



Pharmacognesy III

*From textbooks: (Trease and Evans
Pharmacognosy, 16th Ed.)*

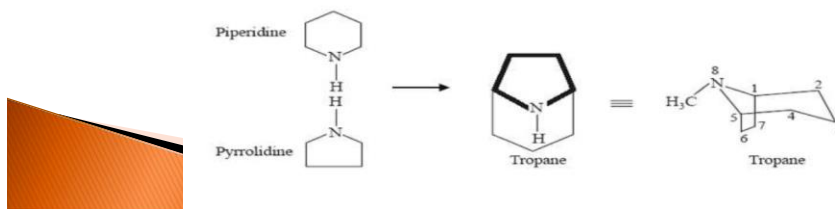
*Pharmacognesy and
Pharmacobiotechnology, 9th ed,
Robbers JE, Speedie MK, Tyler VE.)*

م.د شيرين محمد مكي الحسيني

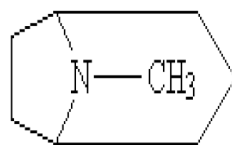
Tropane alkaloids

- ▶ The principal alkaloids of medicinal interest in this group are (–)-hyoscyamine; 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.
- ▶ **They are extremely poisonous.**

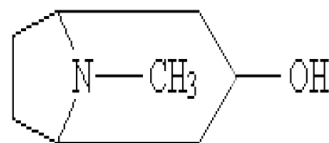
- ▶ Tropane is a bicyclic compound found by the condensation of a pyrrolidine precursor (ornithine) with three carbon atoms derived from acetate.
- ▶ Both pyrrolidine & piperidine ring systems can be recognized in the molecule.



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

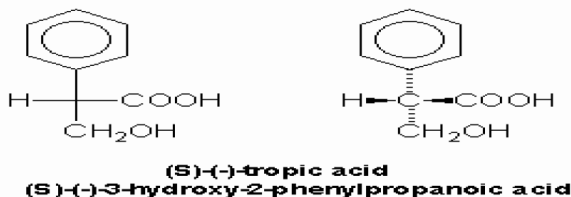


Tropane



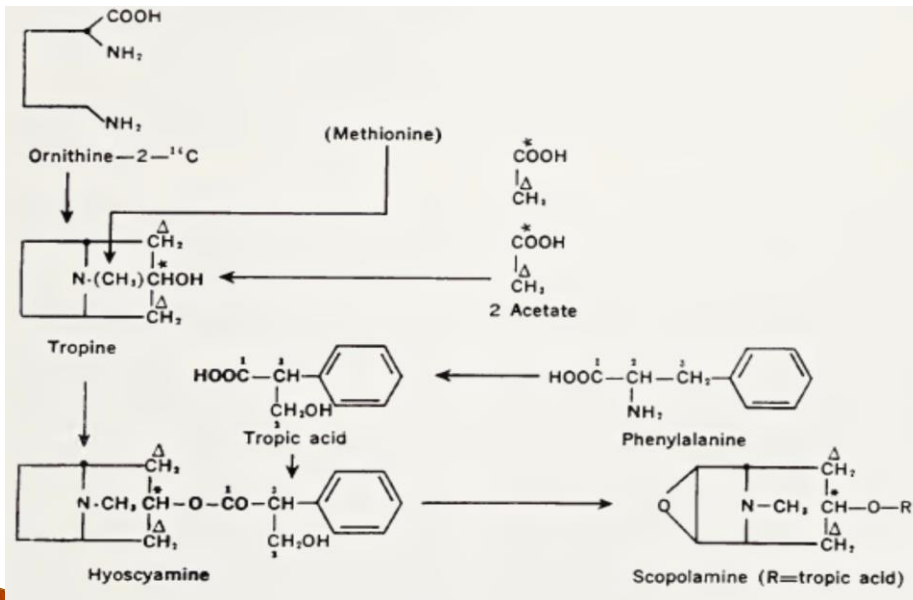
Tropine

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



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 from 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 phenyl alanine.
- ▶ Hyoscyamine, has both + and - isomers. the (-)-isomer is found in the plant.
- ▶ The (±)-isomer is atropine (racemic mixture).
- ▶ Hyoscyamine is more active than atropine.
- ▶ Hyoscine (scopolamine) is an epoxide of atropine & it is the (-)-isomer.
- ▶ The (±)-isomer of scopolamine is atosine.

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.
- ▶ Atropine is formed by racemization during the extraction process.



▶ *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.

5- Coca:

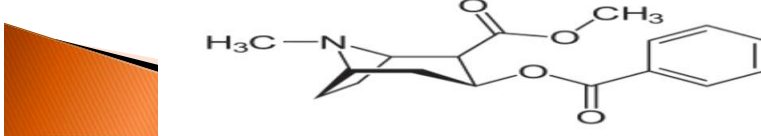
Cocaine is the habit forming drug from the leaves of *Erythroxylum Coca* (F: Erythroxylaceae).

- ▶ The plant is called coca or coca leaves.
- ▶ Coca leaves contain 3 basic types of alkaloids:

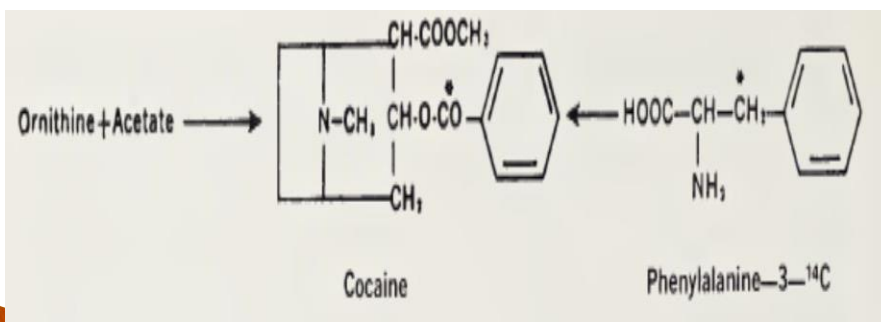
1- Ecgonine derivatives: (cocaine, cinnamy cocaine, and α & β truxilline).

2- Pseudotropine derived (tropacocaine, valerine).

3- Hygrine derived (Hygroline, cuscohygrine).



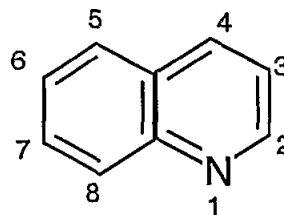
- ▶ Feeding experiments with *Erythroxylum coca* have shown that phenylalanine-3-¹⁴C is incorporated into cocaine, the ecgonine moiety derives from ornithine and acetate in a manner analogous to tropine biosynthesis.



- ▶ 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.

Quinoline Alkaloids

- ▶ In general, the alkaloids containing essentially the ‘quinoline’ nucleus include a series of alkaloids obtained exclusively from cinchona bark.
- ▶ The major members of this particular group are, namely:
 - ▶ quinine
 - ▶ quinidine
 - ▶ cinchonine
 - ▶ cinchonidine.



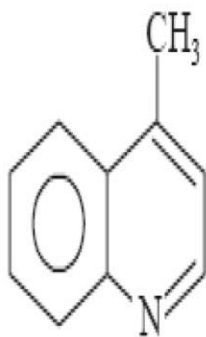
- ▶ More than twenty five alkaloids have been isolated and characterized either from the **Yellow Cinchona i.e. *Cinchona calisaya*** and ***Cinchona ledgeriana***, or from the **Red Cinchona i.e. *Cinchona succirubra*** (F. *Rubiaceae*).



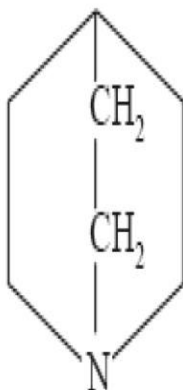
Basic Structures of Cinchona Alkaloids:

- ▶ Cinchona alkaloids usually possess two ring :
 - ▶ (a) 4-methyl quinoline nucleus.
 - ▶ (b) quinuclidine nucleus.
- ▶ These two rings basically form a parent compound known as ruban.
- ▶ Cinchona possess the basic skeleton of 9'-rubanol that is derived from ruban.

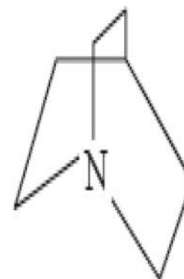




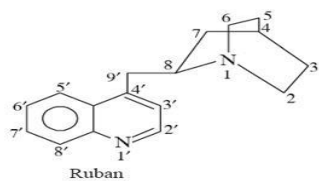
4-Methyl Quinoline
Nucleus



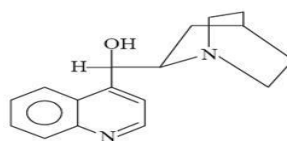
Quinuclidine
Nucleus



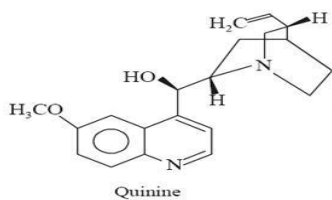
Quinuclidine
Nucleus



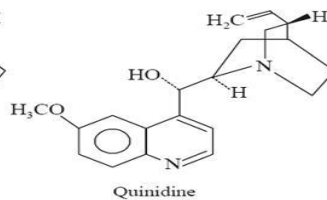
Ruban



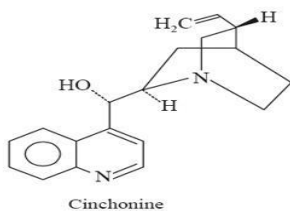
9'-Rubanol



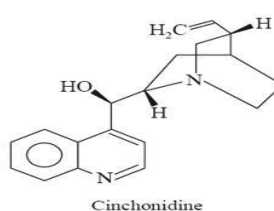
Quinine



Quinidine

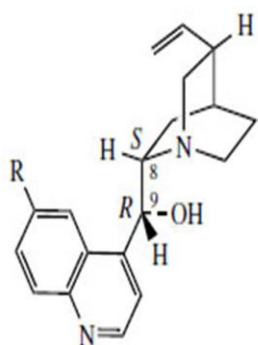


Cinchonine

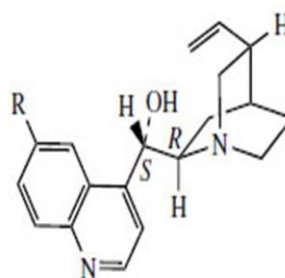


Cinchonidine

- ▶ Quinine & quinidine are stereoisomers.
- ▶ Cinchonine & cinchonidine are stereoisomers .
- ▶ Stereoisomers are isomeric molecules that have the same molecular formula and sequence of bonded atoms (constitution), but that differ *only* in the three-dimensional orientations of their atoms in space.



R = OMe, (-)-quinine
R = H, (-)-cinchonidine



R = OMe, (+)-quinidine
R = H, (+)-cinchonine

For cinchonidine & quinine C8 = S , C9 = R
For cinchonine & quinidine C8= R , C9 = S

Biosynthetic pathway

- ▶ Studies with labeled geraniol and tryptophan indicate that quinine is metabolically derived from the monoterpenoid-tryptophan pathway and involves the formation of an unstable intermediate called (corynantheine) which is also an alkaloid.



Identification Tests of Quinine

1- Fluorescence Test: Quinine gives a distinct and strong blue fluorescence when treated with an *oxygenated acid*, such as: acetic acid, sulphuric acid.

- ▶ This test is very marked and pronounced even to a few mg concentration of quinine.
- ▶ Note: The hydrochloride and hydroiodide salts of quinine do not respond to this fluorescence test.



Identification Tests of Quinine

2- Thalleioquin Test: Add to 2–3 ml of a weakly acidic solution of a quinine salt a few drops of bromine–water followed by 0.5 ml of strong ammonia solution, a distinct and characteristic emerald green color is produced.



Identification Tests of Quinine

- ▶ The colored product is termed as **thalleioquin**, the chemical composition of which is yet to be established.
- ▶ This test is so sensitive that quinine may be detected to a concentration as low as 0.005%.
- ▶ **Notes: Quinidine gives also a positive response to this test; but cinchonine and cinchonidine give a negative test.**



Uses

1- Cinchona & its alkaloids have been used in the treatment of malaria fever for many years.


Quinine sulfate continues to be used for malaria in many parts of the world (it poison the protozoa), as tonic, analgesic, in the treatment of cold.

2- Quinidine is used to treat various cardiac arrhythmias e.g. arterial & ventricular tachycardia, atria fibrillation & ventricular contraction.

Quinidine is found as salts (sulfate & gluconate). It depresses myocardial excitability, conduction velocity & contractility.

- ▶ **Totaquine** : It is a mixture of total alkaloids, containing not less than 7% & not more than 12% of anhydrous quinine.
- ▶ It should contain 70-80% of total alkaloids.
- ▶ It is used as anti malarial & for cold but it cannot be used as cardiac depressant. Usual dose 600mg.

Cinchonism or quinism

- ▶ Treatment with cinchona products result in symptoms of mild cinchonism (which may occur from standard therapeutic doses of quinine).
 - ▶ These symptoms include flushed and sweaty skin, ringing of the ears (tinnitus), blurred vision, impaired hearing, confusion, reversible high-frequency hearing loss, head ache, abdominal pain, rashes, dysphoria, nausea, vomiting and diarrhea.
 - ▶ Ringing in the ears is a symptom of toxicity.
 - ▶ When these symptoms are produced as the result of continuous use of cinchona or of quinine the condition has been called cinchonism.
- 

THANK YOU

