

Introductory Aspects in Pharmacognosy

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ALKALOIDS

- **Definition:** organic compound which is:
 - I. With **limited distribution** in nature.
 - II. Present in; plant, fungi, bacteria, marine creatures.
 - III. It has **physiological** action or **poisonous** effect.
 - IV. Biosynthetic pathway **amino acid**.

HAGNAUER SYSTEM OF CLASSIFICATION:

A.True alkaloids: contain **heterocyclic nitrogen** which is derived from **amino acid** and is always **basic** in nature due to presence of lone pair of electrons on nitrogen.

B. Proto alkaloids: are simple amines in which nitrogen is **not** heterocyclic, and still derived from an amino acid.

- Example: **ephedrine, colchicine, mescaline.**

C. Pseudo alkaloids: they are not derived from amino acids, but they show **positive** test for alkaloids. (**they may contain heterocyclic nitrogen**).

- **Examples:** **purines** (**caffeine**), **steroidal** and **terpenoidal** alkaloids **conessine, solanine, protoveratrine, aconine.**

Just to know

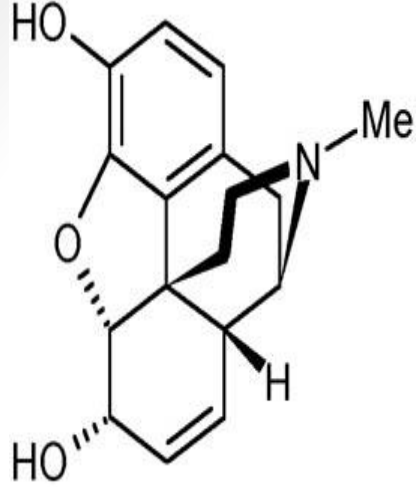
(not demanded from the students):

- ❖ Nearly, **167** alkaloids were tested, whereas, one-third (**35.9%**) is pharmaceutically significant.
- ❖ There are **5750** different structural skeletons in the total of **21,120** known alkaloids.
- ❖ It is estimated that **135,500** natural products are derived from plants, accordingly, alkaloids constitute a percentage of **15.6%**.
- ❖ Represent a vast amount of conformational rigidity to flexibility (tremendous diversity in chemical structures from linear chains, to planar, multi-ring systems).
- ❖ Usually, they are obtained with a high degree of optical purity.

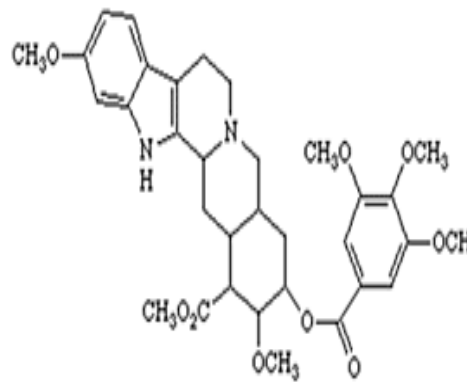
Why plants produce alkaloids

; Role in the plant

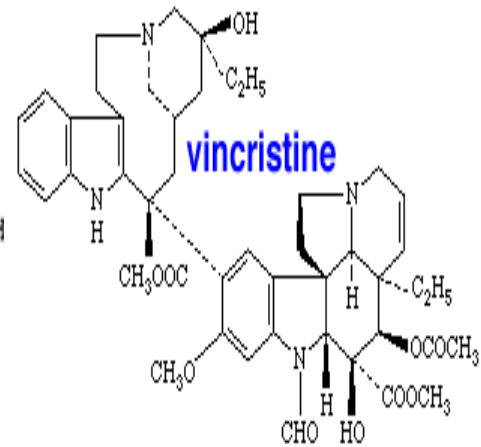
- Venting toxic substances into alkaloids that are less toxic (**detoxification of the poisonous substances produced during metabolism**).
- As a reservoir of nutrients, e.g. **storing nitrogen**.
- To secure **protection** against grazing animals due to the bitter taste and inherent toxicity (**most scientists accept this point more than the other two**).



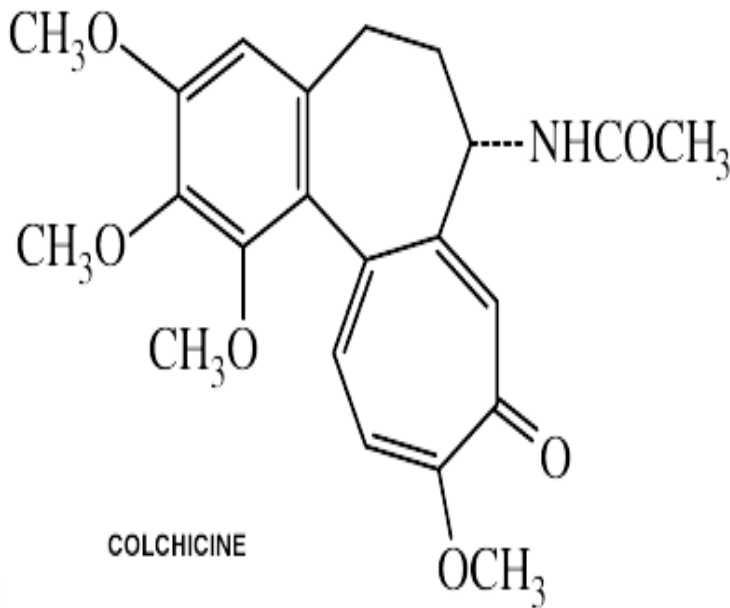
Morphine



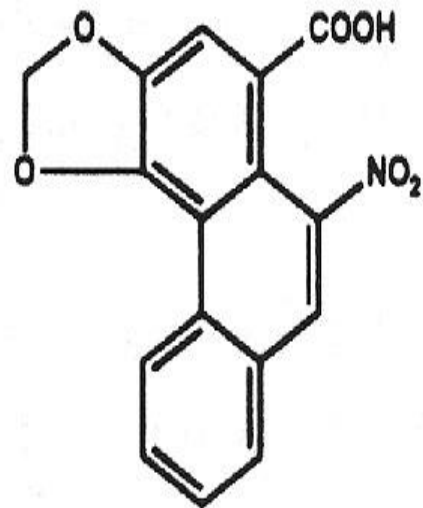
Reserpine



vincristine

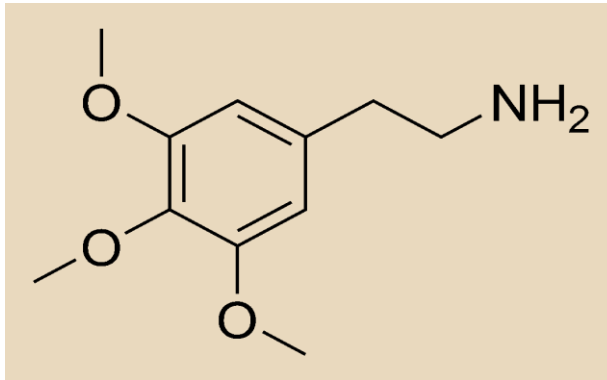


COLCHICINE

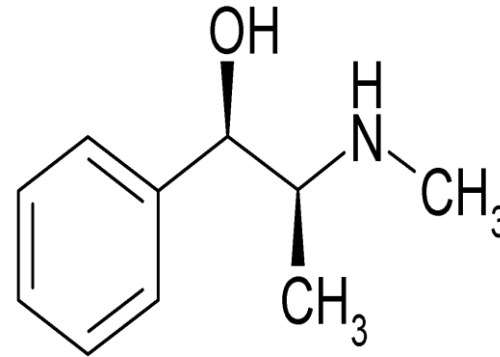


Aristolochic acid

Proto alkaloids:

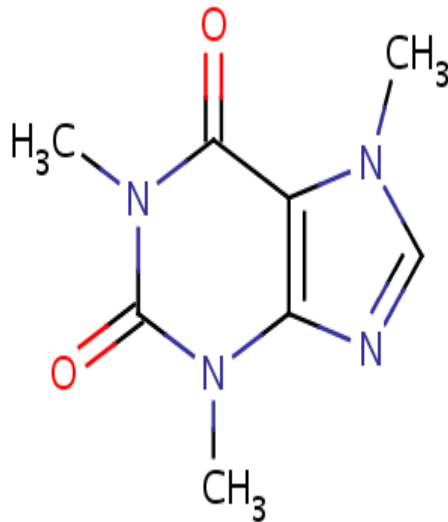


Mescaline

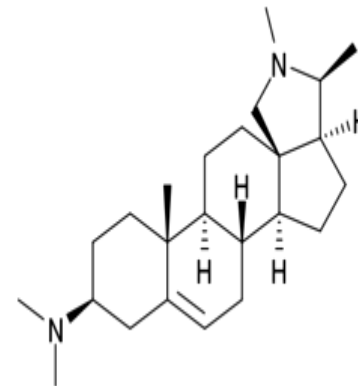


Ephedrine

Pseudo alkaloids:

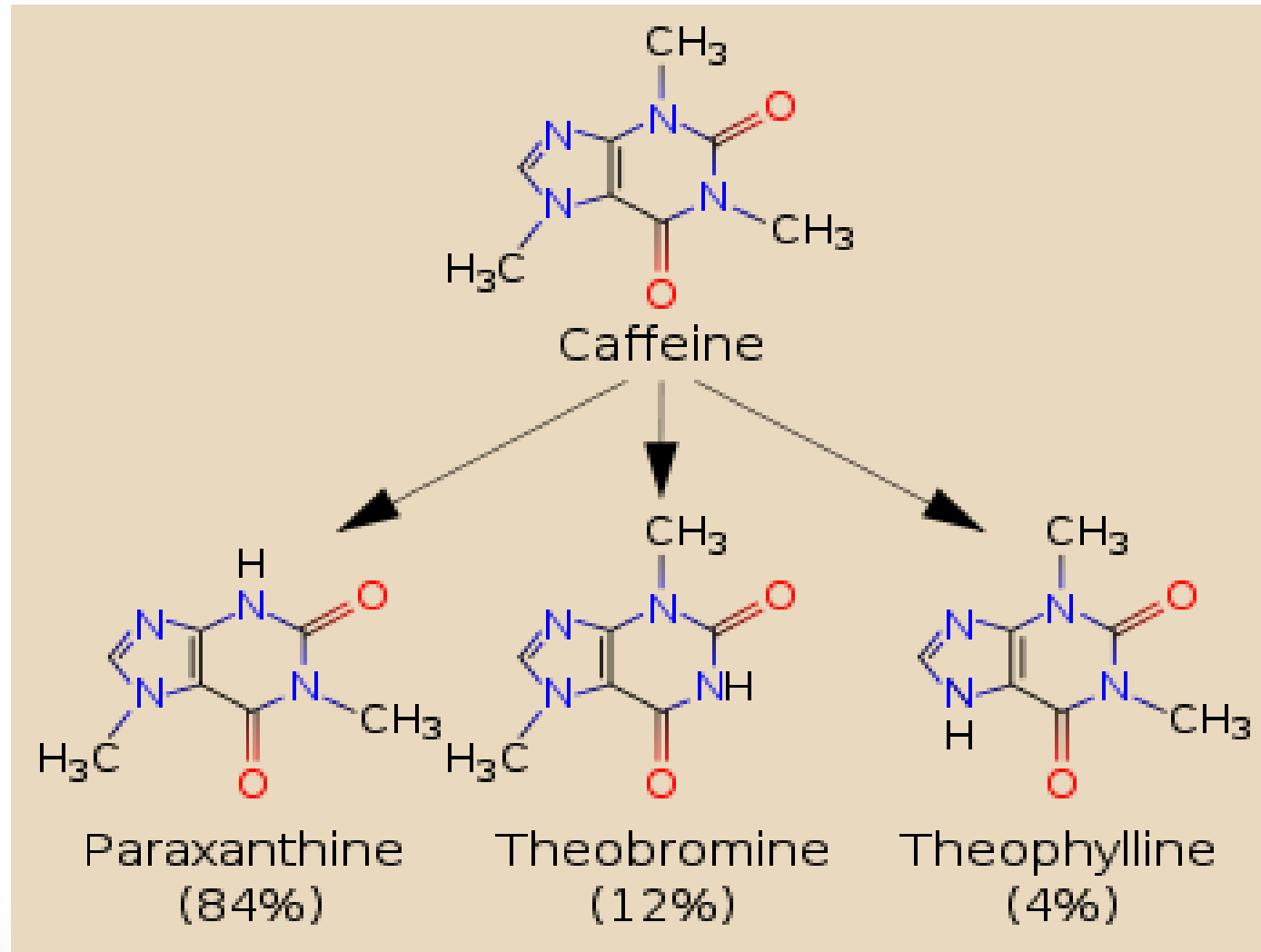


Caffeine



Conessine

Pseudo Alkaloids



Nomenclature:

• According to:

❖ **Genus;** e.g. **Atropine** {*Atropa belladonna*}

❖ **Species;** e.g. **Cocaine;** {*Erythroxylum coca*}

❖ **Physiological activity;** e.g. **Morphine** (named after the Roman god of dreams, **Morpheus**, who also became the god of slumber; nap).

❖ **Ex: Ergometrine:** works on endometrium (uterus lining) ; causes contractions of the uterus to treat heavy vaginal bleeding after childbirth, (from the ergot)

❖ **Discoverer** e.g. **pelletierine** (P. J. Pelletier, French chemist).

❖ It should generally end with the suffix: **~ine.**

❖ CHEMICAL PROPERTIES OF ALKALOIDS:

- Present in plants in different forms as: **salt, ester, N-oxide, quaternary** compound.

N-oxide alkaloids:

- ❖ More water soluble.
 - ❖ Less toxicity.
 - ❖ Less addictive.
- Generally very toxic compounds.
 - Have bitter taste.
 - A lot of them are unstable compounds in **heat, light, pH** changes.

PHYSICOCHEMICAL PROPERTIES:

- ❖ **Solid crystalline** compounds (**exception examples:** coniine and nicotine are **liquid** (they don't have **oxygen** in their structure)).
- ❖ **Colorless** compounds (**exception examples:** berberine (**yellow**), betaine (**red**)).
- ❖ **Sharp melting point** because they are **pure** compounds in crystal form.
 - Can be either 1°, 2°, 3° or 4° alkaloid: Basis of separation; separatory funnel.
 - **Basicity** depends on the availability of lone pair of electrons:
 1. Electron-donating or electron-withdrawing neighbors.
 2. Type of hybridization.
 3. Aromaticity.

❖ Detection of alkaloids:-

1. **Wagner's test:** (I_2/KI): reddish **brown** precipitate.
2. **Mayer's test:** ($HgCl_2$) Creamy precipitate with **true alkaloid**.
3. **Hagger's test:** (Picric acid) Yellow precipitate with **true alkaloid**.
4. **Dragendroff:** (Potassium Bismuth Iodide) **reddish brown** precipitate.
5. **Tannic acid solution:** different alkaloid colored **precipitate** .

EXTRACTION:

-The extraction is fractional extraction (from less polar to more polar).

Defatting by non-polar solvent (e.g. petroleum ether, benzene, alkane,....) To get rid of **chlorophyll, wax, volatile oil, fixed oil.**

-Filtration, for marc, use methanol or ethanol 95%.

-Evaporate by rotary evaporator (to concentrate)

-Add **tartaric acid** 2% and **ethyl acetate**. Separate into two layers:

- Organic layer (for weak or neutral alkaloid)

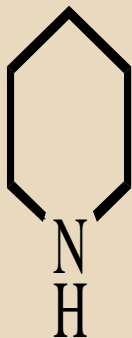
- Aqueous layer (acidic layer, tartaric acid) which has the alkaloidal salts.

- **To break the salt**, add **NH₃** or **sodium bicarbonate**, then add ethyl acetate again so will it separate into two layer again:

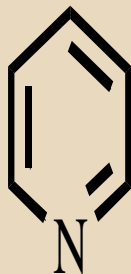
- Aqueous layer (quaternary alkaloids **4°**)

- Organic layer (for basic alkaloid **1°,2°,3°**)

Classification of Alkaloids



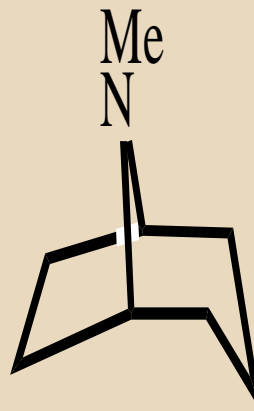
Piperidine



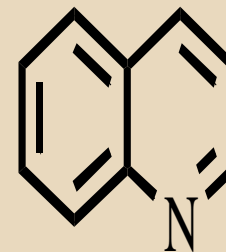
Pyridine



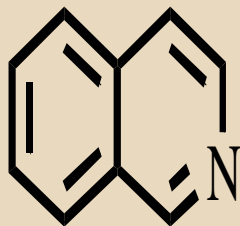
Pyrrolidine



Tropane



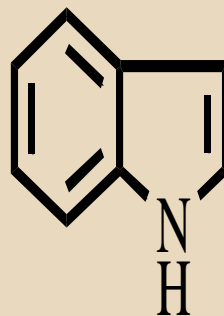
Quinoline



Isoquinoline



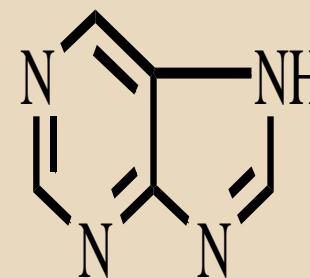
Tetrahydro-
isoquinoline



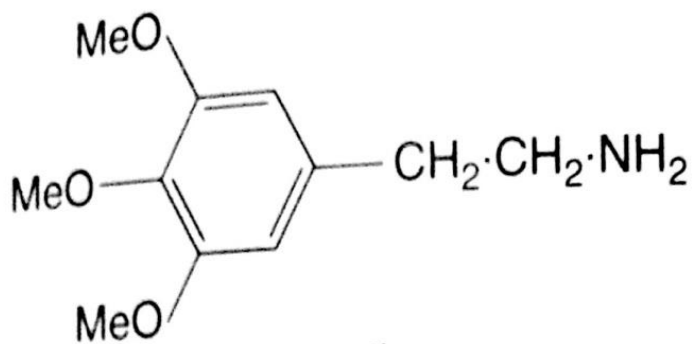
Indole



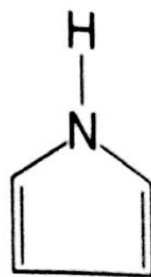
Imidazole



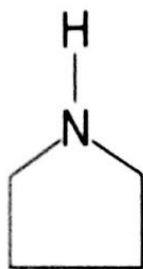
Purine



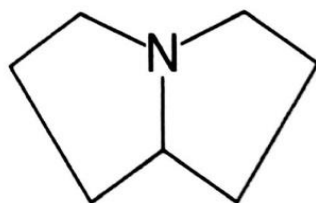
I, Mescaline



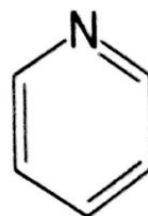
II,1 Pyrrole



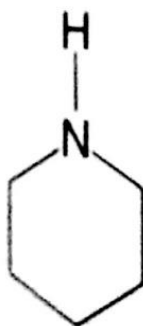
II,1 Pyrrolidine



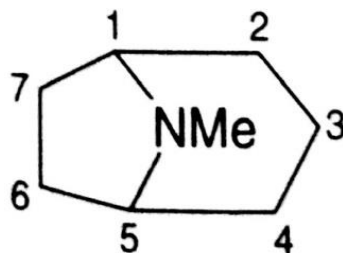
II,2 Pyrrolizidine



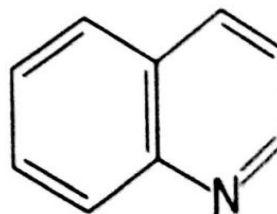
II,3 Pyridine



II,3 Piperidine



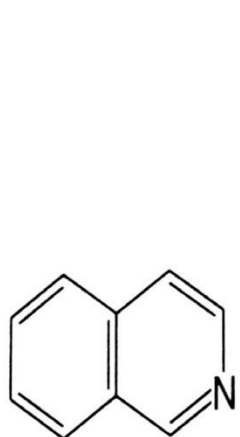
II,4 Tropane



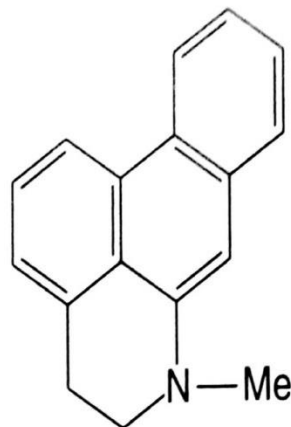
II,5 Quinoline

Skeletal structures of alkaloids found in medicinal plants.

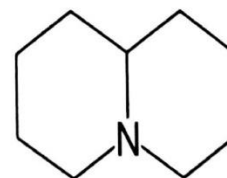
Numbers; I or II refer to the affiliation to the previously mentioned divisions.



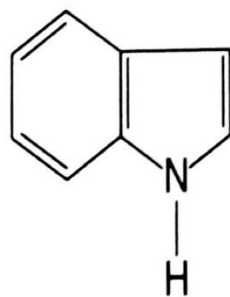
II,6 Isoquinoline



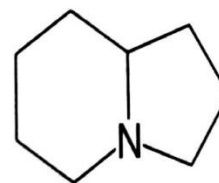
II,7 Aporphine



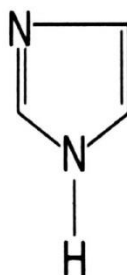
II,8 Quinolizidine



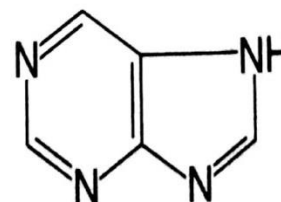
II,9 Indole



II,10 Indolizidine



II,11 Imidazole



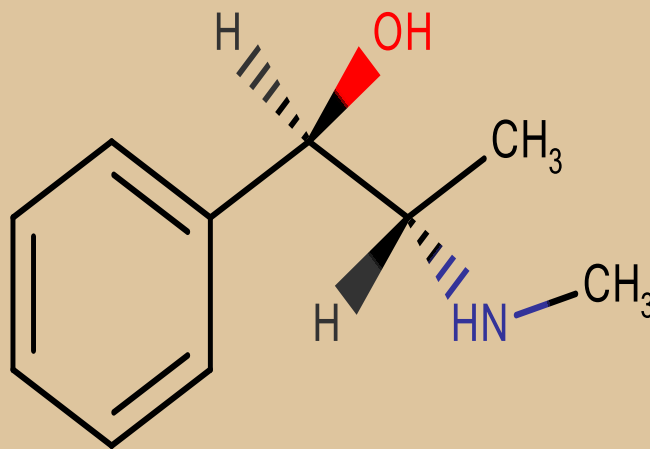
II,12 Purine

Amino Alkaloids

- The nitrogen atom of an amino alkaloid is located in an amino group and is not a member of a heterocycle, a common feature in other alkaloids.

Ephedrine:

- Is obtained from *Ephedra sinica* and related species.



- Ephedrine is a sympathomimetic, which means that its effects are similar to those which arise on the stimulation of sympathomimetic nerves.
- Ephedrine causes increased blood pressure and pulse, contraction of blood vessels, and dilation of the bronchi.
- It **stimulates** the central nervous system like **amphetamine**, but less strongly.
- Ephedrine sulphate and chloride are used as **bronchodilators** in the treatment of **asthma** and **colds**.
- ❖ **Biosynthesis:** is derived from the amino acid **phenylalanine**.

Ephedra:

- The dried aerial parts of *Ephedra sinica* (Gnetaceae)
العندة ، العليق، ذنب الخيل

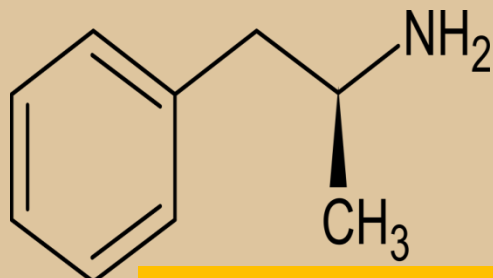


- Comes from china where it has been used for treatment of **common cold**.
- Main sources nowadays are India and Pakistan.
- Collected in autumn.
- **Pseudoephedrine** is a stereoisomer of ephedrine.

- **Pseudoephedrine** has α -adrenergic activity and used in treatment of **rhinitis** because of its ability to decrease swelling of the mucous membranes.

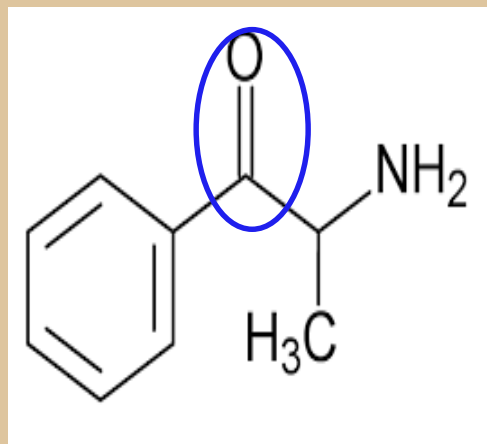
Khat:

- Is the **leaf** of *Catha edulis* (*Celastraceae*) **الفصيلة الحرايبية**
- A shrub or a small tree native to East Africa. It is cultivated in the high lands of Yemen, Ethiopia and Kenya.
- Leaves are chewed or used for preparation tea, that is drunk as a **stimulant**.
- Fresh leaves are preferred.
- Khat counteracts **fatigue**, facilitates strenuous muscular work and causes a light elation (pleasure) with talkativeness and sociability.
- Effect after chewing appears after about half an hour.
- The effects described above are due to **cathinone**. Its effect is similar to that of **amphetamine** (**Structural similarity**)



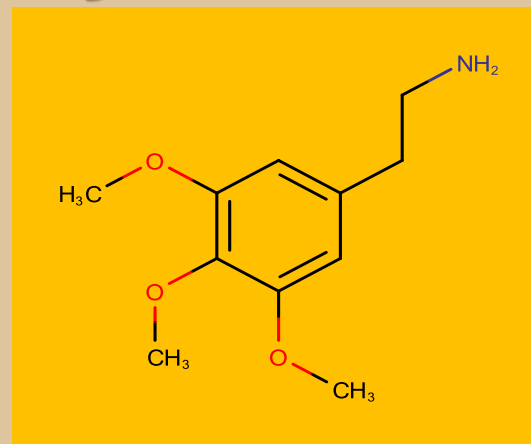
Amphetamine

Cathinone



Mescaline:

- Is a hallucinating alkaloid which is obtained from the cactus *Lophophora williamsii* (*Cactaceae*) الصباريات

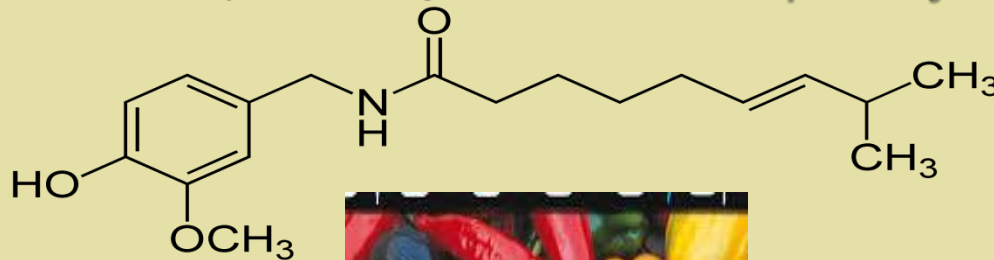


- Oral doses (100-400mg) cause euphoria, changes in the conception of time, and brilliant and colored hallucinations.
- Is used to **induce models** of **psychoses** in studying the etiology of mental diseases.

- Biosynthesized from the amino acid, **tyrosine**.

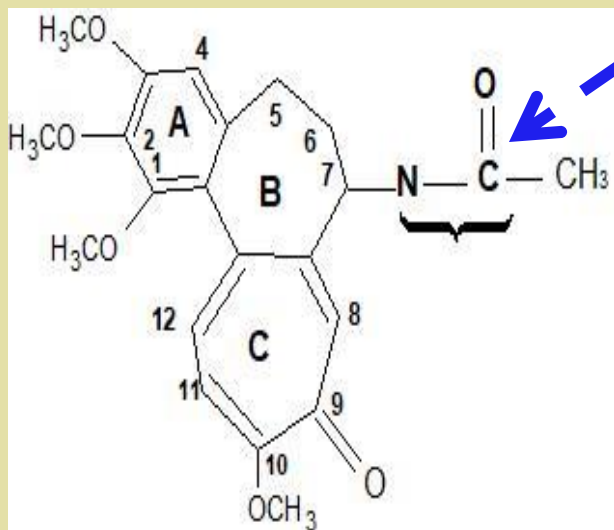
Capsaicin:

- Is a pungent substance occurring in the fruits of certain *Capsicum* species (*Solanaceae*) which causes irritation of the skin (**rubefacient= redness-causing; increase circulation**).
- Biosynthetically, it originates from phenylalanine.

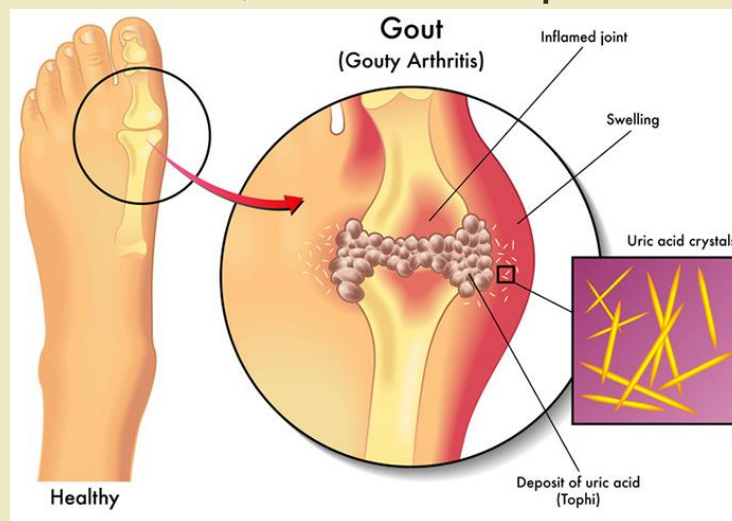


Colchicine {Tropolone Alkaloids}:

- Is an alkaloid that can be obtained from the autumn crocus (the meadow suffron), *Colchicum autumnale* لعلح , or *Gloriosa superba* = flame Lilly (both from the family *Colchicaceae*).
- The molecule consists of an aromatic group (A) with three methoxyl groups , a 7-membered ring (B) carrying an acetylated amino group, and a tropolone ring (C) whose hydroxyl group is methylated.
- As the nitrogen atom is part of an amide functional group, colchicine is non-basic.



- In medicine, colchicine is used as a remedy against **gout**, a disease caused by the disposition of **uric acid** in the joints.
- It is highly poisonous, and the treatment must be carefully supervised.
- It inhibits division of animal cell, but it is too poisonous to be used to arrest tumor growth.



Biosynthesis:

- **Ring A** is derived from **phenylalanine**, which also contributes carbon atoms 5, 6 and 7 of ring B.
- The **tropolone** is derived from **tyrosine** by ring expansion involving β -carbon atom of tyrosine which becomes C-12 of the tropolone ring.
- The **nitrogen atom** in colchicine is also derived from **tyrosine**.
- The **methoxyl substituents** come from **methionine**.

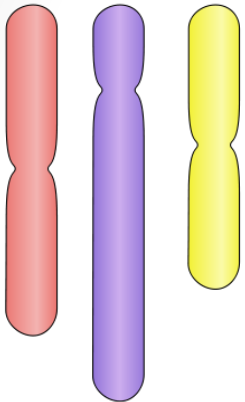
- The **tuber** has been used in the folkloric medicine for suppression of gout.
- The alkaloid is used orally for treatment of gout.
- **Colchicine** induces **POLYPLOIDY** {{ **Polypl**oid cells and organisms are those containing more than two paired (homologous) sets of chromosomes. Most species whose cells have nuclei (Eukaryotes) are diploid, meaning they have two sets of chromosomes—one set inherited from each parent}}
- (**so used:** to multiply the number of chromosomes in other plants to obtain larger flowers, pollen grains and stomata and also to increase the amount of alkaloids).
- Used for familial Mediterranean fever.

Crude drug:

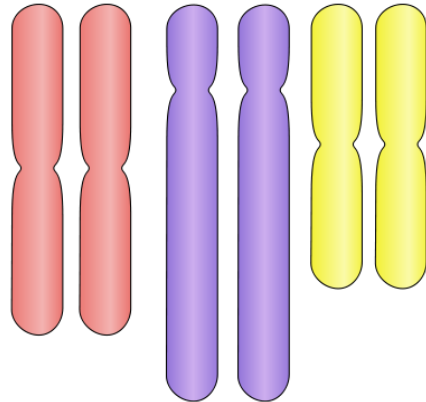
- **Colchicum seed** from the autumn crocus which has an unusual flowering period that gives it its name; in August and September.
- It is a European plant, and seeds are produced in Poland, Yugoslavia and Netherlands.

Polyploidy

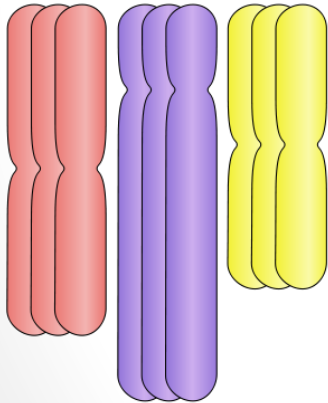
Haploid (N)



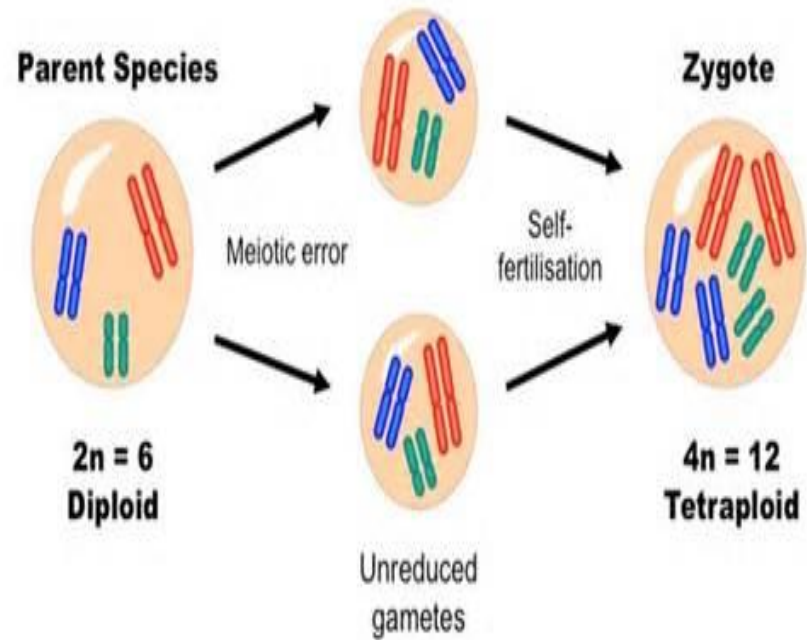
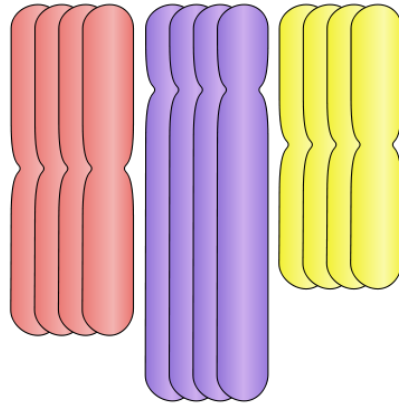
Diploid (2N)



Triploid (3N)



Tetraploid (4N)



Aziridine alkaloids

- Aziridines are the nitrogenous analogues of epoxides.
- The aziridine group is a 3-membered heterocyclic with one amine group and two methylene groups.
- The simplest compound is aziridine, which is present in many natural products with **anticancer** and **antibacterial**.



Mitomycin C:

- Mitomycin C is produced by *Streptomyces lavendulae* {a species of **bacteria** from the genus *Streptomyces*. It is isolated from soils globally and is known for its production of medically useful biologically active metabolites}.
- It is a highly toxic antibiotic with antineoplastic properties which is used for treatment of **solid tumors** of the bladder, breast, cervix, eye, stomach, and prostate.
- It is a **prodrug** that requires activation by enzymes such as **[1] DT-diaphorase** which is an enzyme that targets novel anti-cancer drugs and **reduces** them for sake of activation, or by the enzyme **[2] NADH cytochrome c reductase.**

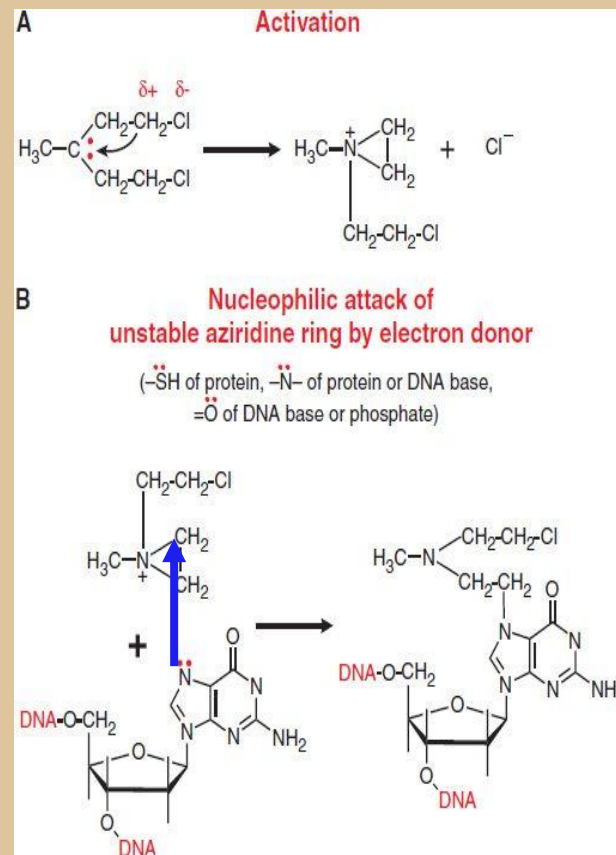
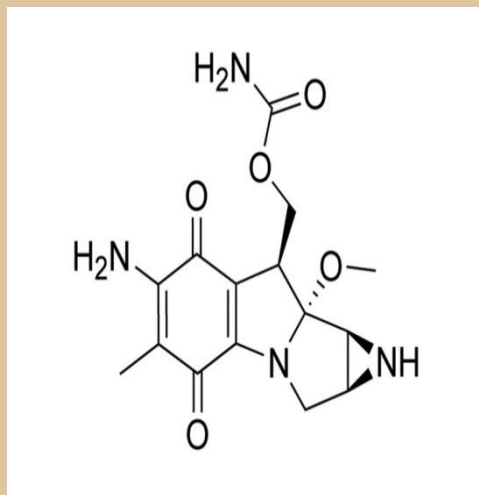
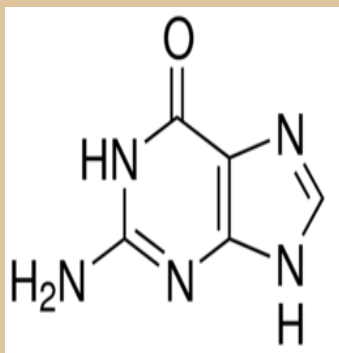
Aziridine alkaloids

- The mechanism of action** involves interaction of the aziridine ring with guanine in DNA causing intra- and inter-strand DNA cross-linking, leading to selective inhibition of DNA synthesis, mutagenesis, induction of DNA repair and induction of apoptosis {**programmed cell death**}.

See the next slide

Guanine

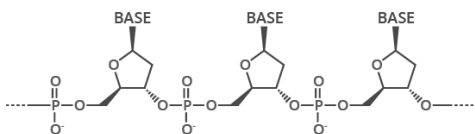
Mitomycin c



DNA structure

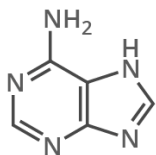
THE CHEMICAL STRUCTURE OF DNA

THE SUGAR PHOSPHATE 'BACKBONE'

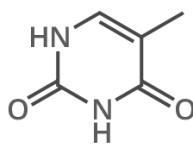


DNA is a polymer made up of units called nucleotides. The nucleotides are made of three different components: a sugar group, a phosphate group, and a base. There are four different bases: adenine, thymine, guanine and cytosine.

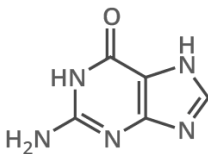
A ADENINE



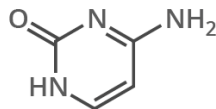
T THYMINE



G GUANINE

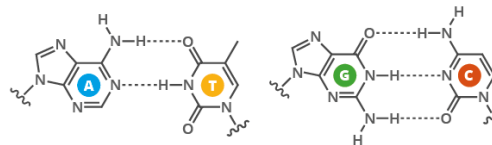


C CYTOSINE



WHAT HOLDS DNA STRANDS TOGETHER?

DNA strands are held together by hydrogen bonds between bases on adjacent strands. Adenine (A) always pairs with thymine (T), while guanine (G) always pairs with cytosine (C). Adenine pairs with uracil (U) in RNA.



FROM DNA TO PROTEINS

The bases on a single strand of DNA act as a code. The letters form three letter codons, which code for amino acids - the building blocks of proteins.



An enzyme, RNA polymerase, transcribes DNA into mRNA (messenger ribonucleic acid). It splits apart the two strands that form the double helix, then reads a strand and copies the sequence of nucleotides. The only difference between the RNA and the original DNA is that in the place of thymine (T), another base with a similar structure is used: uracil (U).



In multicellular organisms, the mRNA carries genetic code out of the cell nucleus, to the cytoplasm. Here, protein synthesis takes place. 'Translation' is the process of turning the mRNA's 'code' into proteins. Molecules called ribosomes carry out this process, building up proteins from the amino acids coded for.



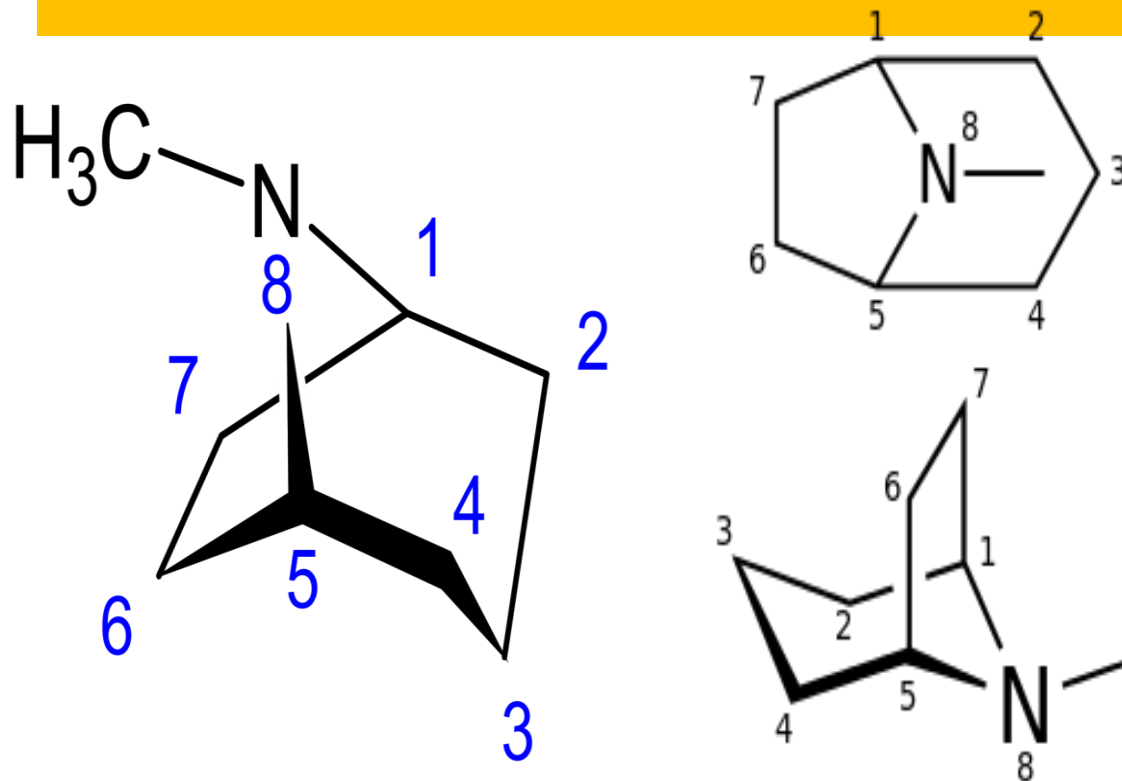
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Aziridine alkaloids

- The compound is unique as an anti-cancer drug in that the activation preferentially occurs in the hypoxic regions of **solid tumors**.
- The main **adverse effects** are:
 1. **Delayed cumulative bone marrow suppression**, and doses have to be adjusted according to the effect on the bone marrow.
 2. **Renal damage.**
 3. **Pulmonary toxicity.**

Tropane Alkaloids



Solanaceous Tropane Alkaloids

Occurrence:

They are mainly found in **Solanaceae** family, but also in **Erythroxylaceae** ----- **كوكيات**

Main Alkaloids are:

1- Atropine.

2- Hyoscyamine.

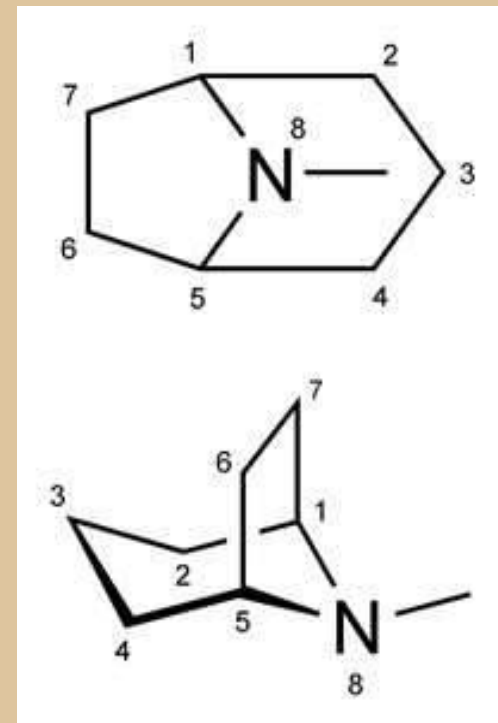
3. Hyoscine (Scopolamine).

Found in the **leaves** of:

a. *Atropa belladonna*.

b. *Datura stramonium*.

c. *Hyoscymus* spp. like:



Hyoscyamus niger (البنج الأسود, henbane, black henbane or stinking nightshade) and *Hyoscyamus muticus* (البنج المصري) which is indigenous to Egypt (*Solanaceae*).



H. niger



H. muticus



Datura stramonium

- These plants are toxic and their berries of belladonna are lethal.
- They are esters of tropic acid and alcoholic base tropanol which have either α - or β - configuration.

d. Mandrake

Mandragora officinarum & *Mandragora autumnalis*

تفاح المجانين - بيض المجانين - تفاحة الشيطان

- ❖ *M. officinarum* (Solanaceae) is limited to small areas of northern Italy and the coast of former Yugoslavia.
- ❖ *M. autumnalis*, the autumn mandrake is native to the Mediterranean countries, like Palestine, Jordan, Tunisia, Turkey, Lebanon, Syria, Morocco, ... etc.





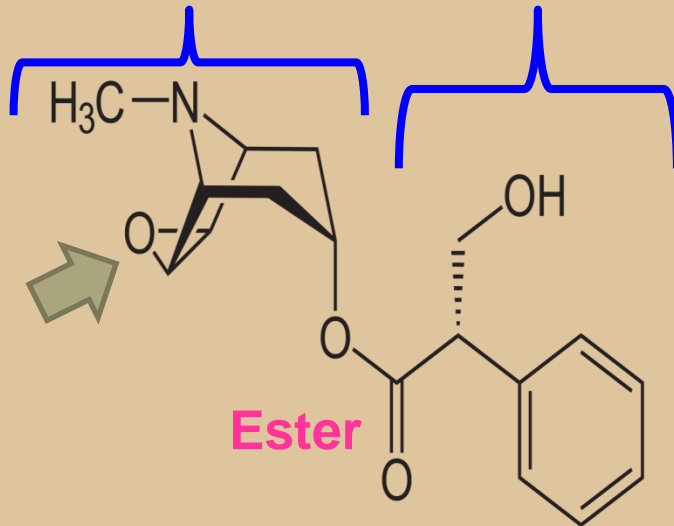
Mandrake and witchcraft



Hyoscine (Scopolamine)

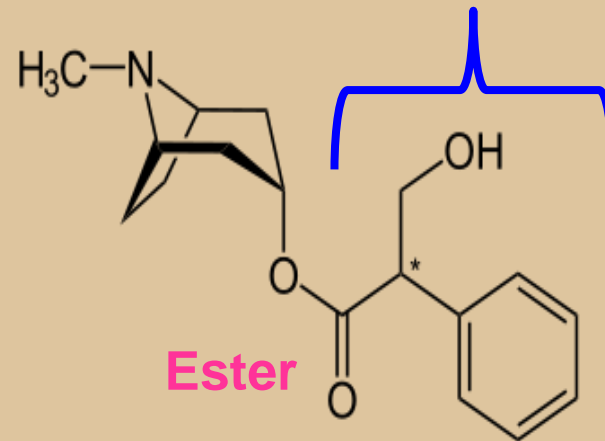
- Hyoscine is an ester of (-)-tropic acid with scopoline base (A tropanol with an oxygen).
- Hyoscine is a syrupy liquid.

Scopoline



(-)-Scopolamine =
(-)-Hyoscine

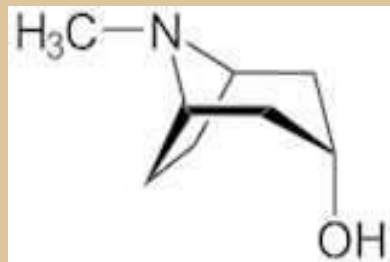
Tropic acid



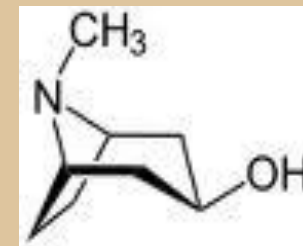
Hyoscyamine

- Atropine does **not** exist in nature but is obtained upon the extraction of hyoscyamine to levo and dextro racemers which, both, give atropine.
- Atropine, thus, is a mixture of (+) and (-)-hyscyamaine. **α -tropanol (tropane-3 α -ol)** gives **atropine**, while **β -tropanol** gives pseudoatropine.
- D and L: polarizes the light domain to the right and left, respectively. So, atropine is optically is **inactive**.

α -tropanol



β -tropanol



- Tropane can be considered a combination of piperidine and pyrrolidine (**Pyrrolidine** is derived from pyrrolinium cation which is formed from ornithine in the same way as in the biosynthetic pathway of nicotine).

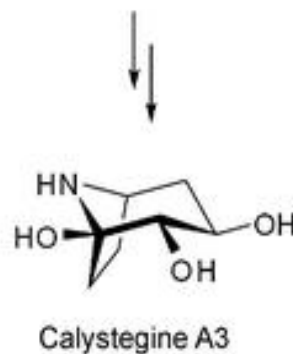
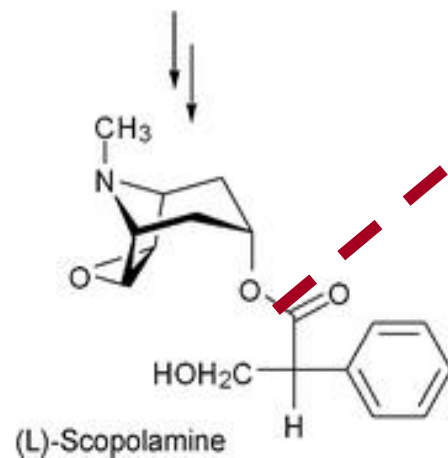
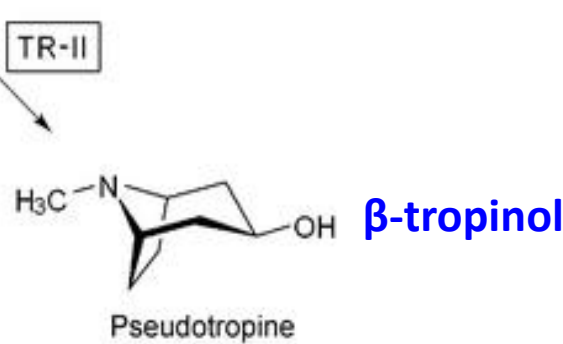
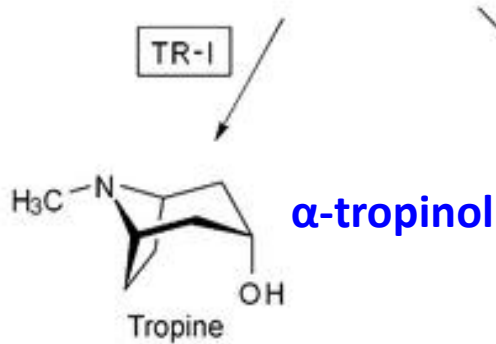
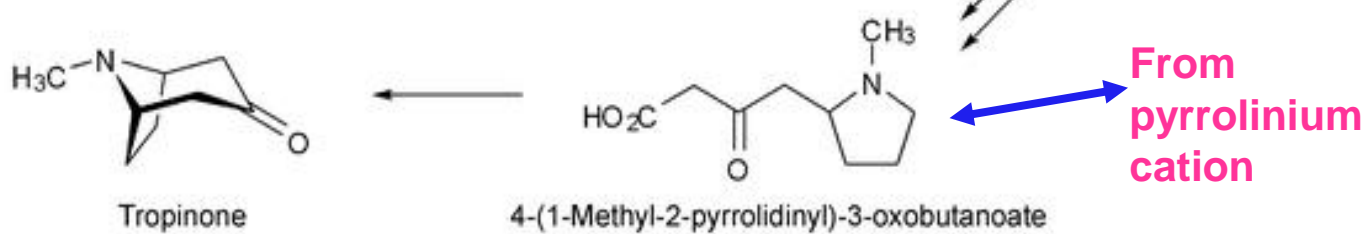
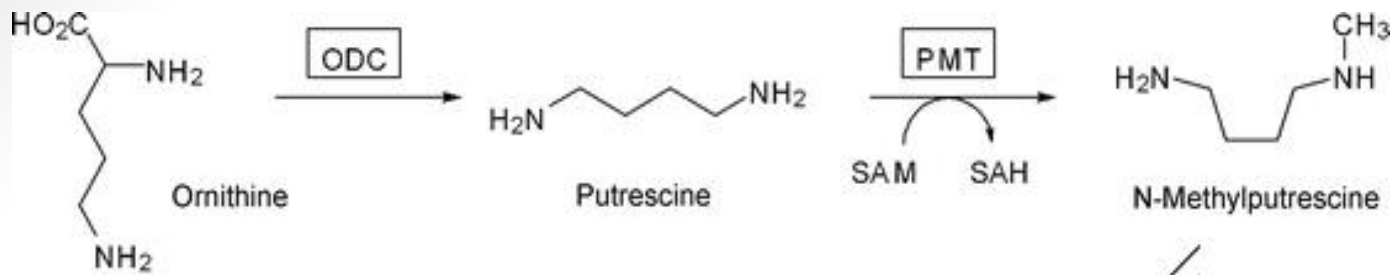
Hyoscyamine:

** is the major natural alkaloid with negative optical rotation (*l*- form) [*(-)*-hyoscyamine that is racemized to atropine].

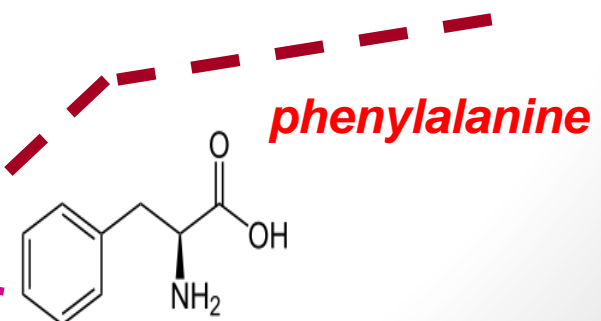
** Because the α -carbon is asymmetric, so two stereoisomers are possible (racemers).

** During extraction hyoscyamine racemizes to the optically inactive *d/l* Atropine.

** Both alkaloids are composed of tropine base and tropic acid.



SAM: S-adenosyl methionine



Alkaloids in the form of HCl salts

Principle:
difference in
basicity

- 1- Alkalinize by NaHCO_3 pH 7.5
- 2- Extract with Ether

Ether
Hyoscine free base
(pKa = 6.2)

Aqueous layer
Atropine & Hyoscyamine HCl
(pKa = 9.3)

Convert to oxalate salts,
Fractional Crystallization
(Acetone/ Ether)

Principle:
difference in
solubility in a
mixture of
acetone and
ether

Atropine Oxalate
Crystals

Hyoscyamine Oxalate
Solution