, a **CNS stimulant**, an anticholinergic and antispasmodic.

  It used **to treat acute enteritis and septic shock** (bacyllary disentery); by dilating the capillaries, it improves microcirculation.

- **Anisodine** is a **CNS depressant** , it is antagonized by physostigmine, and chiephly used **to treat migraine hedache**.



anisodamine



anisodine

Coca, Cocae folium, *Erythroxylum coca*, Erythroxylaceae

Coca is a cultivated shrub , pruned to different heights depending on the geographical area (70-80 cm in the Yungas of Bolivia).

Erythroxylum coca Lam.
Image processed by Thomas Schoepke
www.plant-pictures.de

The branches are reddish , and bear **oval, entire**, and shortly petiolate **leaves**.

The **flowers** are pentamerous and **yellowish-white**.

The **fruit** is a small **red drupe**.

The leaf of the typical species has a slightly acuminate blade (2.5-7.5 x 1.5-4 cm), more or less prominently *marked on the lower side by* two curved lines , which delineate an oval area centered on the midrib.

Coca, Erythoxylum ssp.,

The **Erythroxylum cultivated** to produce leaves **rich in cocaine includes** three taxa, **three varieties linked to two species**:

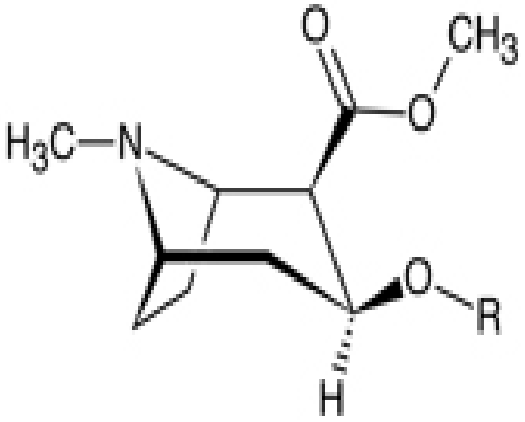
- ***E. coca*** Lam **var. *coca*** grows wild in the **Peruvian and Bolivian Andes** and cultivated **on the damp eastern side of the mountains**. The leaves are dark green; the **blade** is elliptic and **wide**; its midrib forms a prominent ridge on the upper side.
- ***E. novogranatense*** (Morris) Hieron **var. *novogranatense.*** This **forest variety** grows in Columbia and Venezuela. The leaves are bright yellowish-green, the **blade** is elliptic and **elongated**.
- ***E. novogranatense*** (Morris) Hieron **var. *truxillense*** (Rusby) Plowman**.** This variety is characteristic of the dry areas of the north of Peru and of Ecuador. The leaves have an elliptic, **very narrow**, and pale green **blade**, and the midrib ridge is flattened.
- The three taxa are thought to represent stages in evolution, which would have *E. coca* var. *coca* as their ancestor; the latter is the only form capable of reproducing without human invention.

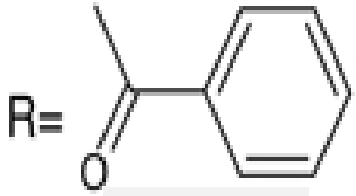
Erythroxylum novogranatense var. *novogranatense*

Cocae folium

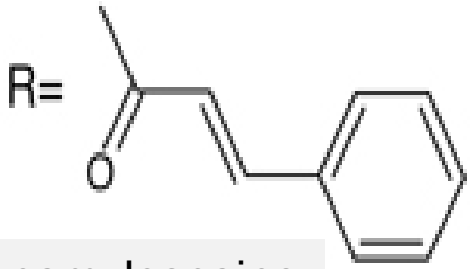
Constituents

- Variable quantites of an **essential oil** including methylsalicilate, **flavonoids**, **tannins**.
- **Alkaloids** (0.5-1.5 %): Cocaine (=methylbenzoylecgonine, 30-50%), cinnamylcocaine (=methylcinnamylecgonine), truxillines (esters of a dicinnamic acid), several pyrrolidines (hygrine, cuscohygrine).

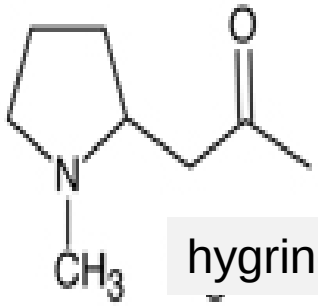




cocaine



cinnamylcocaine



hygrine

Cocae folium, Pharmacological Properties

Cocaine

- **Local** (contact) **anesthetic**. It **blocks ion channels** in neuronal membranes, and interrupts the propagation of action potential corresponding to the sensory message.
- **Sympathomimetic.** It acts as an adrenergic stimulant **by blocking the reuptake of dopamine, and noradrenaline** at the presynaptic neuron **by binding to their transporters**.
- This adrenergic stimulation causes **hyperthermia** , **mydriasis**, and **vasoconstriction** of most of the blood vessels, which increases resistance and contributes to **increasing blood pressure**.
- **Centrally**, the stimulation results in a sensation of **euphoria** with intellectual stimulation, decreased inhibition, hyperactivity, and of effects sought by drug addicts.
- The depletion which follows the reuptake blockade explains the **short term depressant effect** (psychic and physical asthenia, respiratory and vasomotor depression) and **rapid development of an intense psychic dependence** which is reinforced by further abuse.
- Cocaine **does not induce physical dependence**.

Cocae folium

Uses

Neither coca leaf nor its galenicals are used any more, but the **leaves** are still used **to extract cocaine.**

In the United States, **cocaine** is used **in combinations** (phenol, menthol, cocaine) **for local anaeshesia**, for example to stich small wounds.

Traditional uses

- **As a masticatory,** a very ancient habit**;** the **coca leaf** is chewed, and added alkalis facilitate the release of cocaine.
- **In infusion**; the common form is a **tea bag** which yields a strikingly aromatic infusion, consumed like coffee or tea (*mate de coca*) .

Illicit Use of Cocaine

- **Cocaine hydrochloride** is generally „snorted” by the intranasal route, and less often used by IV injection.
- Cocaine intake causes **euphoria, intellectual stimulation, hyperactivity, a feeling of hyperlucidity,** and **acceleration in elaboration of ideas**.
- Its activity resembles that of amphetamines, and also manifests itself by a **decrease in fatigue, insomnia, anorexia, and increased talkativeness** ,
- but also by **irritability**, **altered sensations and impaired judgement**, **physical exhaustion**, and **emotional depression**.
- Cocaine use commonly causes **severe headaches** and sometimes causes **convulsions**;
- **delusions** and **hallucinations** suggesting a serious paranoid psychosis are also described.
- Another effect is compulsive scratching, and *difficulties with verbal expression and memorization* are common.
- The most serious complications are cardiovascular: **hypertensive emergency** , **myocardial ischemia** degenerating into an **infarct**, **cerebral hemorrhage**.
- **Massive overdose** is characterized by **coma , convulsions**, and **cardiac alterations**. The risk is higher in alcohol users: the liver esterases transesterify cocaine into cocaethylene, which is particularly toxic.

Illicit Use of Cocaine

- **Coca paste,** the initial product of the extraction of the leaves, **contains from 40 to 70 % cocaine** (extraction of the leaves with sulfuric acid, alkalinization with carbonate, dissolution of the free base in kerosene). The past is smoked. Kerosene and other residual solvents impart their own toxicity to the preparation.

- **Cocaine is also smoked** (this is „freebasing"). The smoked forms (pure base) have **intense effects with a rapid onset**, but these effects do not last; the profound depression which follows drives the user to take the drug again, and **dependence sets in very rapidly**.