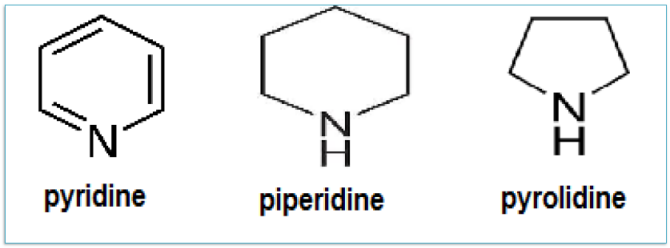
Pharmacognesy III

From textbooks: ***(Trease and Evans Pharmacognosy, 16th Ed.)***
Pharmacognesy and Pharmacobiotechnology, 9th ed, Robbers JE, Speedie MK, Tyler VE.)

Pyridine –piperidine-pyrolidine alkaloids

The amino acid ornithine, its decarboxylation product, putrescine, and proline constitute the basic unit of the tropane, ecgonine, nicotine (pyrrolidine ring).



- **Upon reduction, the tertiary base, pyridine is converted into the secondary base piperidine.**
- **These two nuclei form the basis for this group which sometimes is divided into three subgroups:**

1- **Derivatives of piperidine e.g. lobeline from lobelia.**

2- Derivatives of nicotinic acid e.g. arecoline from areca.

3- **Derivatives of both pyridine-pyrolidine e.g. nicotine from tobacco.**

BIOSYNTHESIS OF PYRIDINE-PIPERIDINE ALKALOIDS

The biosynthetic pathway leading to this compound is summarized as follows:

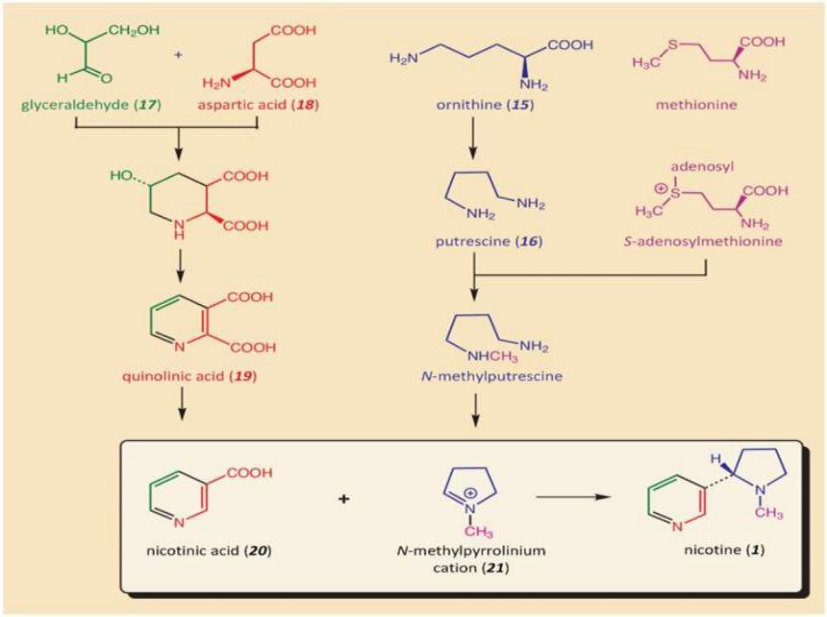
1- Ornithine is incorporated into nicotine in tobacco plants.

2- This incorporation result in a symmetric labeling pattern of nicotine.

3- Putrescine, N- methylputrescine, and N-methylaminobutanal are all incorporated.

4- The N-methylpyrrolinium ion is the key intermediate which, through electrophilic aromatic substitution attached to C-3 of the pyridine ring of nicotinic acid.

5- Nicotinic acid is formed in higher plants and certain microorganisms via quinolinic acid by the condensation of glyceraldehyde-3-phosphate and aspartic acid.

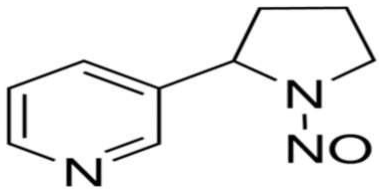


Biosynthetic pathway of nicotine

Drugs containing pyridine-piperidine alkaloids

- **1- Tobacco:**
  - It is the dried leaves of *Nicotiana tobacco* F: Solanaceae.
  - It is cultivated for smoking, it contains alkaloids from 0.6-0.9%, the main one is nicotine which is an oily liquid alkaloid, it is colorless liquid but when oxidized convert to yellow color.
  - nicotine has pronounced effects on the cardio vascular system, where peripheral vasoconstriction, atrial tachycardia & an increase in both systolic & diastolic blood pressure are observed.
  - It is worth noting that 50% of all smokers die of heart disease & 20% of lung cancer.

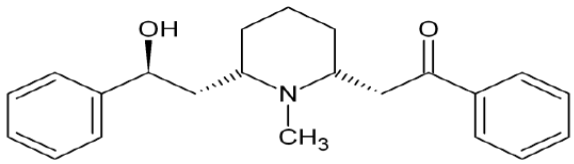
- **The carcinogenicity of tobacco is probably not due to nicotine but rather to a far more potent carcinogen (N-nitroso nor nicotine)**
- **It is found in cigarettes, cigars & chewing tobacco.**
- **levels in the range of (2-90)pp (parts per billion) concentrations of N nitrosamines are considered hazardous to health.**



N-nitroso nor nicotine

2- Lobelia or (Indian tobacco)

- **It is the dried leaves & tops of *Lobelia inflate* F: Lobeliaceae (Campanulaceae).**
- **The drug contains 14 alkaloids, of which lobeline is the major & most important.**



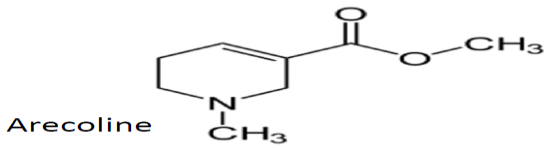
(Lobeline)

- **Lobeline**
- **occurs in colorless crystals very slightly soluble in water, but readily soluble in hot alcohol.**
- **Uses and Dose. Galenical preparations of Lobelia were formerly used for expectorant purposes.**
- **Lobeline is a respiratory stimulant, but its action is somewhat unreliable and of brief duration.**
- **Other effects resemble those of nicotine. For this reason, 0.5 to 1.5 mg doses of lobeline sulfate are incorporated in tablets or lozenges which are intended to aid in breaking the tobacco habit.**

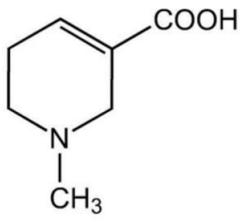
3- Areca:

- **Is the dried, ripe seed of *Areca catechu* (Fam. Palmae).**
- **Areca contains several alkaloids which are reduced pyridine derivatives.**
- **Among them are arecoline (arecaidine methyl ester), arecaidine (Nmethyl guvacine), guvacine (tetrahydronicotinic acid), and guvacoline**

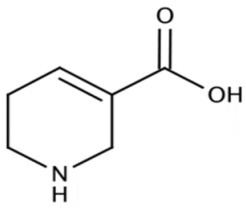
(guvacine methyl ester). The content of total alkaloids ranges up to 0.45%.



Arecoline



Arecidine

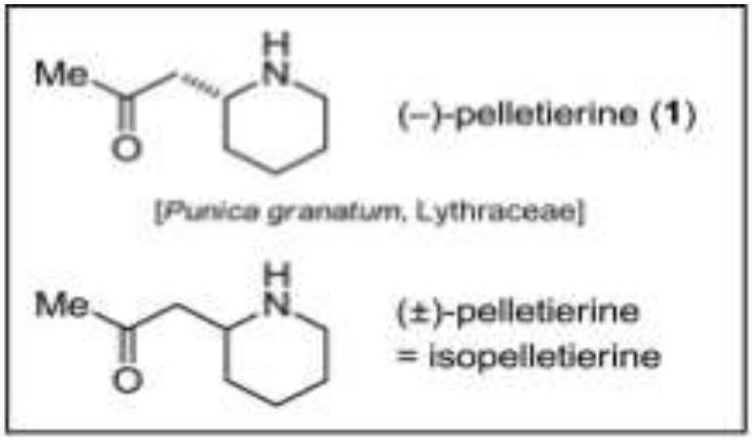


Guvacine (tetrahydronicotinic acid)

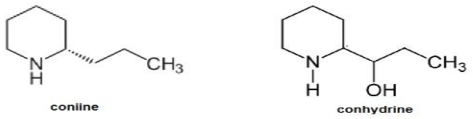
- **Use. Arecoline Hydrobromide is used in veterinary medicine as an anthelmintic drug against parasitic worms especially tenea.**

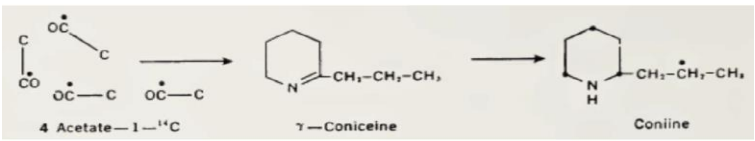
- **4- POMEGRANATE:**
- **Pomegranate Root and Stem Bark or Granatum is derived from *Punica granatum* (Fam. Punicaceae).**
- **They contain about 0.5–0.9% of volatile liquid alkaloids, the chief of which are pelletierine and pseudopelletierine, together with about 22% of tannin.**

- **Pelletierine tannate, a mixture of the tannates of the alkaloids, was included in the BP 1948 and was used as an anthelminthic with a specific action on tapeworms.**



- **4- Conium (poison hemlock):**
- **It is the full grown but unripe fruit of *Conium maculatum (*F:Umbellifareae).**
- **It contains number of alkaloids the important of which is coniine & conhydrine.**

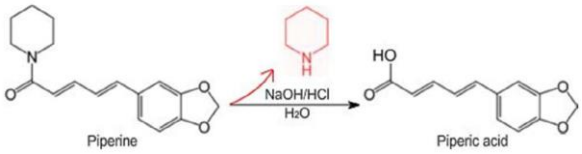




Biosynthesis of coniine

5- Piper:

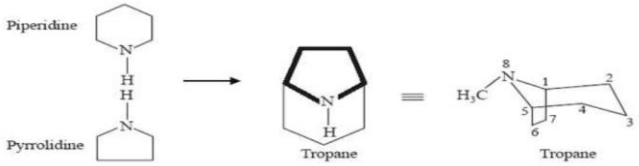
- **It is the dried full grown unripe fruit of *Piper nigrum (*F: Piperaceae).**
- **It contains up to 4.5-8% of piperine.**
- **Mainly used as a condiment.**
- **It has an irritant, stimulant & febrifuge activity (decrease body temperature).**
- **On hydrolysis of piperine we get another alkaloid piperidine which is a liquid alkaloid.**



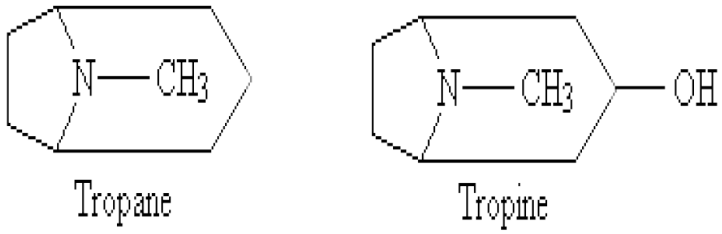
Tropane alkaloids

- **The principal alkaloids of medicinal interest in this group are (–)-hyoscyamine; its more stable racemate atropine, and hyoscine (scopolamine). The compounds are esters and are hydrolyzed by heating at 60°C with baryta water; atropine yields tropic acid and tropine; hyoscine gives tropic acid and oscine (scopine is actually formed by enzymatic hydrolysis but the chemical treatment converts it to the more stable geometric isomer, oscine). They are extremely poisonous.**

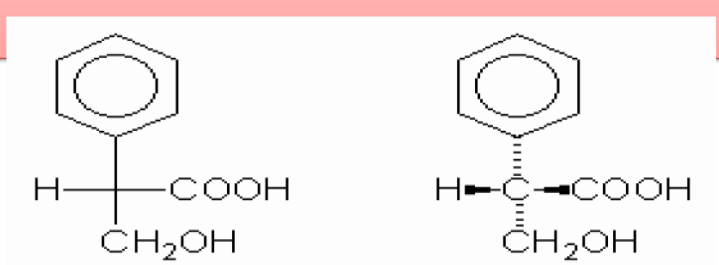
- **Tropane is a bicyclic compound found by the condensation of a pyrrolidine precursor (ornithine) with three carbon atoms derived from acetate.**
- **Both pyrrolidine & piperidine ring systems can be recognized in the molecule.**



The 3-hydroxy derivative of tropane is known as tropine.



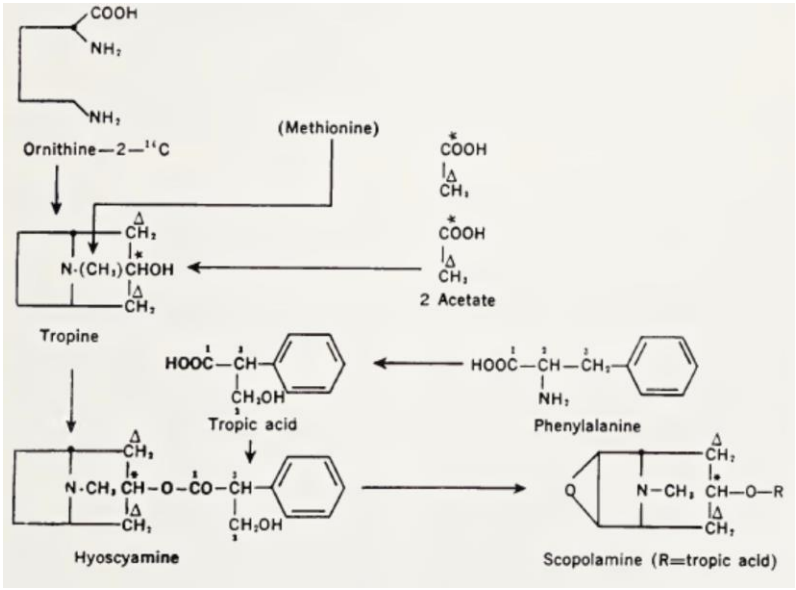
Its esterification with (-)-tropic acid yields hyoscyamine (tropine-tropate) ester, which may racemize to form atropine.



(S)-(-)-tropic acid
(S)-(-)-3-hydroxy-2-phenylpropanoic acid

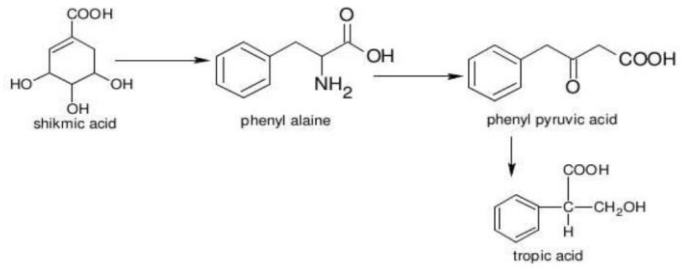
Biosynthesis of tropan alkaloids

- **Hyoscyamine and Scopolamine.**
- **Feeding studies with labeled ornithine have revealed that this amino acid is incorporated stereospecifically to form the pyrrolidine ring of tropine. The remaining three carbon atoms derive from acetate, thus completing the piperidine moiety.**
- **Methylation results via transmethylation front a suitable donor, e.g., methionine, to complete the tropine nucleus. Esterification of tropic acid with tropine produces hyoscyamine.**

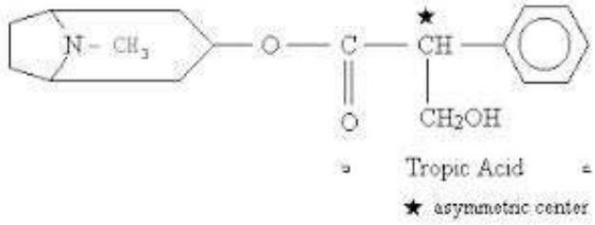


Biosynthesis of hyoscyamine and scopolamine

- **Tropic acid is formed by an intramolecular rearrangement of phenylacetate.**



- **The (-)-isomer is hyoscyamine, the (+)-isomer is not found in the plant, the (±)-isomer is atropine.**
- **Hyoscyamine is more active than atropine.**
- **Hyoscine (scopolamine) is an epoxide of atropine & it is the (-)-isomer.**
- **The (±)-isomer of scopolamine is atrosine.**



- **All together over 200 tropane alkaloids have now been recorded.**
- **Semi synthetic derivatives e.g. N-butyl bromide (buscopan) are of medicinal importance.**

Drugs containing tropane alkaloids

1- Belladonna (Deadly night shade leaf):

- **Two parts of belladonna are official, the root & the leaf.**
- **It is the dried leaf or root of *Atropa belladonna (*F: Solanaceae).**
- **The root is richer than the leaf in alkaloids. The root contains 0.6 % while the leaf 0.4%.**
- **Most of the alkaloids found in the leaf are: (-) hyoscymine, and traces of atropine in fresh plant.**

- **Atropine is formed by racemization during the extraction process.**
- **Small amount of other bases are found in the root but not in the leaf these include:**

(The anhydride of atropine (apoatropine) and it's stereoisomer belladonnine and scopolamine(hyoscine)).


- ***Uses***

- **Belladonna acts as a parasympathetic depressant which accounts for its use as a spasmolytic agent. It possesses anticholinergic properties and is used to control excess motor activity of the gastrointestinal tract and spasm of the urinary tract.**

- **2- Hyoscyamus or Henbane**
- **The dried leaves & flowering tops of *Hyoscyamus niger (*F: Solanaceae).**
- **It contains 0.04% of total alkaloids calculated as hyscyamine, the drug also contains hyoscine & traces of atropine.**
- **Uses: Hyoscyamus is a parasympatholytic, but the crude drug is rarely employed in medicine today.**

3- Egyptian Henbane:

- **It is the dried leaves & flowering tops of *Hyoscyamus muticus*, yield about 1.5% of total alkaloids consisting largely of hyoscyamine.**
- **The plant is indigenous to & cultivated in Egypt.**
- **The plant is used perhaps entirely for the extraction of its alkaloids.**

4- Stramonium:

- It is the dried leaves & flowering tops of *Datura stramonium* (F: Solanaceae).
- It contains up to 0.4% of total alkaloids calculated as hyoscyamine.

- **Use:** Stramonium is an anticholinergic having an action like that of belladonna.
- Powdered Stramonium is an ingredient in preparations which are intended to be burned and the vapor inhaled for the relief of asthma. These so-called asthma powders.
- Food and Drug Administration placed Stramonium-containing asthma powders in the category of drugs which could be dispensed only on prescription.

Uses

- **All these drugs are used as mydriatic (dilate the pupils of the eyes) & as antispasmodic.**
- **As parasympatholytic or anticholinergic & to decrease all the secretions (sweat, saliva, milk etc…).**
- **It is used as adjunctive therapy in the treatment of peptic ulcer, functional digestive disorder, and diarrhea.**

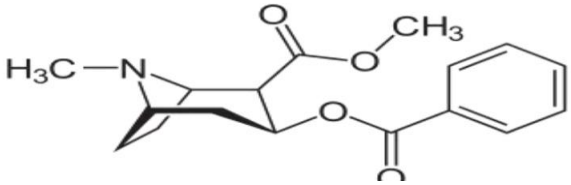
5- Coca:

- **Cocaine is the habit forming drug from the leaves of *Erythroxylum Coca (*F: Erythroxylaceae).**
- **The plant is called coca or coca leaves.**
- **Coca leaves contain 3 basic types of alkaloids:**

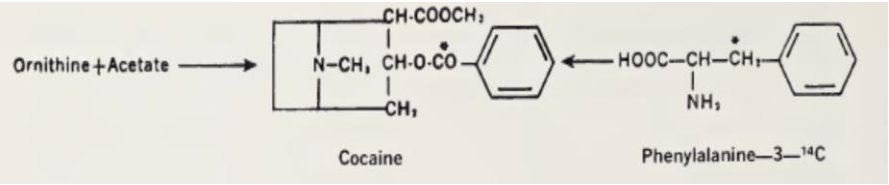
1- Ecgonine derivatives: (cocaine, cinnamyl cocaine, and α & β truxilline).

2- Pseudotropine derived (tropacocaine, valerine).

3- Hygrine derived (Hygroline, cuscohygrine).



- **Feeding experiments with Erythroxylon coca have shown that phenylalanine-3-14C is incorporated into cocaine, the radioactivity being located in the benzoyl group. Presumably, the ecgonine moiety derives from ornithine and acetate in a manner analogous to tropine biosynthesis.**



- **Only the ecgonine derivatives are commercially important.**
- **The most important of these is cocaine.**
- **Cocaine & cocaine hydrochloride, are agents of abuse, that are generally inhaled or sniffed & are rapidly absorbed across the pharyngeal mucosa, resulting in cerebral stimulation & euphoria.**
- **Cocaine hydrochloride is a local anesthetic.**
- **It is applied topically to mucous membrane as 2-5% solution.**

THANK YOU