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_2SO_4**.
- 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 belladona*.
- 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. ergotaminine 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 hyoscine.

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 apoatropine 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 antiarrythmic.
- The **racemic (**optically inactive) *dl*-atropine is physiologically active.

Chemical Properties:

I- Nitrogen:

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

II- Basicity:

- $R_2\text{-}NH > R\text{-}NH_2 > R_3\text{-}N$
- 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 *Alkaloids with Carboxylic groups e.g. Narceine
- Neutral alkaloids e.g. Colchicine

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. NH3.

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- Phosphotungestic acid

c- Silicotungestic Acid

- **Colour Reagents:**

1- Froehd's Reagent: Phosphomolybdic acid

2- Marqui's Reagent: Formaldehyde/ Conc. H_2SO_4

3- Mandalin's Reagent: Sulphovanidic acid

4- Erdmann's Reagent: Conc. HNO_3/Conc. H_2SO_4

5- **Mecke's Reagent:** Selenious acid / conc. H_2SO_4

6- **Shaer's Reagent:** Hydrogen peroxide / conc. H_2SO_4

7- **Rosenthaler's Reagent:** Potassium arsenate / conc. H_2SO_4

8- **Conc. 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.

Plant material and solvent
Organic solvent dissove Alkaloids
Organic solvent dissove Impurities
Extract
Concentration
Acidification
Alkalinization
Acidified Extract (Alk. as salts)
Alkaline aqueous layer

- **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_4OH:**

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_2CO_3, $NaHCO_3$, $Ca(OH)_2$, MgO.

- **Extraction of the free bases:**
- **$CHCl_3$:**

  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 sloution.

➢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:**

Atropine & Hyoscyamineine Oxalates

Atropine Oxalate Crystals

Hyoscyamine Oxalate Solution

- Preparation of Derivatives:

Separation of Primary, Secondary and Tertiary Alkaloids.

- **Fractional Liberation:**

- **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 Rawolfia 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 + $NaNO_2$/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

- **Phenantheren**

  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