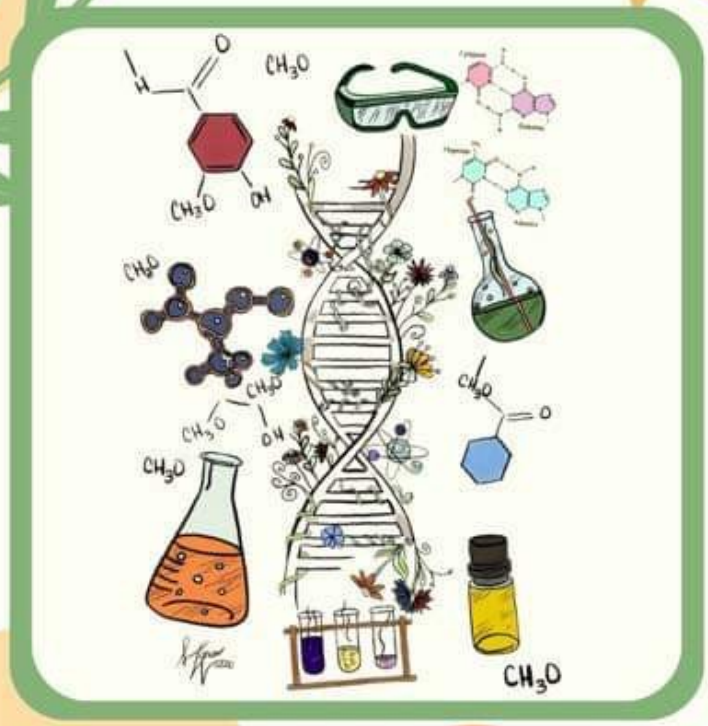
تفريغ عقاقير



اسم الموضوع: Akaloids (2)

إعداد الصيدلاني/ـة: ياسمين خليل

Seul Academy

لجان الدفعات

رَبِّ إِنِّي لِمَا أَنزَلْتَ
إِلَيَّ مِنْ خَيْرٍ فَقِيرٌ

Akaloids (2)

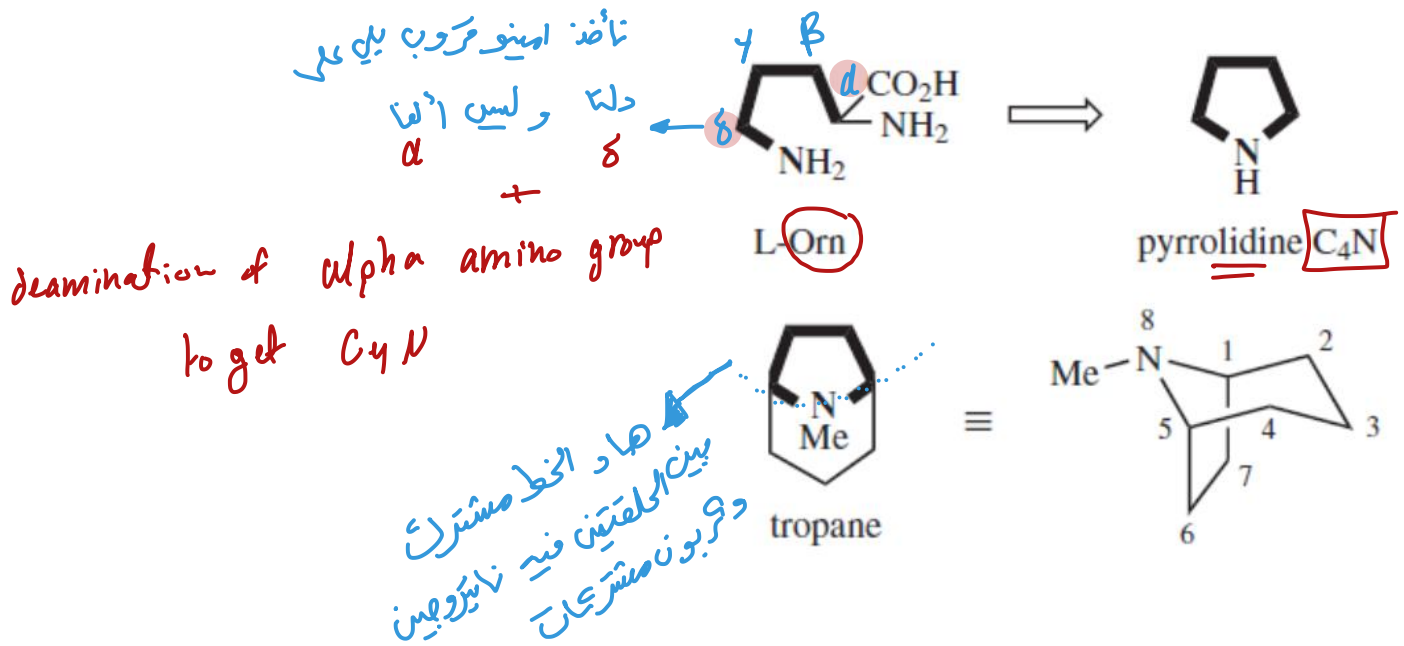
Tropane alkaloids

Dr. Rand Shahin

true / real / typical alkaloids cause N is inside the ring and it came from amino acid

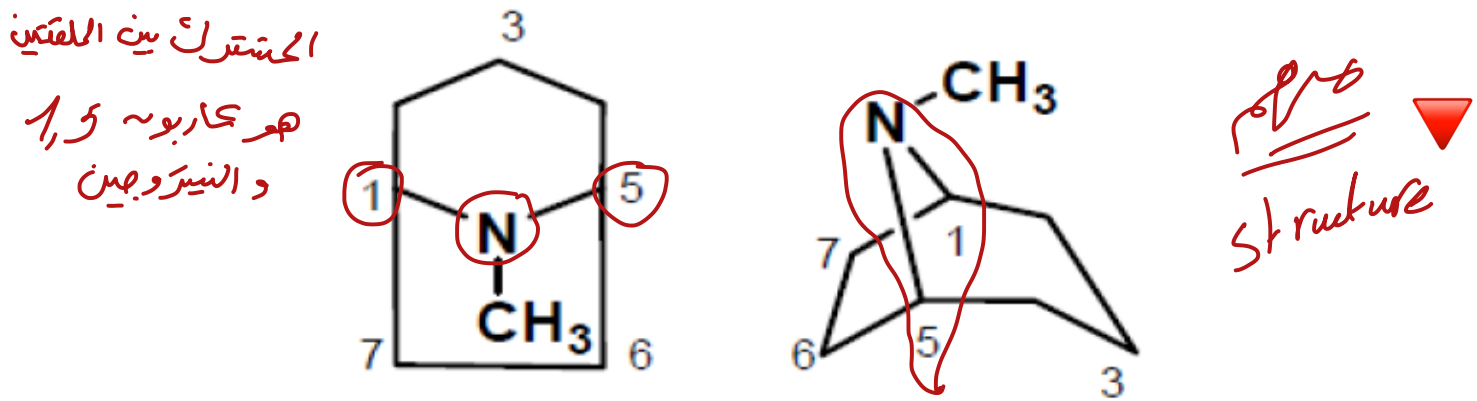
Alkaloids derived from L-Orinthine:

- Orinthine is non-protein amino acid that posses two amino groups one is alpha **(α)** the other is Delta **(δ)** provides C_4N building block to the alkaloids; found with Pyrrolizidine, Indolizidine, Nicotiana and Tropane alkaloids .



Tropane

- Tropane is a bicyclic amine that has a **pyrrolidine** and a **piperidine** ring sharing a common nitrogen atom and 2 carbon atoms. It is the common structural element of all tropane alkaloids
- Tropane is an optically inactive compound has 7 carbons ring with 1,5-nitrogen bridge.



Tropane

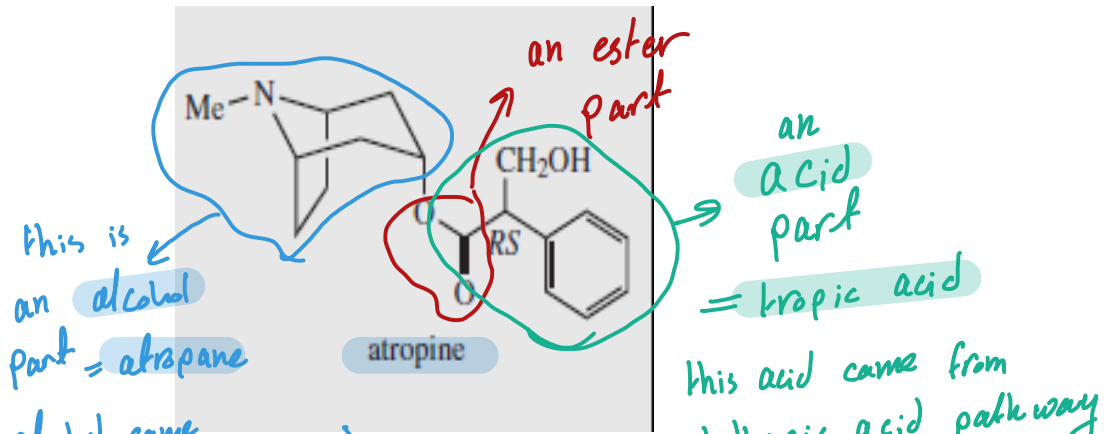
Tropane Alkaloids

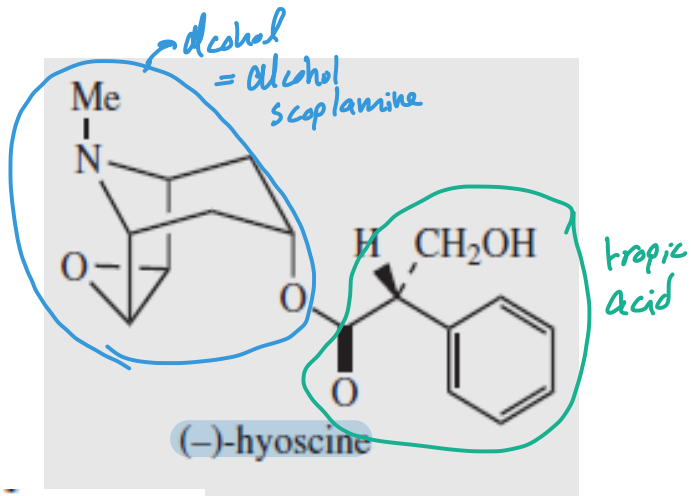
- An example on a compound from this family is **Atropine** which is a natural drug because synthesis isn't economically feasible comparing to the isolation from the nature.
- **Tropane Alkaloids are** not wildly distributed
- **Tropane alkaloids** are developed from the five-membered ring Pyrrolidine.
- **Tropane Alkaloids occurs** in Solanaceae, Erethroxylaceae (small but important family, because **cocaine** is isolated from it) and Convolvulaceae.

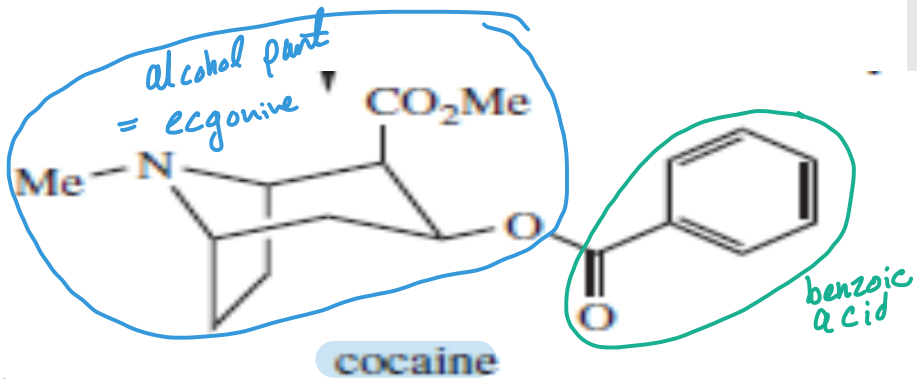
- tropane alkaloids come as esters, each have an alcohol part and acid part

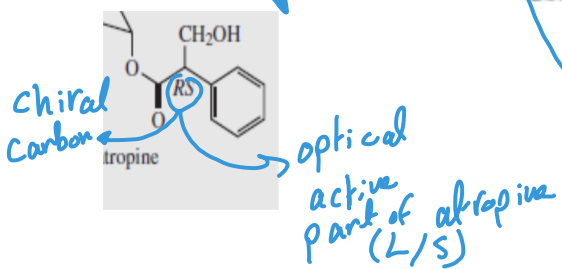
alcohol part react with acid part

يسبب نعاس ويستخدم لتقليل المخض **Scoplamine (hyoscine)**

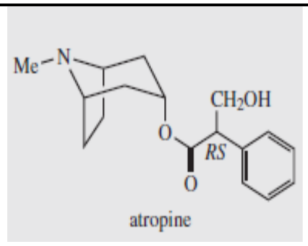
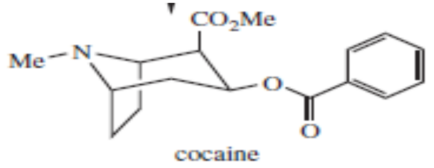
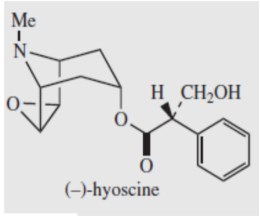








Tropane Alkaloids are :-

	Alcohol part	Acid part	the structure
Atropine	atropane	tropic acid	 atropine
Cocaine	ecgonine	benzoic acid	 cocaine
Hyosci	alcohol Scoplamine	tropic acid	 (–)-hyoscine

لَّا إِلَٰهَ إِلَّا أَنتَ سُبْحَانَكَ إِنِّي كُنتُ
مِنَ الظَّالِمِينَ

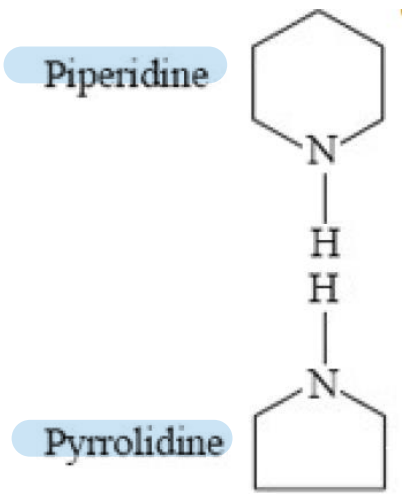
Alcohol part in atropine is tropane ring

- Tropane ring is the parent base of several alkaloids (bi-cyclic). i.e, five-membered heterocyclic ring plus six-membered heterocyclic ring (Pyrrolidine and Piperidine)

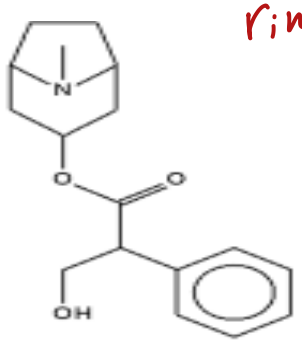
what is the alcohol part that exist in tropine alkaloid? Tropane ring

Piperidine

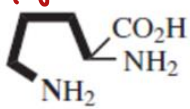
pyrrolidine



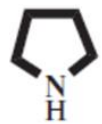
Tropane Ring



Atropine



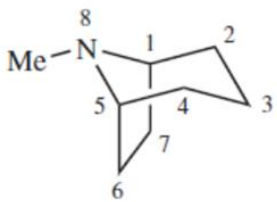
L-Orn



pyrrolidine C_4N

tropane

≡



Tropane comes as alcohol

- Two types of alcohol isomers:

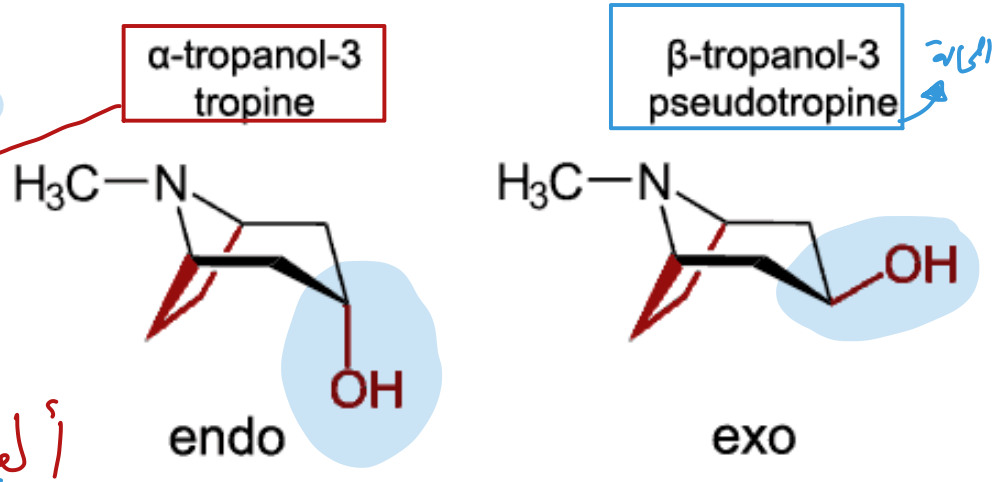
1. Tropan-3α-ol (Tropine) it's the preferred alcohol moiety from the family Solanaceae + Erethroxylaceae → Cocaine + atropine

2. Tropan-3β-ol (Psuedotropine)

إذا كانت hydroxyl group

لتحت يأتي اسم جزء الكحول هو ألفا

إذا كانت مجموعة hydroxyl على جنب فإنها بيتا بهاي الحالة

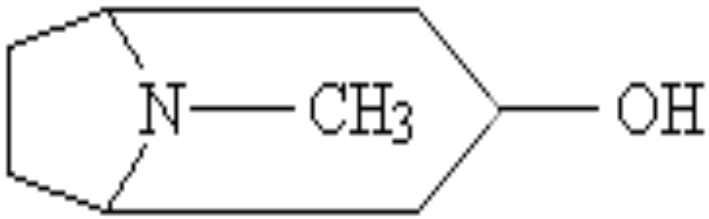


ألفا مضلة أكثر من بيتا

تحت على جنب

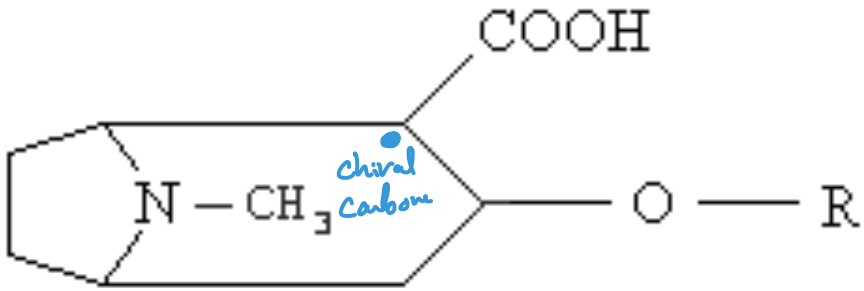
• Chiral center of cocaine is in an alcohol part but in tropine in acid part

Different alcohol parts in tropane alkaloids



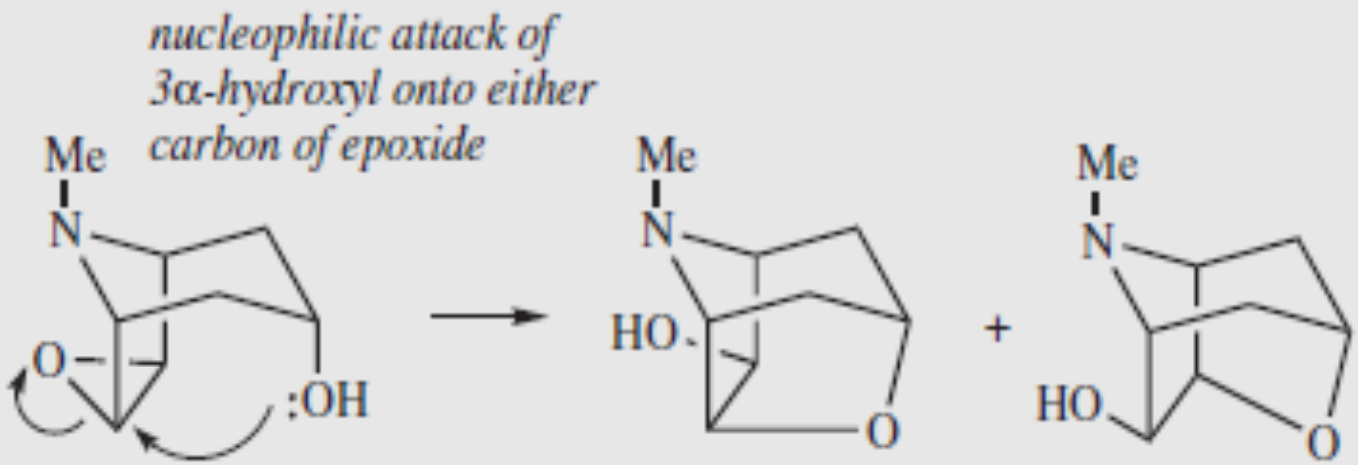
Tropine

alcohol part of tropine



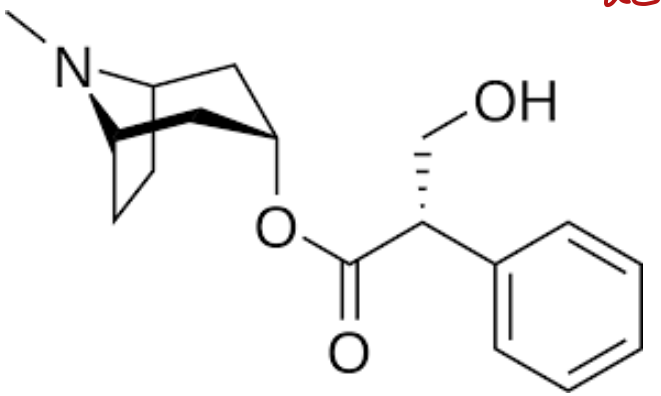
Ecgonine

alcohol part of cocaine

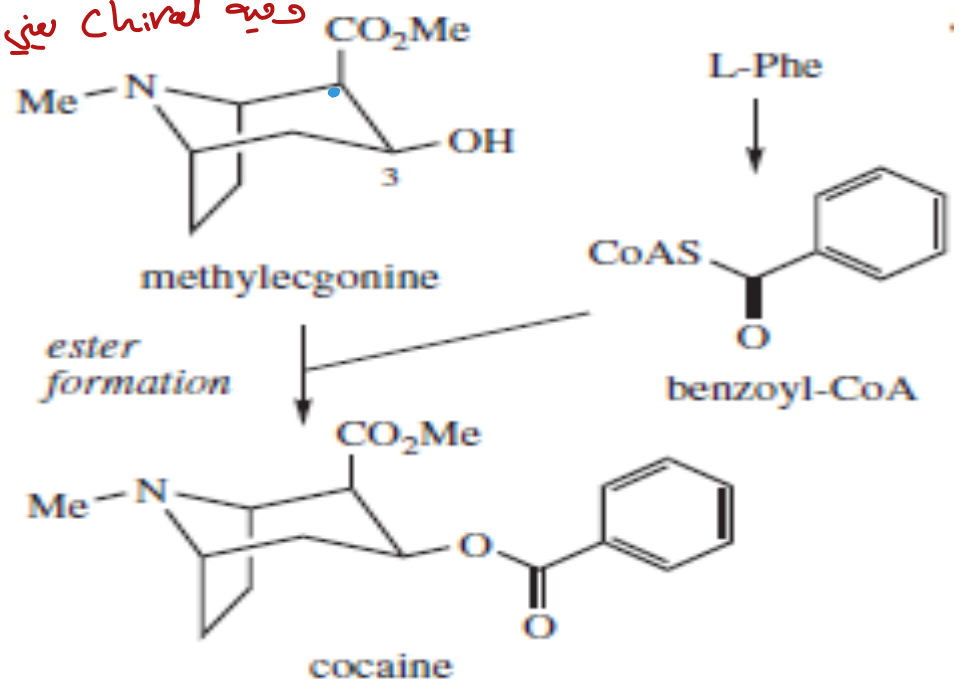


has an epoxide on C_7 + C_6

- In the case of **cocaine** : we use **ecgonine** as optically active alcohol moiety and benzoic acid that is optically inactive. Presumably the optical activity of cocaine is due to the alcohol moiety while in hyoscyamine is due to the acid moiety.



hyoscyamine



The acid part of the ester

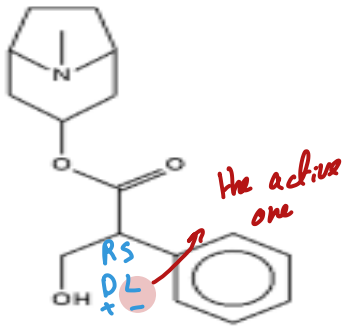
- As we have differences in the alcohol moieties, we also have different acids forming the alkaloids , several acid are used , to start with there are many aliphatic acids occurring in the plant and all of them can form their corresponding tropane esters , the most important acid that is found in all solanaceae alkaloids is '**tropic acid**', the carbon adjacent to the aromatic ring (the carboxyl group) is asymmetric carbon and is responsible for the optical rotation of tropic acid.
- Tropic acid can be dehydrated (-H_2O) to→ atropic acid. Atropic acid can be dimerized to give→ isotropic acid, so tropic acid and its derivative as well as its isomers (L-tropic, D-tropic and their racemate) are important acid moiety of the tropane alkaloids.

cause of chiral center, make the acid part of tropine active

Tropic acid [dehydration (-H_2O) → atropic acid
dimerized → iso tropic acid

Aromatic acids originating from shikimic acid pathway “SAP”

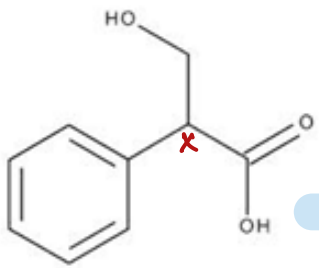
Tropane Ring →



Atropine → alcohol part is inactive but acid " " active

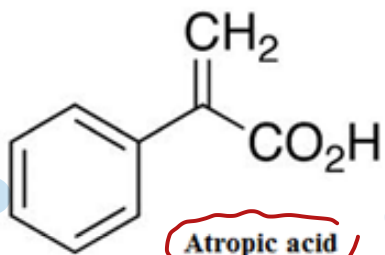
عكس طبيعي

Cocaine



Tropic acid

$-H_2O$ dehydration



Atropic acid

dimerized

Isotropic acid
(di-carboxylic acid)

Tropane alkaloids are composed of 2 parts

- Tropane alkaloids are esteric compound of atropine nucleus in alcoholic form bound to an acidic moiety (tropic acid).
- **Atropine**: → Solanaceae
- The most important compound related to this group (atropine alkaloids) is Atropine.
- Atropine comes in nature a racemic mixture the levo rotatory compound in this mixture is named as Hyoscyamine.
- Hyoscyamine is the active form of atropine.
- Unfortunately, hyoscyamine tends to racemise after isolation.
- The major use of atropine at first as antidote.

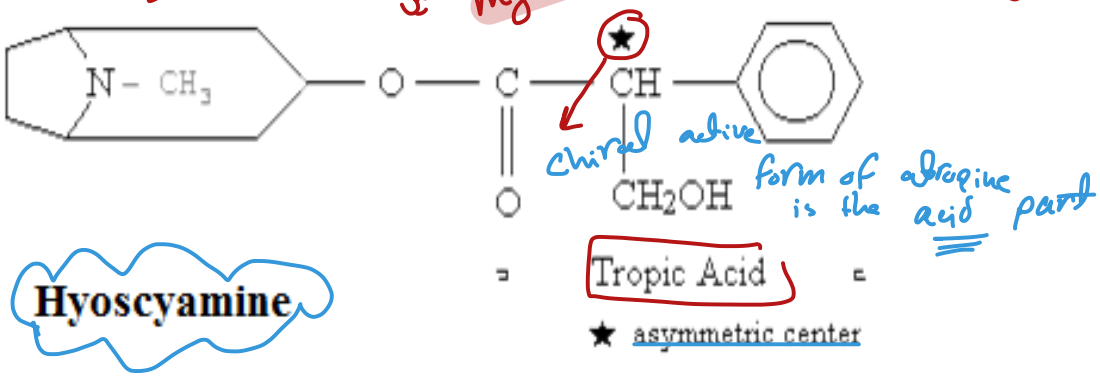
L → active form = hyoscyamine

[atropa belladona]

توسيع وتيبّس العين

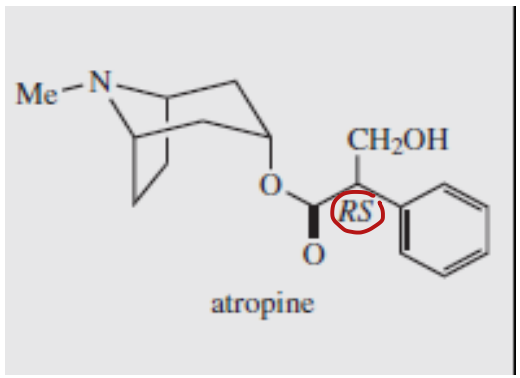
Mydriasis (1) (2)

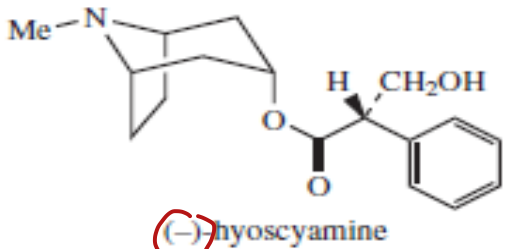
high conc of acetyl choline



chiral active form of atropine is the acid part

Hyoscyamine





levo /S

Pharmacological uses of Cholinergic **Antagonists** (Muscarinic receptor) **Atropine** as an example

Clinical effects

- **Decrease of saliva and gastric secretions**
- **Relaxation of smooth muscle**
- **Decrease in motility of GIT and urinary tract**
- **Dilation of pupils**

Uses

- **Shutting down digestion for surgery**
- **Ophthalmic examinations**
- **Relief of peptic ulcers**
- **Treatment of Parkinson's Disease**
- **Treatment of anticholinesterase poisoning**
- **Treatment of motion sickness**

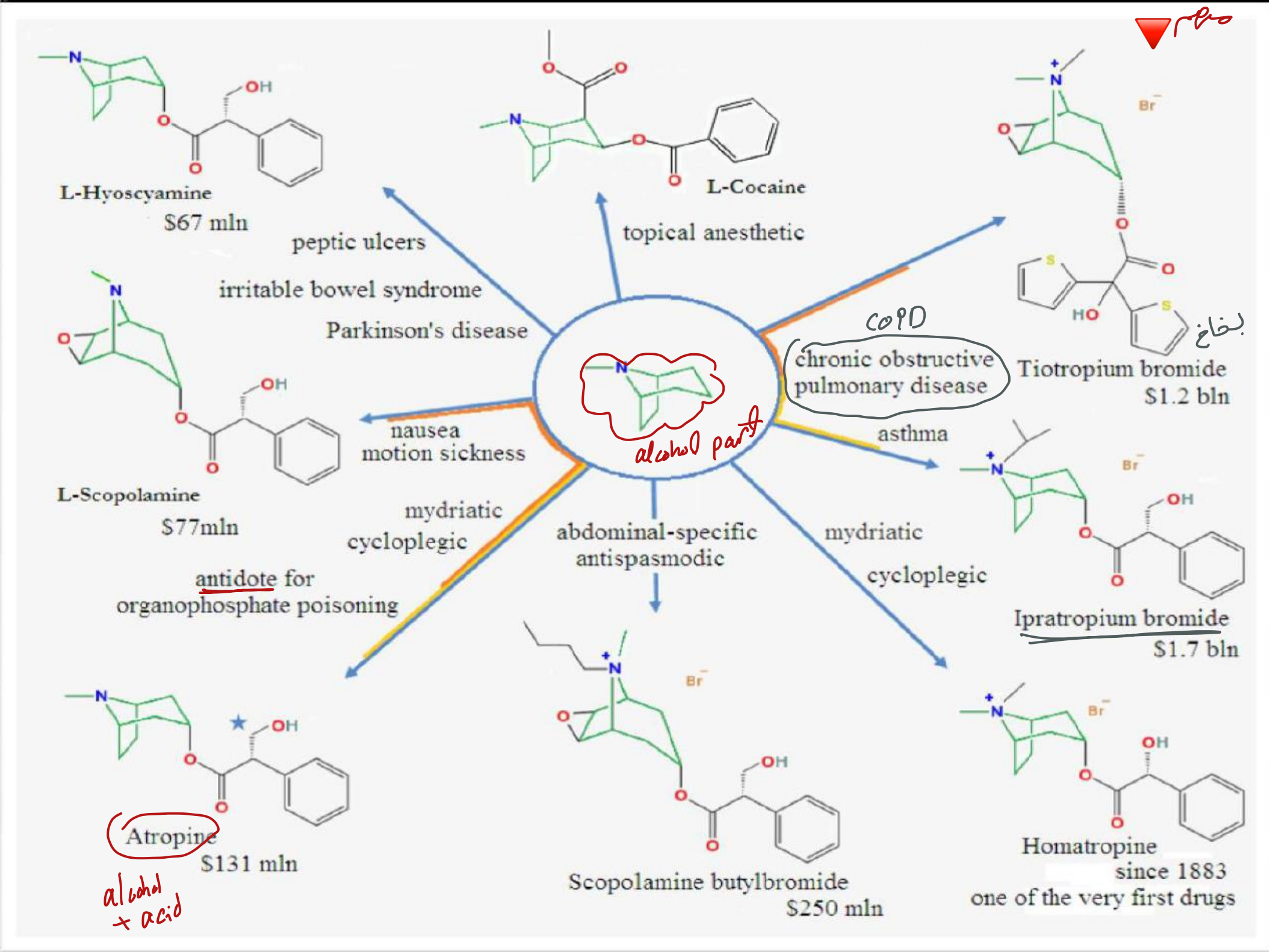
This table shows most important tropane alkaloids (major ones) found in atropa spp ,datura spp, hyoscyumus spp, duboiasia …in all solanaceae plants:

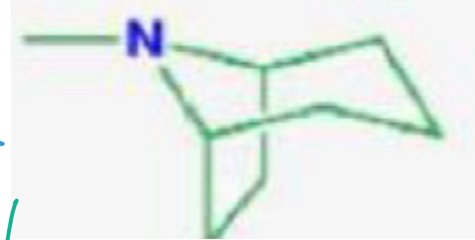
L: Levo D: Dexro

Alkaloid	Alcohol	Acid
Hyoscyamine	Tropine	L-tropic acid
Atropine	Tropine	D,L tropic acid
Scopolamine	Scopine	L tropic acid
Atroscine	Scopine	D,l tropic acid
Apoatropine	Tropine	Atropic acid
Belladonine	Tropine	Isotropic acid
Aposcopolamine	Scopine	Atropic acid
Homatropine	Tropine	Mendelic acid

same acids

same acids


L-Hyoscyamine
$67 mln
L-Cocaine
topical anesthetic
peptic ulcers
irritable bowel syndrome
Parkinson's disease
COPD
chronic obstructive pulmonary disease
Tiotropium bromide
$1.2 bln
بخاخ
L-Scopolamine
$77mln
nausea
motion sickness
alcohol part
asthma
mydriatic
cycloplegic
antidote for
organophosphate poisoning
abdominal-specific
antispasmodic
mydriatic
cycloplegic
Ipratropium bromide
$1.7 bln
Atropine
$131 mln
alcohol
+ acid
Scopolamine butylbromide
$250 mln
Homatropine
since 1883
one of the very first drugs



alcohol part

- atropine ← + acid
- as antidote

alcohol with hydroxyl + acid ←
- L-scopolamine
- for nausea

+ tropic acid (Levo)
↓
- L-hyoscyamine
- Peptic ulcers

+ ecgonine
↓
- L-Cocaine
- topical anesthetic

→ same with tropine but with propyl → Ipratropium bromide

مطلوب ت كاملهم و طلبهم / فقط —

Plants containing Tropane Alkaloids

لا إلَهَ إلّا اللَّهُ وحدَهُ لا شَريكَ لَهُ ، لَهُ الملكُ ، ولَهُ الحمدُ ، يُحْيي ويُميتُ ، وَهوَ علَى كلِّ شيءٍ قديرٌ

Stramonium leaf (Jimson weed or Thorn apple) التفاح الشوكي

- Origin: is the dried **leaves** or the dried leaves **and flowering tops** of *Datura stramonium,* Solanaceae

Poison سام

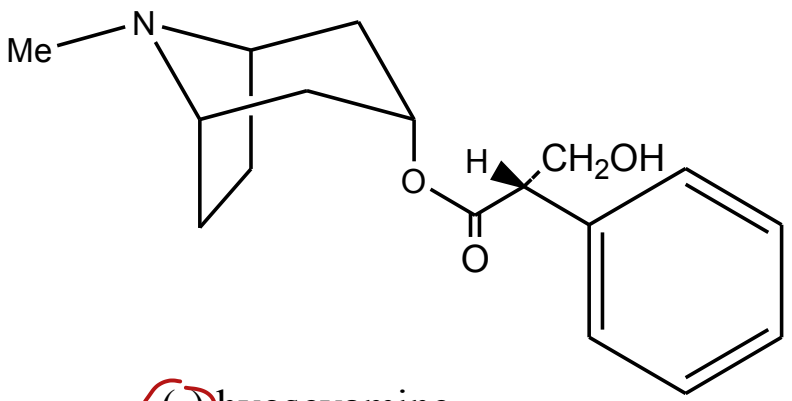
- The generic name Datura comes from the name of the *poison, dhat*, which is prepared from Indian species

Content

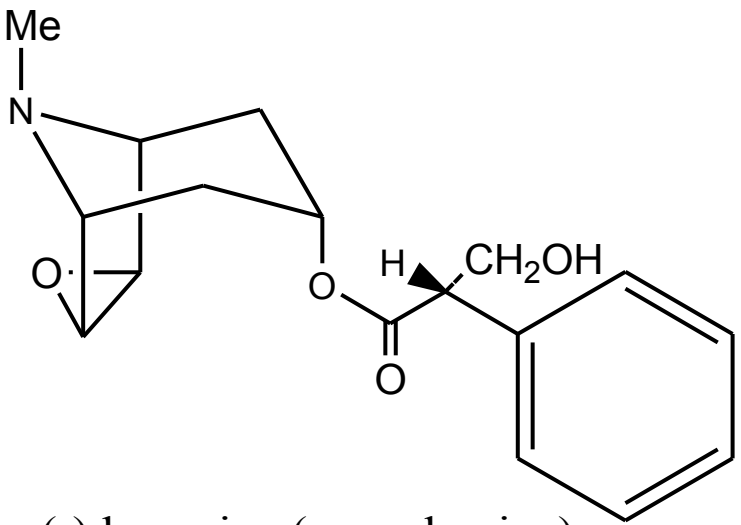
atropine
hyoscine
hyoscyamine

- The leaves contain 0.2-0.45 % of alkaloids; (-) **hyoscyamine** and **(-) hyoscine** and a little ***atropine*** may be formed from hyoscyamine by racemization

This plant has active form of tropine [hyoscyamine + hyoscine] more than atropine



(-) hyoscyamine



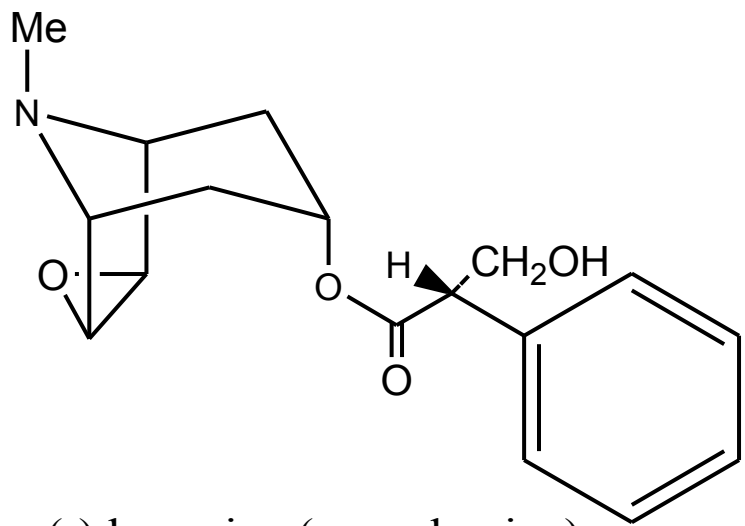
(-) hyoscine (scopolamine)

has epoxy group on C_7, C_6

 # Scoplamine (hyoscine) activity :

-different from atropine structure; it has 6,7 epoxy group on the alcohol moiety

-Hyoscine under its synonym **scopolamine** is also well known to have a CNS depressant activity, also it is used as a sedative to control motion sickness. In the past it was used to ease childbirth (combination of sedation, lack of will, and amnesia was first employed in childbirth)



(-) hyoscine (scopolamine)

Uses

- Hyoscine (scopolamine): has **a depressant action** on the central nervous system so used as a **sedative** in motion sickness via an impregnated patch worn behind the ear to avoid the dry mouth side effect of the oral administration (hyoscine hydrobromide)
- Atropine: has **stimulant action** on the central nervous system. It has useful **antidote** action in cases of poisoning caused by cholinesterase inhibitors as physostigmine.
- Hyoscine and atropine are used in ophthalmic practice to dilate the pupil of the eye
- Toxicity: considered very toxic in high concentrations causing skin flushing, raised body temperature, mouth dryness, blurred vision due to dilated pupil.

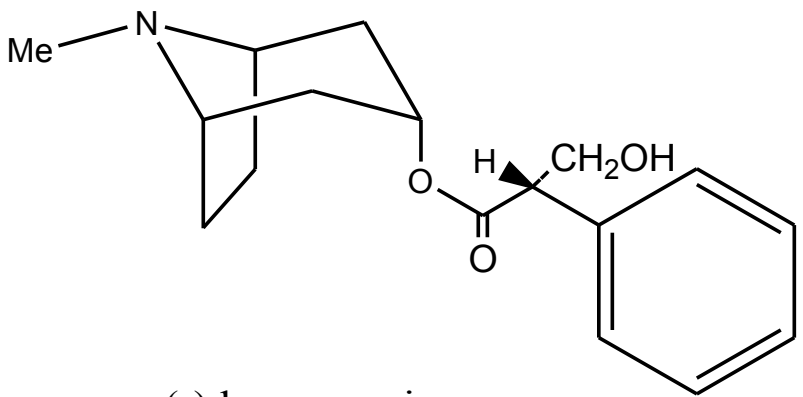
Hyoscyamus leaf (henbane)
البنج أو السكران

- Origin: is the dried **leaves and flowering tops** of *Hyoscyamus muticus*: Solanaceae
- **Indigenous to desert regions** in Egypt, Saudi Arabia

موجود في صحراء السعودية ومصر

Contents/uses

- 0.7-1.7 % alkaloids, most of which is **hyoscyamine**
- Hyoscyamine or atropine are anticholinergics so used
  - As antispasmodics
  - For the suppression of secretions
  - As antidotes for cholinesterase inhibitors poisoning



(-) hyoscyamine

Belladonna herb

نبات ست الحسن

- Origin: is the dried **leaves and flowering tops** of *Atropa belladonna*: Solanaceae
- **Cultivated in Europe and USA**
- The name belladonna come from the **mydriatic effect** of the alkaloid content where it means beautiful lady referring to the ladies who applied the juice of the fruit to the eyes giving widely dilated pupils and a striking appearance though at the expense of blurred vision
- Is called "the deadly nightshade" and in USA is called "Poison Black Cherry". The berries are particularly dangerous, but all parts of the plant contain toxic alkaloids even handling of the plant is dangerous since the alkaloids are readily absorbed through skin.

رغم أنه البشر تتسمم من هاي
الا لكالويدز بس في حيوانات مثل
الارانب إذا أكلوها يصير لها اشي عادي

All plant containing tropane alkaloids are poisonous toxic plants for human being, on the other hand, some animals are less susceptible, e.g., rabbits won't die from this plant. There are also several birds feed on these solanaceae plants but are not affected by their toxicity.

Some cases were recorded where the consumption of rabbits or birds that have ingested belladonna has led to human poisoning. Its toxicity is specific to human rather than to animals or birds.

Content/uses

belladonna has inactive form of hyoscyamine

- 0.3-0.6 % alkaloids the major of which is **(+)hyoscyamine** while the minor is (-)hyoscine (inactive)
- The mixed alkaloid extract from belladonna herb is used as **gastrointestinal sedative** and **external pain relief** as belladonna plasters.

كل النبات إلي فوه من عائلة Solanaceae يعني hyoscine وهيدي

COCA LEAVES

- Origin: the **leaves** of the small shrubs *Erythroxylum coca* (Bolivian coca) and *E. truxillense* (Peruvian coca).
- **Cultivated in Peru, Colombia, Indonesia**
- History: coca leaf *chewing* has been practiced by south American Indians for many years. The leaf is mixed with lime to liberate **the principal alkaloid cocaine** as the free base and the combination is then chewed.
- Cocaine acts as a potent **antifatigue agent** allowing the laborers to ignore hunger, fatigue and cold enhancing physical activity and endurance.

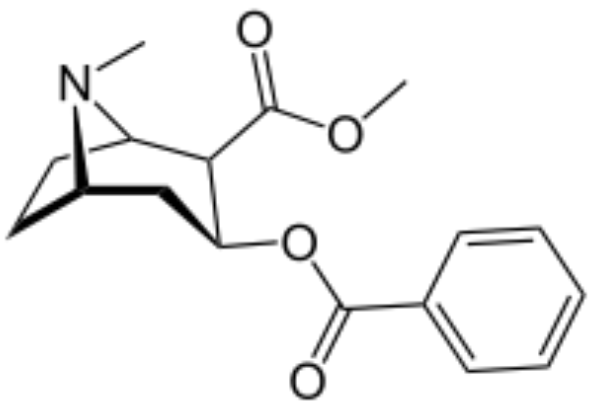
Action:

- Cocaine produces a **hyperadrenergic state**.
- Cocaine stimulate the cortex for a short time followed by depression.
- Regular usage **induces depression, addiction** and **damage to the nasal membranes**.
- Cocaine is used as a **local anesthetic** .
- Synthetic drugs developed from cocaine have been introduced to provide safer, less toxic local anesthetics. e.g., benzocaine, lidocaine.

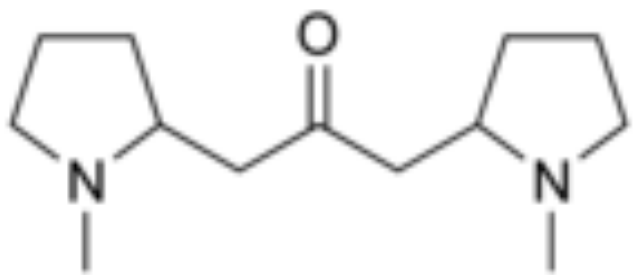
Contents

- 0.7-1.5 % total alkaloids: (40-50 %) is (-) **cocaine**, cuscohygrine (20-30 %)
- Essential oil: methylsalicylate
- Cocaine is Benzoylmethyl ecgonineester

active part



(-) cocaine



cuscohygrine

How Does Cocaine Affect the Brain?

Cocaine is a strong central nervous system stimulant that increases levels of the neurotransmitter dopamine in brain circuits regulating pleasure and movement.

Normally, dopamine is released by neurons in these circuits in response to potential rewards (like the smell of good food) and then recycled back into the cell that released it, thus shutting off the signal between neurons. Cocaine prevents the dopamine from being recycled, causing excessive amounts to build up in the synapse, or junction between neurons. This amplifies the dopamine signal and ultimately disrupts normal brain communication. It is this flood of dopamine that causes cocaine's characteristic high.

هو الشخص بضل يزيد الجرعة عشان يرجع يحس بالسعادة زي قبل
بس صار يقدر

With repeated use, cocaine can cause longterm changes in the brain's reward system as well as other brain systems, which may lead to addiction. With repeated use, tolerance to cocaine also often develops; many cocaine abusers report that they seek but fail to achieve as much pleasure as they did from their first exposure. Some users will increase their dose in an attempt to intensify and prolong their high, but this can also increase the risk of adverse psychological or physiological effects.

What Are the Other Health Effects of Cocaine?

It constricts blood vessels, dilates pupils, and increases body temperature, heart rate, and blood pressure. It can also cause headaches and gastrointestinal complications such as abdominal pain and nausea. Because cocaine tends to decrease appetite, chronic users can become malnourished as well. Most seriously, people who use cocaine can suffer heart attacks or strokes, which may cause sudden death. Cocaine-related deaths are often a result of the heart stopping (cardiac arrest) followed by an arrest of breathing

بصدمة وفاة

نستخدم petrol + alkali بعدين نستخلص البترول في aqueous acid وبعدين بنحط base عشان يصير paste

أو crack بعدين بعطي تحضيرة Carrier مع Cocaine (10-12%) وبيتم استنشاقها بعدين

Illegal production

1. The alkaloids are extracted from crushed leaves using **alkali and petrol**.
2. The petrol extract is then re-extracted with **aqueous acid**
3. This alkaloid fraction is then **basified** and allowed to stand yielding the free alkaloid as a paste (**crack**).
4. The coca alkaloids are often diluted with a carrier to give a preparation of **10-12 % of cocaine**
5. The powder is usually sniffed or *inhaled* into the nostrils where it is rapidly absorbed by the mucosa (the free base is used to increase volatility). The drug may also be injected *intravenously*.

IV

Coca Cola = Cocaine + Caffeine

- In the 1800s, coca drinks were fashionable (like a black tea), a pharmacist invented Coca-Cola he is the father of *Cocacola* , he used coca leaves and the cola seeds[coca: providing cocaine, and cola: supplying caffeine, and its red color was due to tannins ,the coca content was omitted from 1906 onwards because of physiological dependence also pharmacological studies showed that cocaine is an addictive drug, but the name and popularity continue. (now contains cola extract only).
- Some people consume cocaine and alcohol concurrently→ one of the most addictive problems in the world (increased toxicity).

Coca-Cola Bottle Evolution

حديث صحيح

سيِّدُ الاستغفارِ أن يقولَ العبدُ اللَّهُمَّ أنتَ ربِّي لا إلَهَ إلّا أنتَ خلَقتَني وأَنا عبدُكَ وأَنا على عَهْدِكَ ووعدِكَ ما استطَعتُ أعوذُ بِكَ من شرِّ ما صنعتُ أبوءُ لَكَ بنعمتِكَ عليَّ وأبوءُ بذَنبي فاغفِر لي فإنَّهُ لا يغفرُ الذُّنوبَ إلَّا أنتَ من قالَها حينَ يصبحُ موقنًا بِها فماتَ من يومه دخلَ الجنَّةَ ومن قالَها حينَ يمسي موقنًا بِها فَماتَ من ليلتِهِ دخلَ الجنَّةَ