College of pharmacy /Al-Nahrain University

3rd stage/ 2nd coarse

Tropane alkaloids

Lecture 3

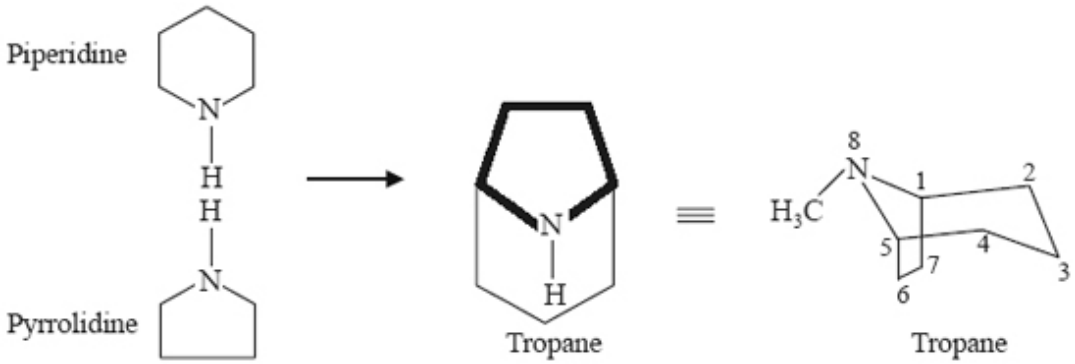
Lecturer Ayah Al-Qrimli

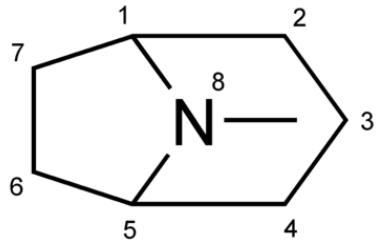
MSc pharmacognosy

Tropane alkaloids

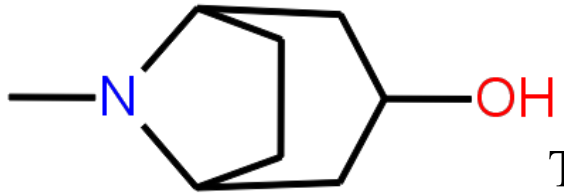
- Tropane is a **bicyclic** compound found by the condensation of **ornithine**

  (pyrrolidine precursor) 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.**
- **Tropine** esterification with **(-)-tropic acid** yields **hyoscyamine** (**tropine-tropate ester**), which may racemize to form **atropine.**
- **Hyoscine** **(scopolamine) is** **an epoxide of atropine.**

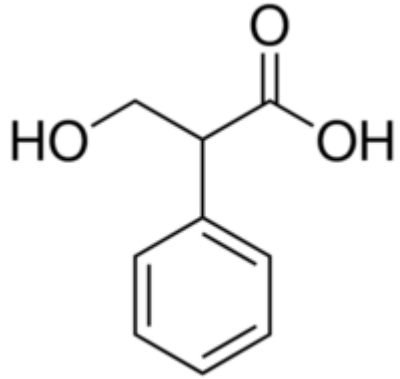




Tropane



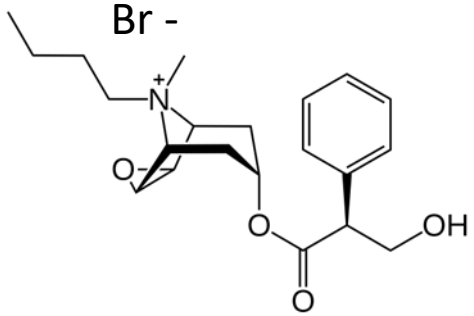
Tropine.



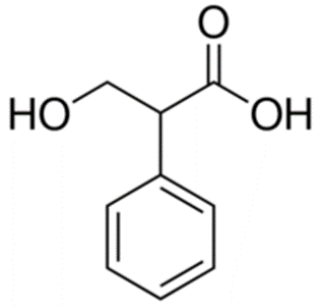
Tropic acid

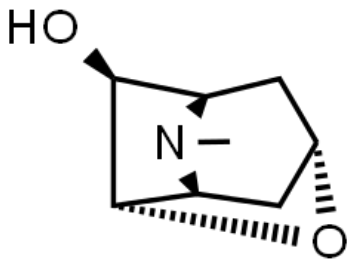
Tropane alkaloids

- The principal alkaloids of medicinal interest in this group are **(-)-hyoscyamine**; its more stable racemate **Atropine**, and **Hyoscine** (scopolamine).
- All together over 200 tropane alkaloids have now been recorded. Semi synthetic derivatives e.g., **N-butyl bromide (buscopan)** are of medicinal importance
- The compounds are **esters** and are hydrolyzed by **heating** at 60°C with boiling water, strong **acids** and strong **base** :
- **Atropine** yields **tropic acid** and **tropine**;
- **Hyoscine** gives **tropic acid** and **oscine** (**scopine** is formed by **enzymatic hydrolysis** but the **chemical treatment** **converts it to the more stable geometric isomer**, **oscine**).
- **They are extremely poisonous.**

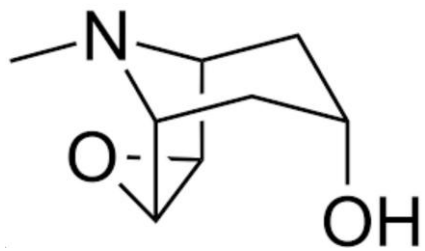




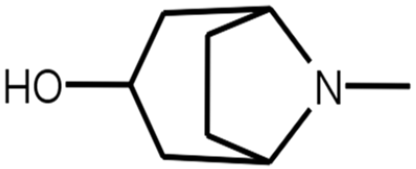




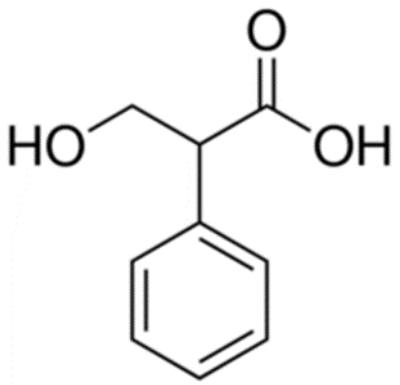
Oscine



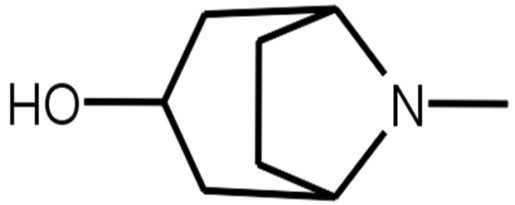
Scopine



Tropine



Tropic acid

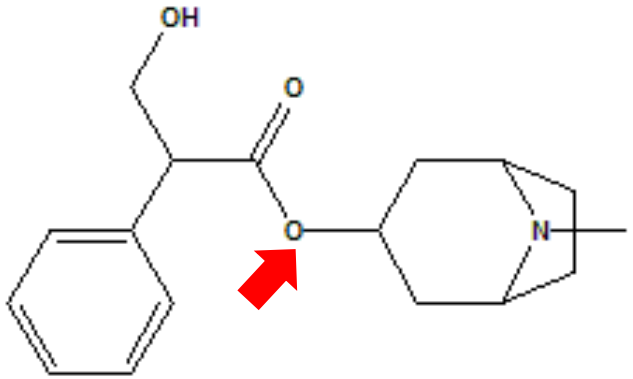


Tropine

1.Esterification of tropic acid with tropine yield atropine

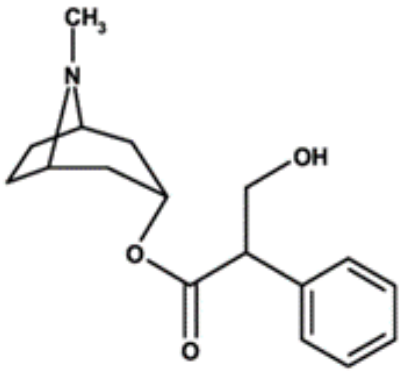
-Hyoscyamine is the tropine ester of (-)-tropic acid & is readily hydrolyzed by **boiling in dilute acids or alkalis yielding tropine + tropic acid.**

2.hyoscine (scopolamine) is an epoxide of atropine

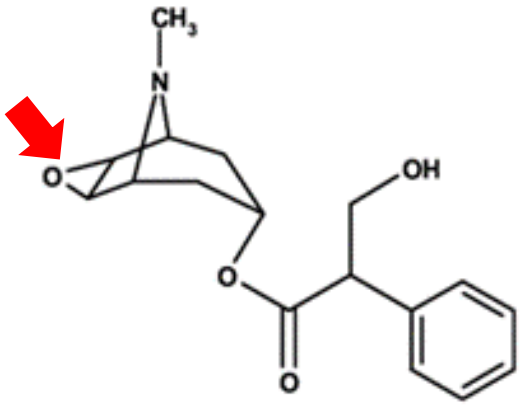


atropin

Hyoscyamine



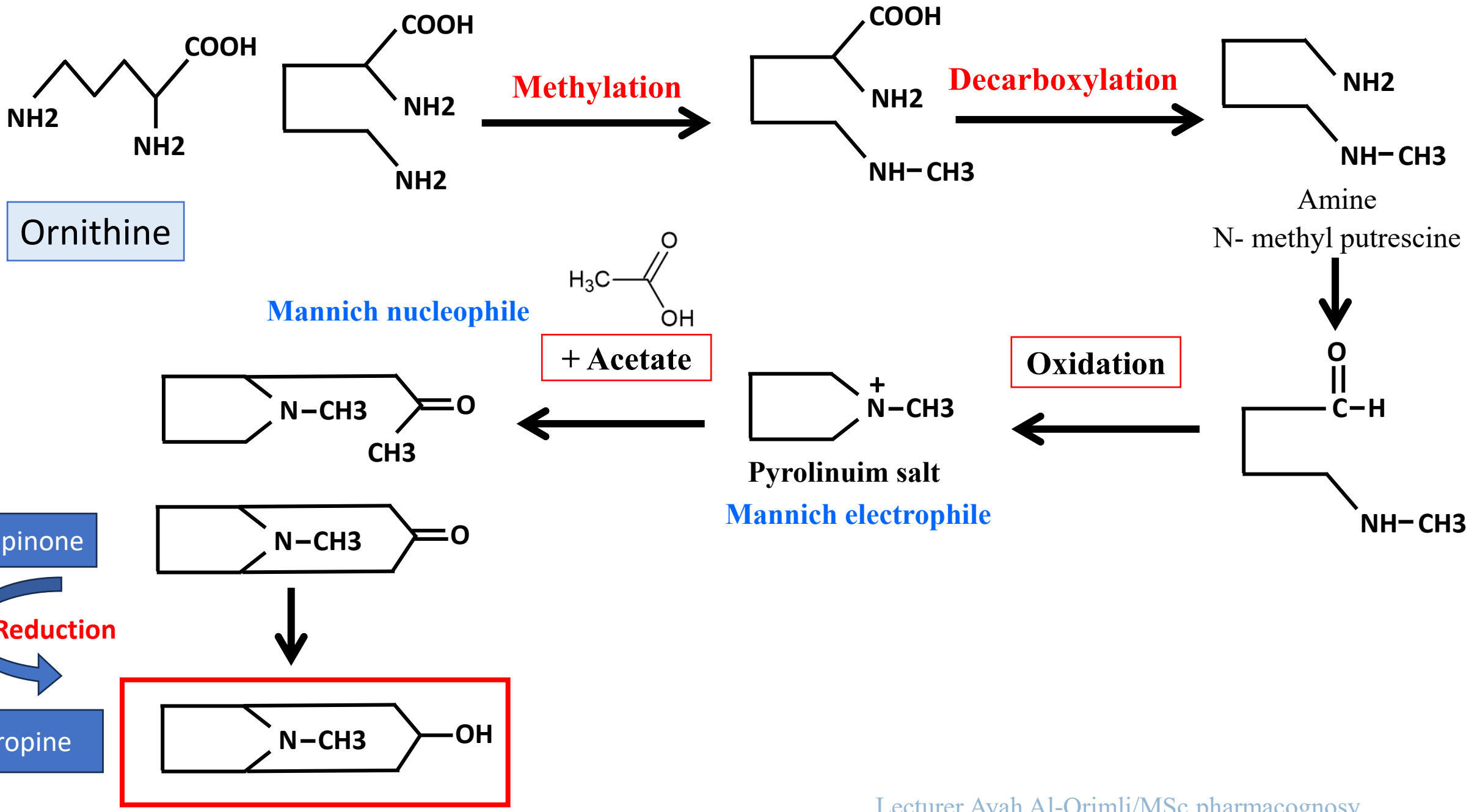
Hyoscyamine



Scopolamine

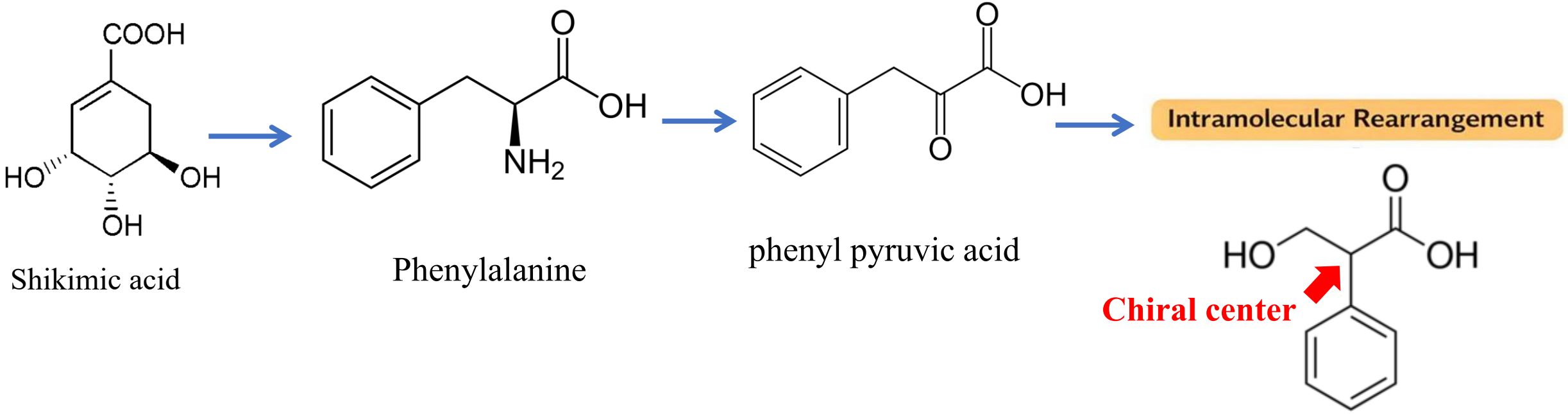
Biosynthetic pathway of hyoscyamine and scopolamine (Tropine)

- Investigation of tropane alkaloids biosynthesis pathway has been extensive, because of their commercial importance of hyoscyamine,
- **Ornithine** is the amino acid incorporated to form the **pyrrolidine** ring of tropine.
- The remaining **3 carbon** atoms are derived from **acetate** & thus complete the **piperidine moiety**.
- Methylation results from methionine.
- Esterification of tropic acid with tropine produces hyoscyamine
- **Summary :**
- In the biosynthesis of tropane alkaloids, a **Mannich-type reaction** occurs when the **N-methyl-Δ^1-pyrrolinium ion** reacts with **acetate-derived enol intermediates**. This reaction forms the carbon–carbon bond that builds the **tropane skeleton**.


COOH
NH2
NH2
COOH
NH2
NH2
Methylation
COOH
NH2
NH−CH3
Decarboxylation
NH2
NH−CH3
Ornithine
Amine
N- methyl putrescine
Mannich nucleophile
H3C
O
OH
+ Acetate
Oxidation
O
C−H
NH−CH3
+
N−CH3
Pyrolinuim salt
Mannich electrophile
N−CH3
O
CH3
N−CH3
O
Tropinone
Reduction
Tropine
N−CH3
OH

Biosynthesis of **Tropic acid**

- Tropic acid is biosynthesized from **phenylalanine** by transamination to form **phenyl pyruvic acid**
- **Tropic acid is formed by an intramolecular rearrangement of phenyl acetate.**



Shikimic acid

Phenylalanine

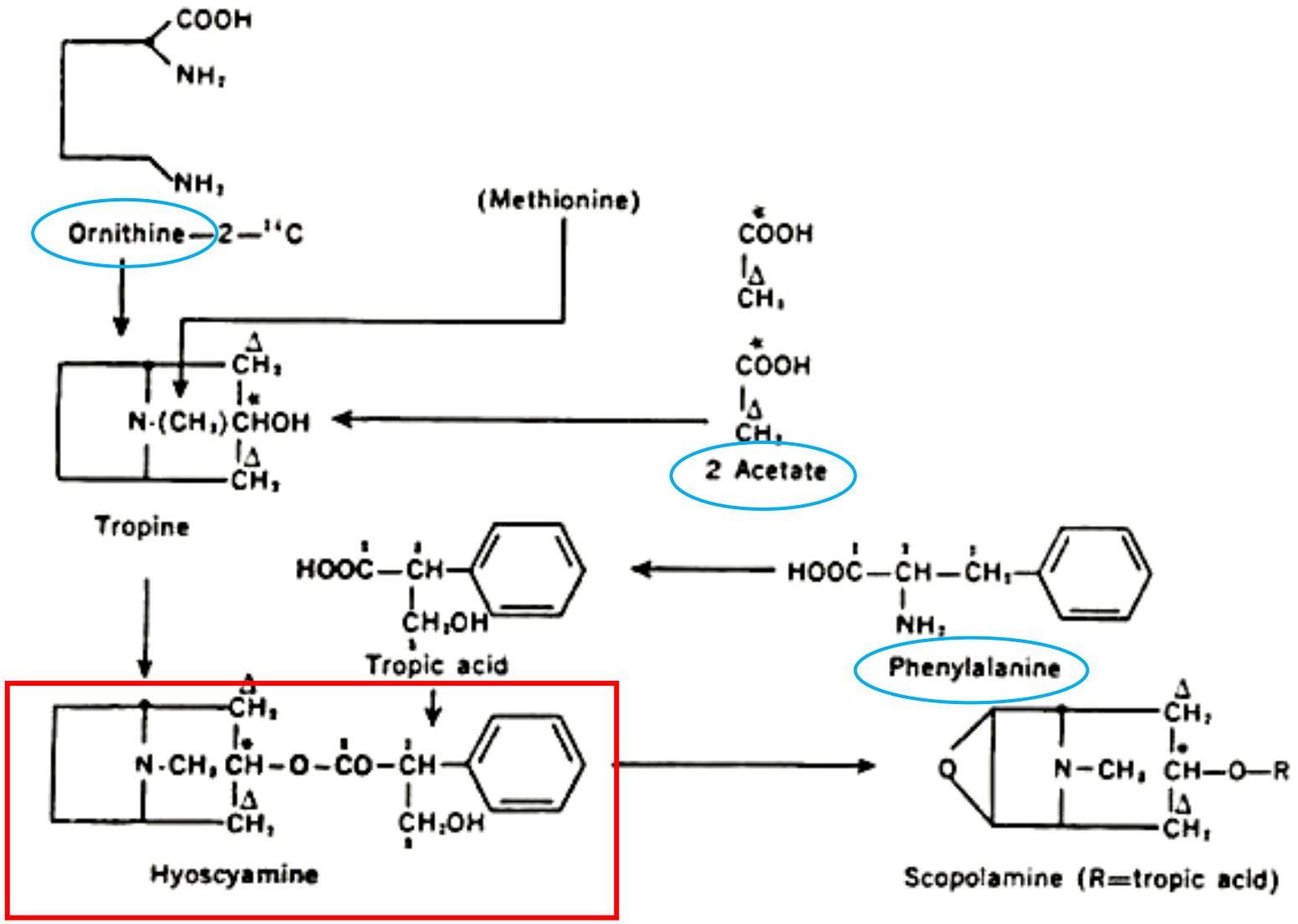
phenyl pyruvic acid

Tropic Acid

* Chiral, (S)-(-)-stereochemistry

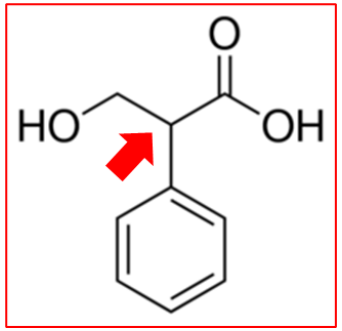
Optically Active*

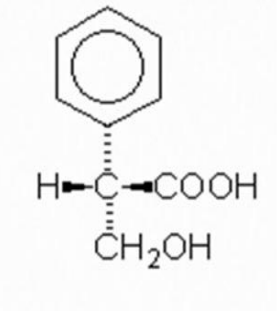
Biosynthetic pathway of
Hyoscyamine and Scopolamine

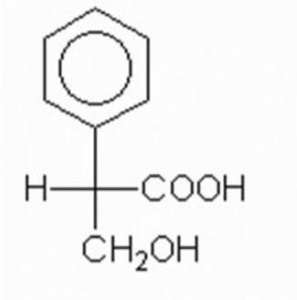


Optical isomerism

- The carbon atom attached to the carboxyl group of tropic acid **is asymmetric (chiral center)** & account for the natural occurrence of the **optical isomers**.
- The **(-)-isomer is hyoscyamine which is found in the plant.**
- **the (+)-isomer is not found in the plant**, **the (+)-isomer is atropine**.
- **Hyoscyamine is more active than atropine (Once planar → chirality is lost).**
- **Hyoscine (scopolamine) is an epoxide of atropine & it is the (-)isomer.**
- **The (±)-isomer of scopolamine is Atrosine** not optically active.
- **Plants biosynthesize only (–)-hyoscyamine, When (-)-hyoscyamine is extracted from the plants in which it occurs, it is usually racemized during the extraction process, thus converted to the isomer which is atropine.**
- WHY? Atropine is not found if amount But is isolated in good quantities.

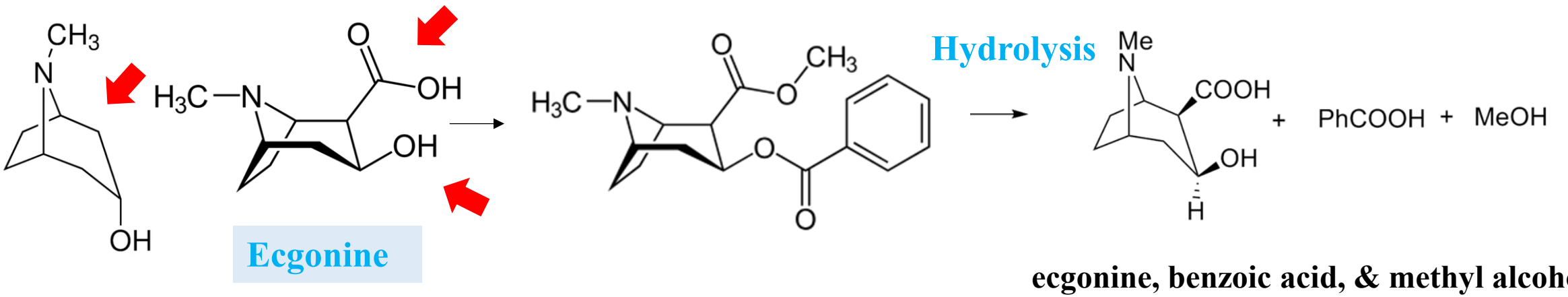






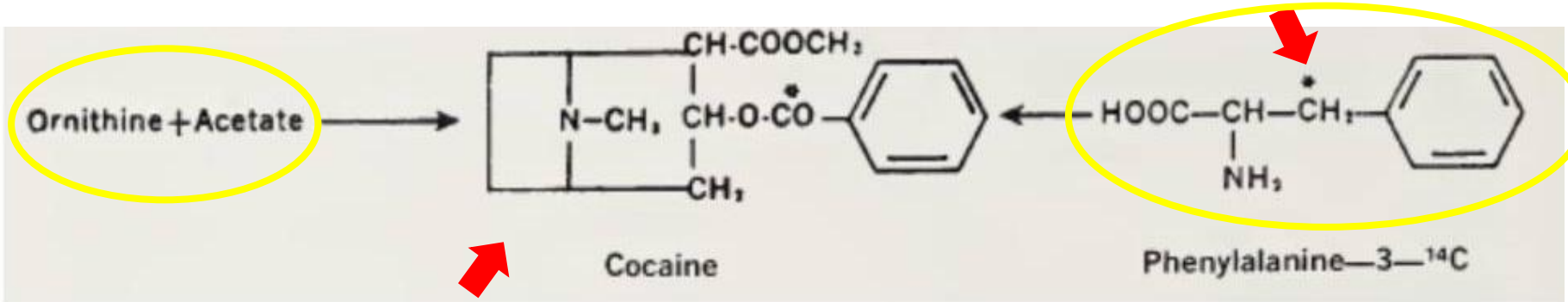
Cocaine

- Cocaine is also considered as a tropane alkaloid. It **is the methyl ester of benzoyl ecgonine**. When hydrolyzed, it splits into **ecgonine, benzoic acid, & methyl alcohol**
- Feeding experiments with ***Erythroxylum coca*** have shown that **phenylalanine** is incorporated into **cocaine** .
- Presumably the **ecgonine** moiety derives from **ornithine** and **acetate** in a manner analogues to tropine biosynthesis.
- In cocaine biosynthesis: **Ecgonine nucleus** is formed via: Pyrrolinium iminium ion, Acetate-derived enol, Mannich-type condensation. The difference from atropine is **post-Mannich modifications**, not the core reaction.



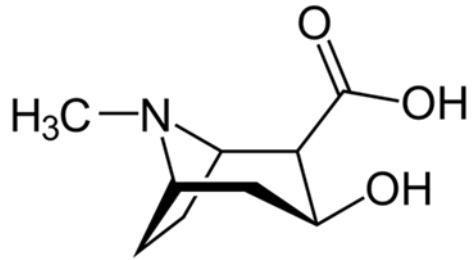
ecgonine, benzoic acid, & methyl alcohol

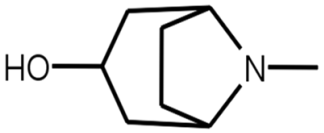
Cocaine



Ecgonine

- Cocaine is Based on **Ecgonine = tropane + carboxylic acid** which has: **Carboxyl group at C-2** . No free tropine-like alcohol
- **Two ester functions: Benzoyl ester- Methyl ester (diester)**
- Tropine → more basic, more lipophilic
- Ecgonine → **less basic, more polar**
- This is why cocaine has different pharmacokinetics and crosses membranes differently





Tropine

Comparison: Atropine -Hyoscyamine vs Cocaine

Feature	Atropine / Hyoscyamine	Cocaine
Alkaloid class	Tropane alkaloids	Tropane alkaloids
Core nucleus	Tropine nucleus	Ecgonine nucleus
Key functional group	Alcohol (–OH at C-3)	Carboxyl group (–COOH at C-2)
Type of esterification	Single ester (tropic acid)	Di-ester (benzoyl + methyl)
Polarity	Less polar	More polar
Basicity	More basic tertiary amine	Less basic (–COOH effect)
Main pharmacological action	**Antimuscarinic**	**CNS stimulant / local anesthetic**

Drugs containing tropane alkaloids

1. Belladonna (Deadly night shade leaf)

- Bella comes from the Italian Bella meaning beautiful and Dona meaning lady.
- Its juice was used in eye-drops by women to dilate the pupils of the eyes to give wider eyes.
- **Two parts of belladonna are official,** the **root and 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 are **(-)hyoscyamine, hyoscine** (scopolamine) which have **typical anticholinergic** properties that is the main mechanism for their medicinal uses as well as its toxic effect.
- Smaller amounts of other bases **are found in the root** but not in the leaves these include the **anhydride of atropine** (**apoatropine**) and its isomer **belladonine.**





Anti-muscarinic anticholinergic effects of Atropine



- Belladonna acts as a **parasympatholytic depressant** which accounts to its **anti spasmodic effect** , it has **anticholinergic effect** to **control excess motor activity of GIT and spasm of UTI.**
- **Uses**

1. **It decreases the flow of most secretions** e.g., **saliva, milk, sweat**.

2. It has a **sedative effect** on the movement of stomach & intestine, also on uterus &bladder (**anti-spasmodic**).

3. **It dilates the pupils**; **mydriatic.**

4. **Life saving in cardiac arrest** (it increases COP) in **emergency units.**

5. Antidote to the **toxicity of organophosphorus** and carbamate insecticides

- Belladonna leaf, in the form of the official **belladonna tincture** is an anti-cholinergic the usual dose of the tincture if **0.6ml tid**.







Atropine ophthalmic uses

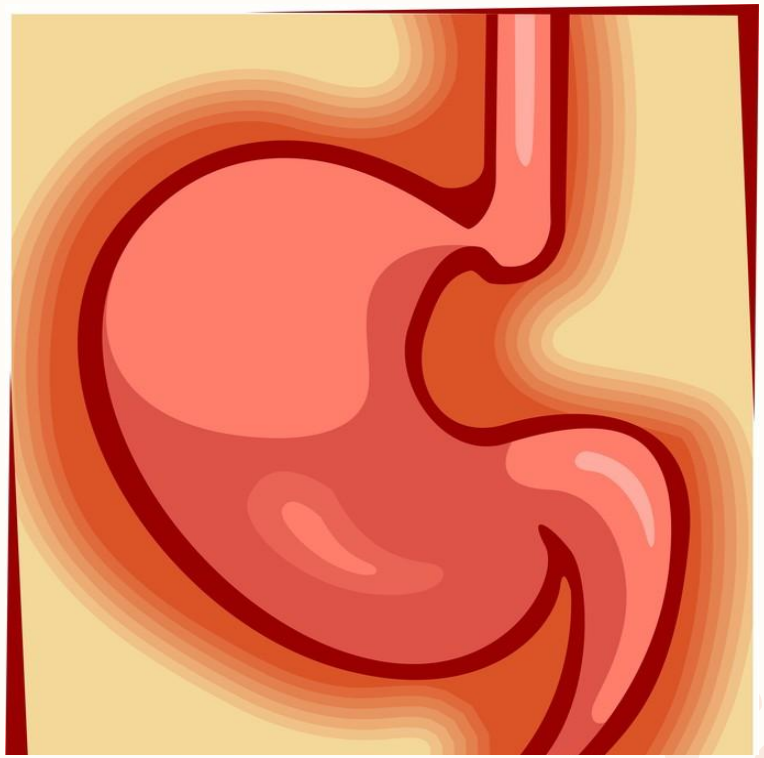
Atropine **1%** eye drops are used in **mydriasis** and **cycloplegia** (in children refraction)

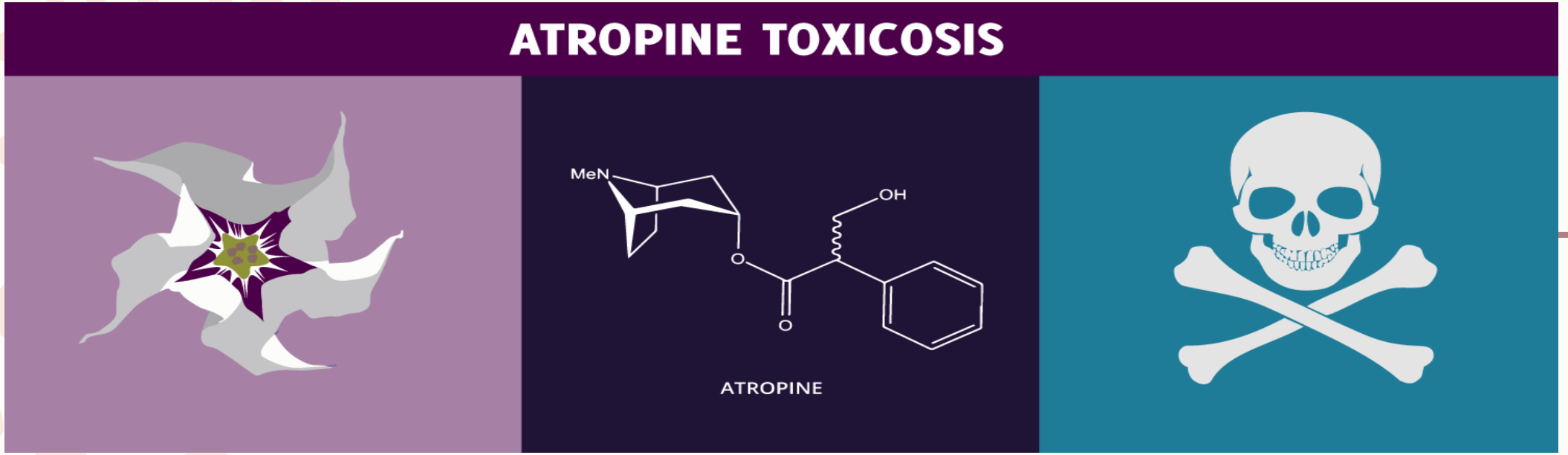
Used in **eye examination** to better visualize the retina

Medicinal use of (hyoscine) scopolamine

– Motion sickness and antispasmodic



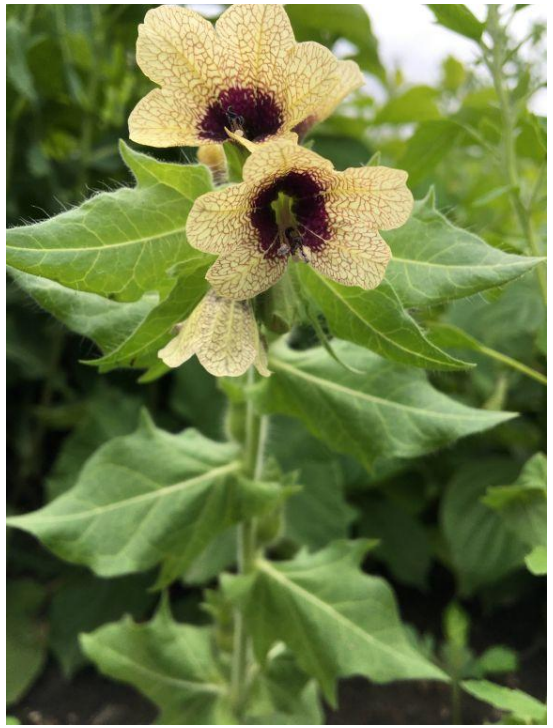




Atropine has a narrow therapeutic index where only slightly higher amounts than the medicinal dosage can be fatally toxic and can result in hospitalization and deaths

Mainly due to tachycardia and respiratory arrest

2. Hyoscyamus or Henbane



- The dried **leaves & flowering tops** of ***Hyoscyamus niger*** F: **Solanaceae.**
- **Most important commercial source of hyoscyamine**.
- It contains 0.04% of total alkaloids calculated **as hyoscyamine**, the drug also contains **hyoscine & traces of atropine**.
- **Egyptian henbane** : The dried **leaves & flowering tops** of ***Hyoscyamus muticus.***
- *Which yields 1.5 % total alkaloids consisting mainly of hyoscyamine*
- *Its indigenous and cultivated in Egypt*

3. Stramonium (jimson weed):



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

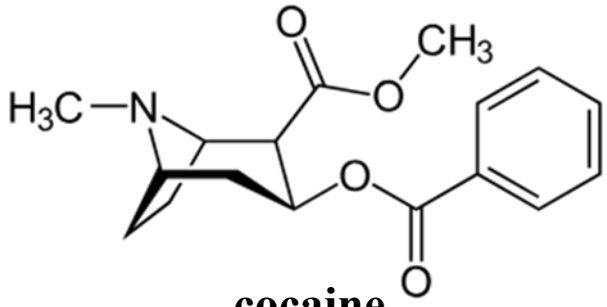
4.Cocaine:



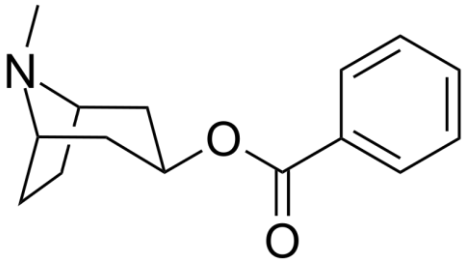


- It is a habit-forming drug from the **leaves** of ***Erythroxylum coca*** F: Erythroxylaceae.
- The plant is also called coca or coca leaves.
- **Coca leaves contain 3 basic types of alkaloids:**

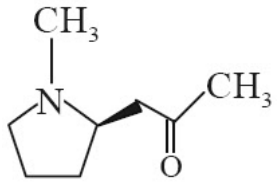
1. Derivatives of **Ecgonine** (cocaine, cinnamyl cocaine, β-truxilline)
2. Derivatives of Tropine (Tropacocaine, valerine)
3. Derivatives of Hygrine (Hygroline, Cusco-hygrine)



cocaine



Tropacocaine



Hygrine

- **Only the Ecgonine derivatives are commercially important**. The most important of these is **cocaine**.
- Because Ecgonine nucleus is the **main biosynthetic endpoint of nitrogen metabolism in coca:** Have a **rigid structure, Show high stability and strong CNS activity** •
- Tropine derivatives (valerine): **Are minor side-branch products, which are Less stable and less biologically potent**•
- **So, coca accumulates the most effective defensive alkaloid → cocaine**
- **Cocaine & cocaine hydrochloride, are agents of abuse**, are generally inhaled or sniffed & are rapidly absorbed across the pharyngeal mucosa, resulting in **CNS stimulation & euphoria.**
- **Cocaine hydrochloride is a local anesthetic**. **It is applied topically to mucous membrane as 2-5% solution**.



THANK YOU

