

# Alkaloids

**Definition:** the term “alkaloid” (alkali-like) is commonly used to designate basic heterocyclic nitrogenous compounds of plant origin that are physiologically active.

## **Deviation from Definition:**

- **Basicity:** Some alkaloids are not basic e.g. Colchicine, Piperine, Quaternary alkaloids.
- **Nitrogen:** The nitrogen in some alkaloids is not in a heterocyclic ring e.g. Ephedrine, Colchicine, Mescaline.
- **Plant Origine:** Some alkaloids are derived from Bacteria, Fungi, Insects, Frogs, Animals.

# Classification:

- **True (Typical) alkaloids** that are derived from amino acids and have nitrogen in a heterocyclic ring. e.g Atropine
- **Protoalkaloids** that are derived from amino acids and do not have nitrogen in a heterocyclic ring. e.g Ephedrine
- **Pseudo alkaloids** that are not derived from amino acids but have nitrogen in a heterocyclic ring. e.g Caffeine
- **False alkaloids** are non alkaloids give false positive reaction with alkaloidal reagents.

**New Definition: Alkaloids are cyclic organic compounds containing nitrogen in a negative state of oxidation with limited distribution among living organisms.**

## **Distribution and occurrence:**

- Rare in lower plants.
- Dicots are more rich in alkaloids than Monocots.
- Families rich in Alkaloids: Apocynaceae, Rubiaceae, Solanaceae and Papaveracea.
- Families free from Alkaloids: Rosaceae, Labiatae

# **Distribution in Plant:**

- All Parts e.g. Datura.
- Barks e.g. Cinchona
- Seeds e.g. Nux vomica
- Roots e.g. Aconite
- Fruits e.g. Black pepper
- Leaves e.g. Tobacco
- Latex e.g. Opium

# Forms of Alkaloids:

- Free bases
- Salts with Organic acids e.g. **Oxalic, acetic acids**
- Salts with inorganic acids e.g. **HCl, H<sub>2</sub>SO<sub>4</sub>**.
- Salts with special acids: e.g.  
**Meconic acid** in Opium  
**Quinic acid** in *Cinchona*
- Glycosidal form e.g. Solanine in *Solanum*.

# Function in Plants

- They may act as **protective** against insects and herbivores due to their bitterness and toxicity.
- They are, in certain cases, the final **products of detoxification (waste products)**.
- **Source of nitrogen** in case of nitrogen deficiency.
- They, sometimes, act as **growth regulators** in certain metabolic systems.
- They may be utilized as a **source of energy** in case of deficiency in carbon dioxide assimilation.



# Nomenclature:

**Trivial names** should end by "**ine**". These names may refer to:

- The **genus** of the plant, such as Atropine from *Atropa belladonna*.
- The plant **species**, such as Cocaine from *Erythroxylon coca*.
- The **common name** of the drug, such as Ergotamine from ergot.
- The name of the **discoverer**, such as Pelletierine that was discovered by Pelletier.
- The **physiological action**, such as Emetine that acts as emetic, Morphine acts as narcotic.
- A prominent **physical character**, such as Hygrine that is hygroscopic.

# Prefixes and suffixes:

## Prefixes:

- "**Nor-**" designates N-demethylation or N-demethoxylation, e.g. norpseudoephedrine and nornicotine.
- "**Apo-**" designates dehydration e.g. apomorphine.
- "**Iso-, pseudo-, neo-, and epi-**" indicate different types of isomers.

## Suffixes:

- "**-dine**" designates isomerism as quinidine and cinchonidine.
- "**-ine**" indicates, in case of ergot alkaloids, a lower pharmacological activity e.g. ergotamine is less potent than ergotamine.

# Physical Properties:

## I- Condition:

- **Most** alkaloids are crystalline **solids**.
- Few alkaloids are amorphous solids e.g. emetine.
- **Some** are **liquids** that are either:
  - Volatile** e.g. nicotine and coniine, or
  - Non-volatile** e.g. pilocarpine and hyoscyne.

## II- Color:

The **majority** of alkaloids are **colorless** but **some** are **colored** e.g.:

- Colchicine and berberine are yellow.
- Canadine is orange.
- The salts of sanguinarine are copper-red.

# Physical Properties:

## III- Solubility:

- Both **alkaloidal bases** and their **salts** are **soluble in alcohol**.
- Generally, the **bases** are **soluble in organic solvents** and **insoluble in water**

### Exceptions:

- Bases **soluble in water**: caffeine, ephedrine, codeine, colchicine, pilocarpine and quaternary ammonium bases.
- Bases **insoluble or sparingly soluble in certain organic solvents**: morphine in ether, theobromine and theophylline in benzene.
- **Salts** are usually **soluble in water** and, **insoluble or sparingly soluble in organic solvents**.

### Exceptions:

- Salts **insoluble in water**: quinine monosulphate.
- Salts **soluble in organic solvents**: lobeline and apatropine hydrochlorides are soluble in chloroform.

## IV- Isomerization:

- Optically active isomers may show different physiological activities.
- *l*-ephedrine is 3.5 times more active than *d*-ephedrine.
- *l*-ergotamine is 3-4 times more active than *d*-ergotamine.
- *d*-Tubocurarine is more active than the corresponding *l*-form.
- Quinine (*l*-form) is antimalarial and its *d*-isomer quinidine is antiarrhythmic.
- The **racemic** (optically inactive) *dl*-atropine is physiologically active.

# Chemical Properties:

## I- Nitrogen:

- Primary amines       $R-NH_2$       e.g. Norephedrine
- Secondary amines       $R_2-NH$       e.g. Ephedrine
- Tertiary amines       $R_3-N$       e.g. Atropine
- Quaternary ammonium salts  $R_4-N$       e.g. *d*-Tubocurarine

## II- Basicity:

- $R_2-NH > R-NH_2 > R_3-N$
- Saturated hexacyclic amines is more basic than aromatic amines.

# According to basicity Alkaloids are classified into:

- Weak bases e.g. Caffeine
  - Strong bases e.g. Atropine
  - Amphoteric
    - \* Phenolic Alkaloids e.g. Morphine
    - with Carboxylic groups e.g. Narceine
  - Neutral alkaloids e.g. Colchicine
- \*Alkaloids

### III- Oxygen:

- Most alkaloids contain Oxygen and are solid in nature e.g. Atropine.
- Some alkaloids are free from Oxygen and are mostly liquids e.g. Nicotine, Coniine.



# IV- Stability:

- Effect of heat:

Alkaloids are decomposed by heat, except **Strychnine** and **caffeine (sublimable)**.

- Reaction with acids:

1- Salt formation.

2- Dil acids hydrolyze Ester Alkaloids e.g. Atropine

### 3- Conc. acids may cause:

- Dehydration:

Atropine → Apoatropine

Morphine → Apomorphine

- Demethoxylation:

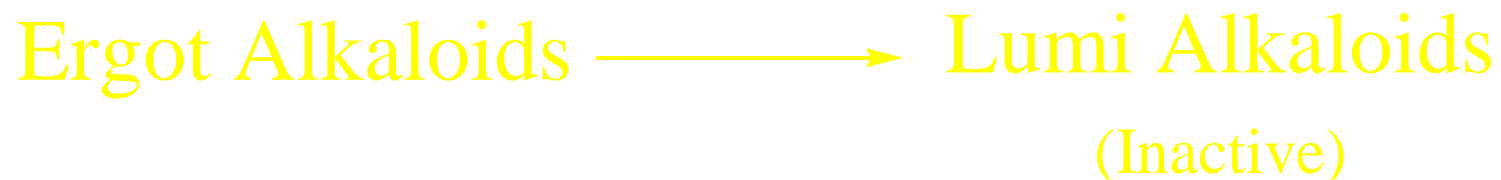
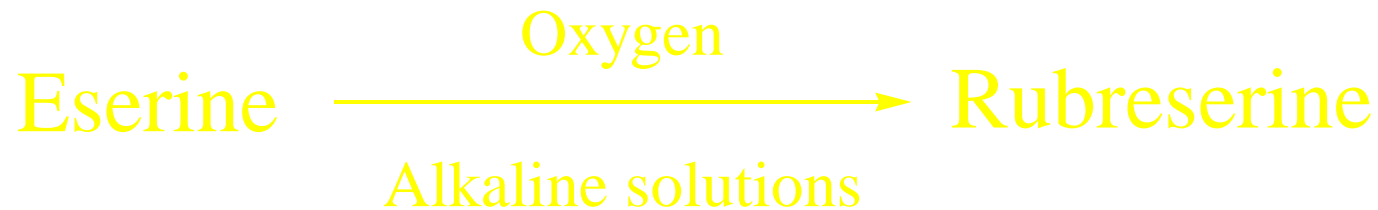
e.g. Codeine

- **Effect of Alkalies:**

- 1- Dil alkalis liberate most alkaloids from their salts e.g.  $\text{NH}_3$ .
- 2- They may cause isomerization (racemization) of alkaloid as the conversion of hyoscyamine to atropine.
- 3- They also can **form salts with alkaloids containing a carboxylic group** e.g. narceine.
- 4- **Strong alkalis:** such as aqueous NaOH and KOH form salts with phenolic alkaloids.
- 5- **Strong alkalis cause hydrolysis of Ester alkaloids** (e.g. atropine, cocaine and physostigmine) and **Amide alkaloids** ( colchicines).
- 6- **Strong alkalis cause opening of lactone ring.**

- **Effect of light and Oxygen:**

Some alkaloids are unstable when exposed to light and Oxygen:



# **Qualitative test for Alkaloids:**

- **Precipitation Reagents:**

They are used to:

- 1- Indicate the absence or presence of Alkaloids
- 2- Test for complete of extraction

**Disadvantages:** Some non alkaloids interfere such as  
Proteins, lactones, coumarins

- **Classification of Alkaloidal precipitating agents:**

- 1- Reagents that form double salts:**

- a- Mayer's Reagent: Potassium Mercuric Iodide.
- b- Dragendorff's Reagents: Potassium Iodobismethate.
- c- Gold Chloride.

- 2- Reagents Containing Halogens:**

- a- Wagner's Reagent: Iodine/ Potassium Iodide.

- 3-Organic Acids:**

- a- Hager's Reagent: Picric Acid
- b- Tannic Acid.

- 4- Oxygenated High Molecular Weight Acids:**

- a- Phosphomolybdic acid
- b- Phosphotungstic acid
- c- Silicotungstic Acid

- **Colour Reagents:**

**1- Froehd's Reagent:** Phosphomolybdic acid

**2- Marqui's Reagent:** Formaldehyde/ Conc.  $\text{H}_2\text{SO}_4$

**3- Mandalin's Reagent:** Sulphovanidic acid

**4- Erdmann's Reagent:** Conc.  $\text{HNO}_3$ /Conc.  $\text{H}_2\text{SO}_4$

**5- Mecke's Reagent:** Selenious acid / conc.  $\text{H}_2\text{SO}_4$

**6- Shaer's Reagent:** Hydrogen peroxide / conc.  $\text{H}_2\text{SO}_4$

**7- Rosenthaler's Reagent:** Potassium arsenate / conc.  $\text{H}_2\text{SO}_4$

**8- Conc.  $\text{HNO}_3$**

# Extraction, Purification and Isolation of Alkaloids from Powdered plants

- Extraction and purification

## Method I:

The powder is treated with alkalis to liberates the free bases that can then be extracted with water immiscible organic solvents.

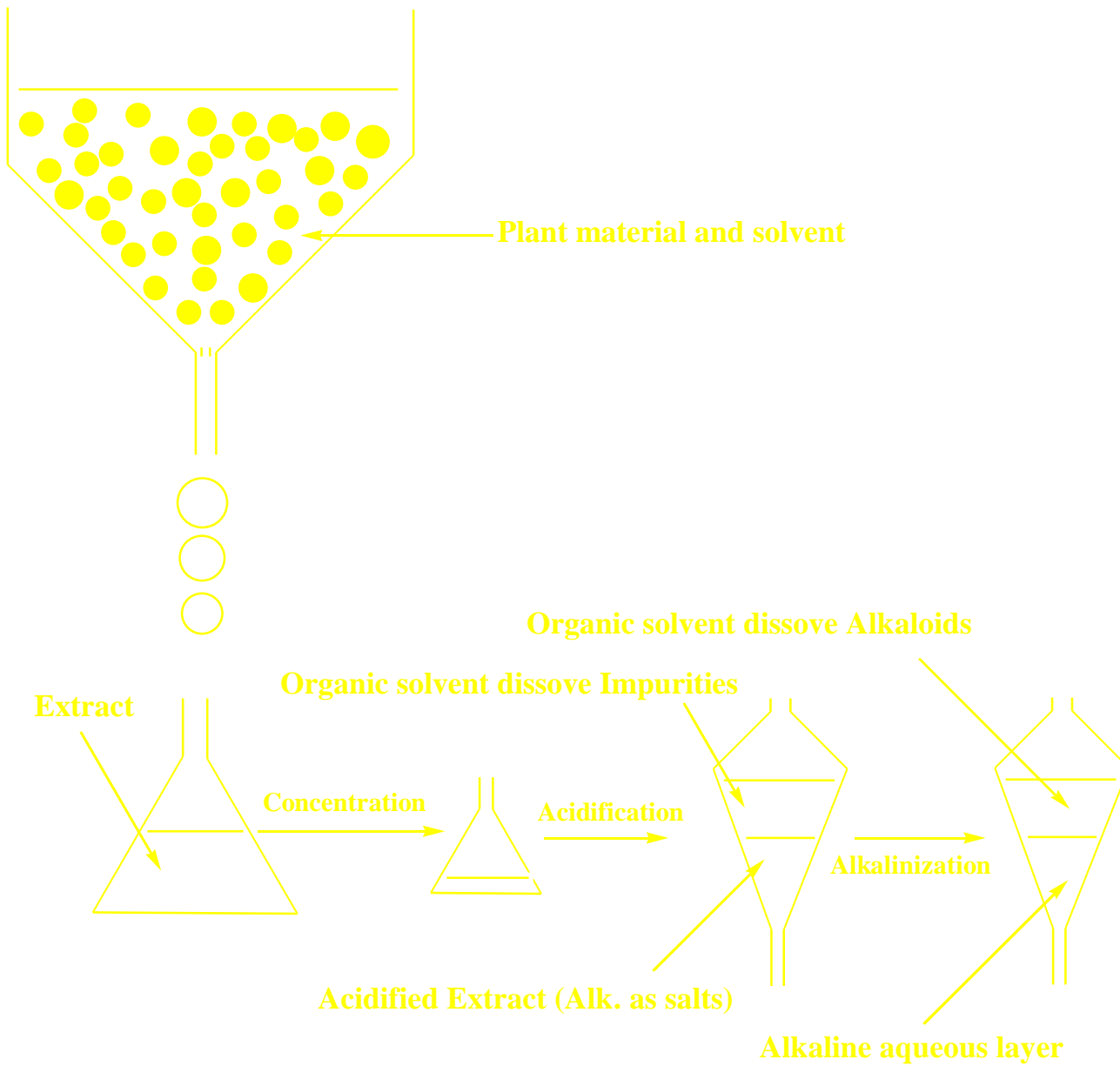
## Method II:

The powdered material is extracted with **water or aqueous alcohol** containing **dilute acid**. **Alkaloids** are extracted as their **salts** together with accompanying **soluble impurities**.

## Method III:

The powder is extracted with water soluble organic solvents such as MeOH or EtOH which are good solvents for both salts and free bases.





- **Liberation of the free bases:**

Alkalis are used to liberate free bases. Alkalis must be strong enough to liberate free bases. However, choice of strong alkalis must be avoided in some cases:

1- Ester Alkaloids      e.g. Solanaceous Alkaloids

2- Amide Alkaloids      e.g. Colchicine

3- Phenolic Alkaloids   e.g. Morphine

4- Lactone Alkaloids    e.g. Pilocarpine

5- Fatty Drugs due to saponification and emulsion formation.

- **NH<sub>4</sub>OH:**

**Most widely used due to many advantages:**

- 1- Strong enough to liberate most of alkaloids from their salts.**
- 2- Milder than fixed alkalis so more safe.**
- 3- Volatile so easy to get rid of it.**

- **Other Alkalis:**

**Na<sub>2</sub>CO<sub>3</sub>, NaHCO<sub>3</sub>, Ca(OH)<sub>2</sub>, MgO.**

- **Extraction of the free bases:**

- **CHCl<sub>3</sub>:**

**Strong solvent can extract most of the alkaloids.**

**Extracts contain more impurities.**

**Carcinogenic.**

- **Ether:**

**Gives cleaner Extract but have some disadvantages:**

**1- High volatility**

**2- Peroxide formation**

**3- High water miscibility**

# Volatile Alkaloids

- The best way for their extraction is steam distillation.
- Plant material + water + Fixed alkali  
Heat  
—————→ steam contain  
alkaloids received in  
acidic solution.

## ➤ Purification of the Crude Alkaloidal Fractions:

- **Repeated Acid-Base procedures:**

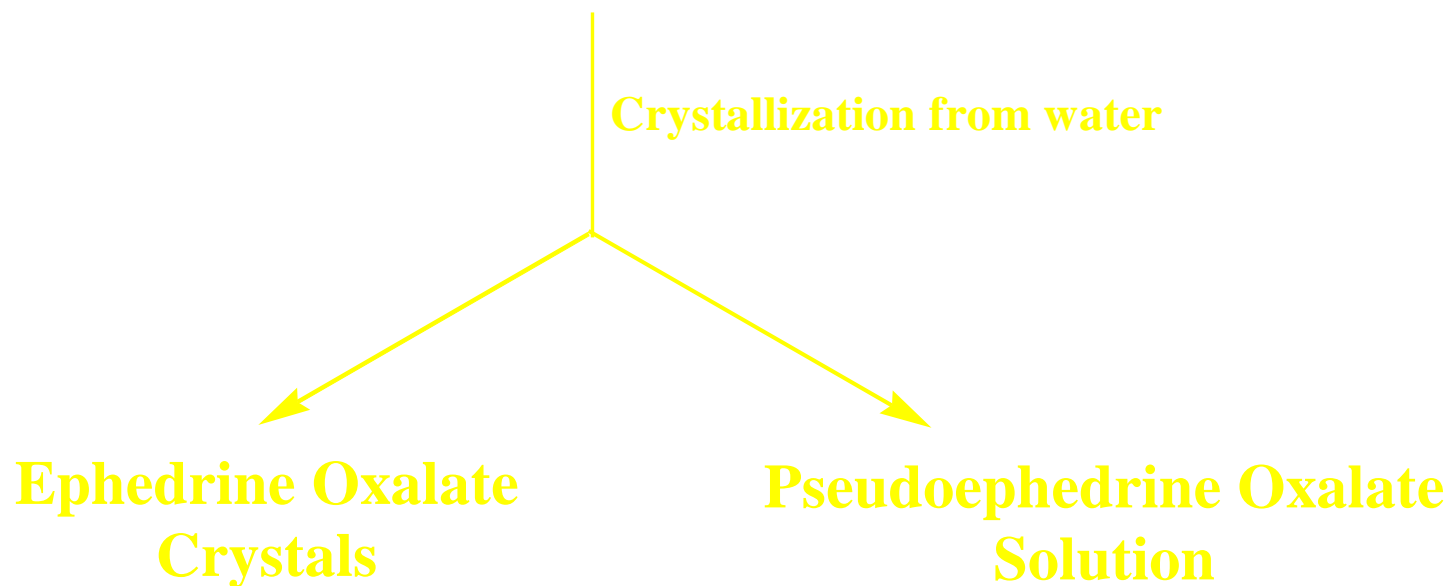
Render extract **Acidic**, extract with **organic solvent** (dissolve non alkaloidal impurities), **Alkalinize** and extract again with **organic solvents** (Dissolve Alkaloids).

- Precipitation with alkaloidal precipitating agent.
- Convert to crystalline salts.

# ➤ Separation of Alkaloidal Mixtures:

- Fractional Crystallization:

## Ephedrine & Pseudoephedrine Oxalates



# Atropine & Hyoscyamineine Oxalates

Crystallization from  
Acetone/Ether



```
graph TD; Title[Atropine & Hyoscyamineine Oxalates] --- Junction(( )); Junction --> Atropine[Atropine Oxalate Crystals]; Junction --> Hyoscyamine[Hyoscyamine Oxalate Solution];
```

**Atropine Oxalate  
Crystals**

**Hyoscyamine Oxalate  
Solution**



- Preparation of Derivatives:

## Separation of Primary, Secondary and Tertiary Alkaloids.

- **Fractional Liberation:**

**Atropine & Hyoscyamine & Hyoscine  
the form of HCl salts**

1- Alkalinize by  $\text{NaHCO}_3$  pH 7.5  
2- Extract with Ether

**Ether**

**Hyoscine free base  
(pKa = 6.2)**

**Aqueous layer**

**Atropine & Hyoscyamine HCl  
(pKa = 9.3)**

- **Fractional Distillation:**  
e.g. Separation of Nicotine and Anabasine
- **Chromatographic Separation.**

# Identification of Alkaloids:

- Melting point
- Colour test
- Optical Rotation
- Microcrystal test
- HPLC, GC, GC-MS
- UV, IR, NMR, MS.

# Quantitative Determination of Alkaloids:

- **Volumetric methods:**
- These are based on reaction of alkaloidal bases with acids (Acid-Base titration).  
They include:
  - **Aqueous titration:** This is carried by either:
    - 1- **Direct titration** of the alcoholic solution of the alkaloidal residue with standard acid, or
    - 2- **Back titration** by dissolving the residue in a known amount of standard acid and back titration of residual acid against standard alkali.
  - **Non-aqueous titration:** This method is suitable for determination of weak bases e.g. Caffeine.

- **Gravimetric methods:**

These methods are recommended for determination of:

**1- Very weak bases** which can not be determined by volumetric methods e.g. caffeine and colchicine.

**2- Mixtures of alkaloids** that are obtained from the same plant but differ greatly in their molecular weight e.g. Cinchona and Rauwolfia alkaloids.

They can be performed by either:

1- Direct Weighing of the alkaloidal mixtures

2- Precipitation of the total alkaloids and determination of the weight of the precipitate obtained.

The major **drawbacks** of the gravimetric methods are:

1- They are insensitive to microamounts of alkaloids.

2- They could not be applied in case of thermolabile and volatile alkaloids.

3- Lipophilic impurities in the residue are calculated as alkaloids.

- **Colourimetric Method:**

e.g. Morphine +  $\text{NaNO}_2/\text{HCl}$

Ergot + p-dimethylaminobenzaldehyde

- **Spectrophotometric Methods.**

- **Polarimetric Method.**

- **Fluorimetric Method.**

- **Chromatographic Methods**

# Classification of Alkaloids

- Biogenetic.

Based on the biogenetic pathway that form the alkaloids.

- Botanical Source.

According to the plant source of alkaloids.

- Type of Amines.

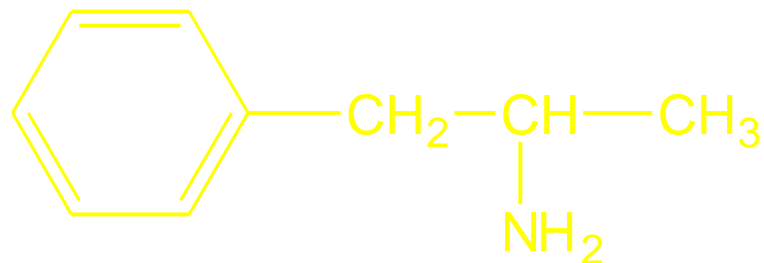
Primary, Secondary, Tertiary alkaloids.

- Basic Chemical Skeleton



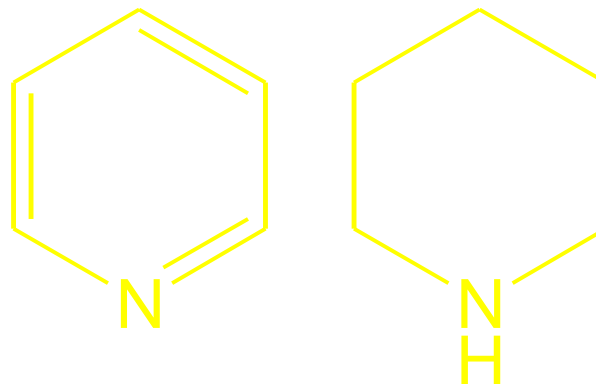
- **Phenylalkylamines:**

e.g. Ephedrine



- **Pyridine and piperidine**

e.g. lobeline, nicotine



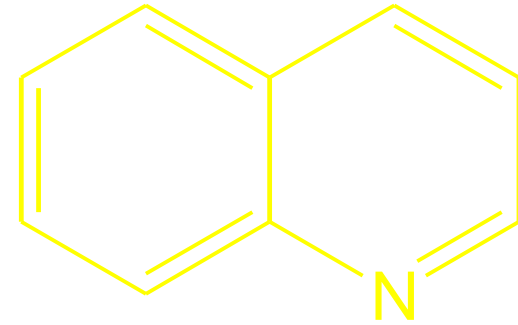
- **Tropane**

e.g. Atropine.



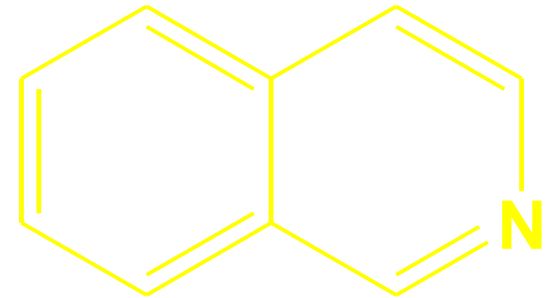
- **Quinoline**

e.g. quinine and quinidine



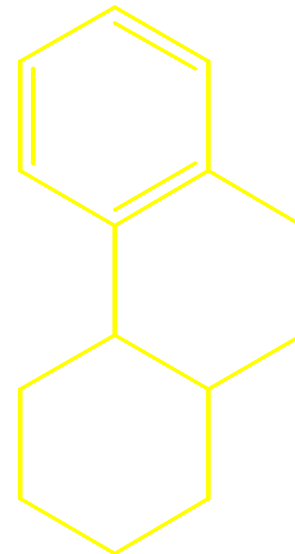
- **Isoquinoline**

e.g. papaverine



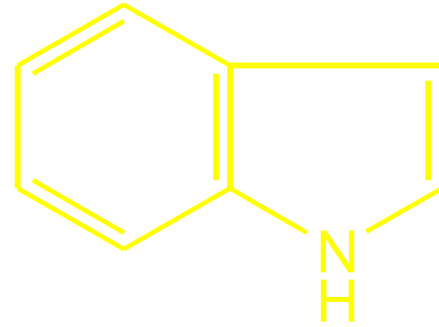
- **Phenanthrenen**

e.g. Morphine



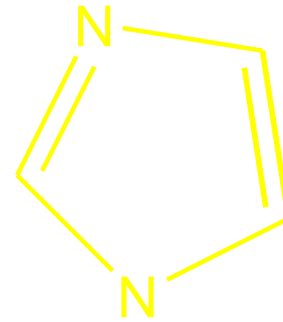
- **Indole**

e.g. ergometrine



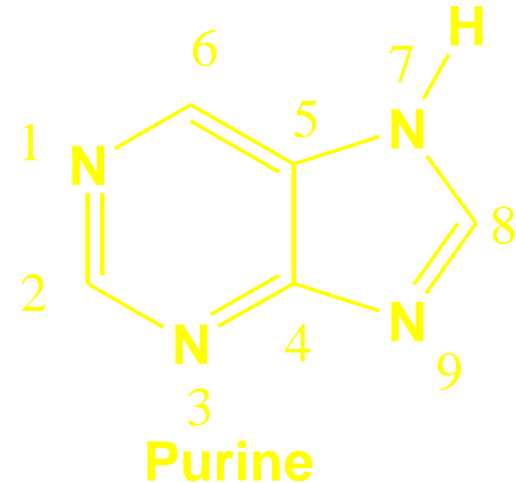
- **Imidazole**

e.g. pilocarpine



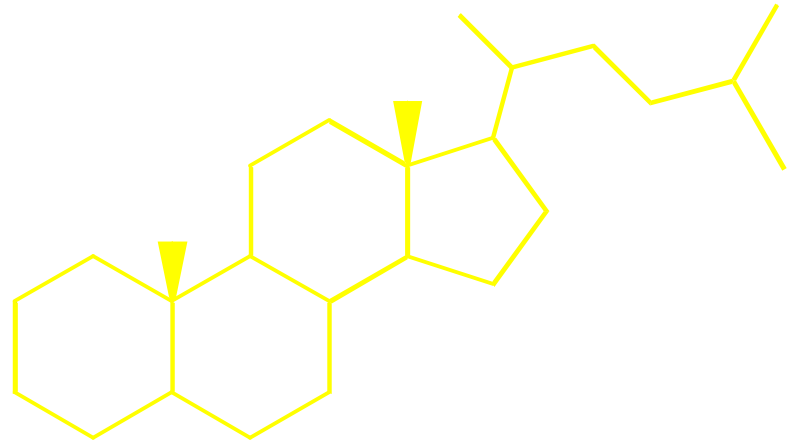
- **Purine**

e.g. caffeine



- **Steroidal**

e.g. Solanum and *Veratrum*  
alkaloids



- **Terpenoid**

e.g. Taxol

