Alkaloids:

An Introduction

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Introduction...

- **Alkaloids represent a group of natural products that has a great influence on the economic, medical, political and social affairs of human beings.**
- **Many have potent physiological effects and therefore, are considered as important therapeutic agents**
  - **e.g. atropine, morphine, quinine, reserpine etc.**
- **They are widely used to treat diseases ranging from malaria to cancer.**
- **Some Alkaloids are extremely poisonous:**
  - **Ergot alkaloids are poisonous**
  - **The extracts of plants containing alkaloids have long been used as arrow poisons in hunting and warfare e.g. curare extract contains tubocurarine alkaloid.**
  - **At the time of the Roman Empire, Belladonna (the source of atropine) has been mixed with food with the purpose of murdering.**
  - **Cleopatra, the queen of Egypt used Egyptian henbane (*Hyoscyamus muticus*) that contains hyoscyamine, for suicidal purpose.**
- **Certain alkaloids are widely used for their psychotropic effects**
  - **e.g. Caffeine acts as CNS stimulant**

Alkaloids…

A precise and general definition of the term "alkaloids" is quite difficult, as they do not represent a homologous group of compounds from the chemical, biochemical or physiological point of view. Despite these variations the term alkaloid is commonly used to designate basic nitrogenous compounds of plant origin that are physiologically active.

Definition:

Alkaloids are basic, nitrogen containing compounds of plant origin. They have complex molecular structure with the nitrogen atom involved in a heterocyclic ring and they manifest a significant pharmacological activity.

Alkaloids…

- **Many widely distributed bases of plant origin such as methyl, trimethyl and other open chain simple alkylamines and cholines are not classified as alkaloids.**
- **These are known as biological amines or proto-alkaloids.**

Alkaloids…

- **Usually alkaloids have complex molecular structure with the nitrogen atom involved in a heterocyclic ring, but thiamine, a heterocyclic compound with nitrogenous base, is not regarded as alkaloid because of its universal distribution in living matter.**
- **Interestingly, Colchicine does not contain nitrogen atom in a heterocyclic ring but classified as alkaloid because of its particular pharmacological activities.**

Restrictions to the common definition

- **All alkaloids are nitrogenous, but not all the nitrogenous compounds are alkaloids.**
- **Plants are a rich source of alkaloids but some have been found in animals and fungi and almost all alkaloids have been synthesized.**
- **alkaloids have a restricted distribution to certain plant families**
- **Most but not all possess basic properties due to the presence of the amino nitrogen. Some Alkaloids are even acidic e.g. Colchicine.**

Occurance and distribution…

- **More than 1000 alkaloids are known**
- **They are distributed in :**
  - **100 Families**
  - **500 Genera and**
  - **1200 Species.**
- **Not equally distributed in plant kingdom**
- **Nearly absent in Algae and lower plants (with some exceptions of Fungi)**
- **Fungal examples:**
  - **Ergot and some Mushrooms**
  - **Strptomyces sp. Produce antibiotic alkaloids**
    - **Chloromycetin (Chloramphenicol)**
    - **Erythromycin**
- **Examples of Gymnosperm:**
  - **Taxus baccata**
  - **Ephedra**

Occurance and distribution…

- **Majority of Alkaloids are present in Dicotyledons. Example:**
  - **Apocynaceae**
  - **Papaveraceae**
  - **Ranunculaceae**
  - **Rubiaceae**
  - **Solanaceae**
  - **Berbaridaceae**
- **Labiateae and Rosaceae are almost free from Alkaloids**

Occurance and distribution

- **Alkaloids are not Organ specific**
- **Alkaloids may present in all organs:**
  - **Datura**
- **In Barks:**
  - **Cinchona**
- **In Roots:**
  - **Rauwolfia, Belladonna, Aconite**
- **In fruits:**
  - **Black pepper**
- **In Leaves:**
  - **Hyoscyamus, Datura**
- **In Seeds:**
  - **Nux-vomica, Areca**

Occurance and distribution

- **Alkaloids are usually present in plants in the form of salts of**
  - **Acetic acid**
  - **Malic acid**
  - **Oxalic acid**
  - **Tartaric acid**
  - **Succinic acid**
  - **Tannic acid…etc.**
- **Sometimes they are present in combination with special acids like**
  - **Aconitic acid (Aconitine),**
  - **Maconic acid (Opium alkaloids),**
  - **Quinic or**
  - **Cinchotannic acid (Cinchona alkaloids).**
- **Alkaloidal salts with inorganic acids may also be present**
  - **Morphine is present as sulfate in Opium**

Occurance and distribution

Few alkaloids occur in glycosidal combination with sugars and known as Gluco-alkaloids:

- **Solanine (potato tubers) when hydrolysed, yields:**
  - **Sugars and**
  - **Aglycone Solanidine (an Alkaloid)**

Nomenclature…

- There is no systematic nomenclature of Alkaloids.
- As a chemical rule an alkaloid should end with suffix **'-ine'**
- Names of Alkaloids are obtained in different ways:
  - From the generic name of plant (atropine, hyoscyamine)
  - From the specific names of plant (cocaine,belladonine, ergotamine)
  - From the physiological properties (emetine, narcotine)
  - From their physical properties (hygrine, hygro = moist)
  - Sometimes a suffix is added to the name of principal alkaloid to designate other alkaloids of the same group (quinine, quinidine, hydroquinine)
  - Occasionally the prefix **'-iso'**, **'-pseudo'**, **'-neo'** or **'-epi'** are also added

Physical Properties…

- **Alkaloids are usually odorless, colorless, crystalline, non-volatile, bitter solids.**
- **Few are colored eg. Berberine and colchicine are yellow.**
- **Some colorless alkaloids may have colored salts eg. Hydrastinine salt is yellow and Sanguinarine salt is red.**
- **In pure state, alkaloids and their salts are crytallizable solids.**
- **Few bases are oily liquids eg. Arecoline, Coniine, Nicotine, Pilocarpine and sparteine.**
- **Few alkaloids are amorphous eg. Emetine**

Solubility

- **Free alkaloidal bases:**
  - Usually soluble in organic solvents such as Chloroform, Ether or other non-polar immiscible solvents as well as lower Alcohols.
  - Practically insoluble or sparingly soluble in Water.
  - Exceptions:
    - Few alkaloidal bases are sparingly soluble in organic solvents eg. Morphine in Ether (1:5000), Pilocarpine and Narceine are insoluble.
    - Few alkaloidal bases are soluble soluble in Water eg. Caffeine, Ephedrine, Colchicine, Pilocarpine and quaternary alkaloidal bases like Tubocurarine and Berberine.
- **Alkaloidal Salts:**
  - Generally soluble in Water
  - Less soluble in Alcohols
  - Insoluble or sparingly soluble in Organic Solvents.
  - Exceptions:
    - Quinine sulfate is sparingly soluble in Water (1:1000)
    - Few alkaloidal salts are soluble in organic solvents eg. Apoatropine hydrochloride and Lobaline hydrochloride is soluble in Chloroform.

Optical activity

- Many alkaloids are optically active due to the presence of one or more asymmetric carbon atoms in their molecule.
- Optically active isomers show different physiological activities.
- Usually the l (-) isomer is more active than the d (+)-isomer e.g.
  - l-ephedrine is 3.5 times more active than the d-isomer and
  - l-ergotamine is 3-4 times more active than d-ergotamine.
- Exceptions:
  - d-tubocurarine is more active than the corresponding l-isomer.
  - Both, quinine (l-form) and its d-isomer quinidine are active.
  - The racemic dl-atropine is physiologically active.

Stability...

- **The influence of different factors such as exposure to light, heat, oxygen, acids and alkalis should be considered during preservation and manipulation of alkaloids.**
- **In general, alkaloids are less stable in solution than in the dry state.**

Effect of heat:

Alkaloids are decomposed by heat, except caffeine that sublimes without decomposition.

Effect of heat and light in presence of oxygen:

Most tertiary amine alkaloids are easily transformed to the N-oxides when exposed to light and oxygen at elevated temperature.

N-oxides are water soluble and are characterized by their delayed release properties, low toxicity and low addictive properties as compared to the parent tertiary alkaloids.

(Cont…)

Stability...

Effect of acids:

Hot dilute acids and concentrated mineral acids may cause:

- **Dehydration to produce anhydro- or apo alkaloids, e.g. dehydration of morphine to produce apomorphine and that of atropine to yield apoatropine,.**
- **O-demethylation of certain alkaloids such as quinine, narcotine and codeine to produce phenolic alkaloids by treatment with HI e.g. conversion of codeine to morphine.**
- **Hydrolysis of ester alkaloids, such as atropine, reserpine, and glucoalkaloids such as solanine.**

(cont…)

Stability...

Effect of alkalis:

This includes the effect of weak, strong and hot alkalis.

- **Weak alkalis liberate most alkaloids from their salts e.g. ammonia.**
- **Strong alkalis such as aqueous sodium hydroxide and potassium hydroxide form salts with phenolic alkaloids.**
- **Hot alkalis result in hydrolysis of ester alkaloids e.g. atropine, cocaine and physostigmine are hydrolysed. Cleavage of lactone ring may also occur e.g. pilocarpin is transformed into pilocarpic acid salt.**

Chemical properties

- **Nitrogen in alkaloids:**
  - **Alkaloids usually contain one nitrogen atom, yet certain alkaloids may contain more than one and up to 5 nitrogen atoms in their molecule e.g. nicotine contains two nitrogen atoms and ergotamine has five N atoms.**
  - **These nitrogen atom usually exists in a heterocyclic ring.**
  - **In a number of alkaloidal amines (eg. Ephedrine, Mescaline and Colchicine) nitrogen is not present in a ring but in a side chain.**
- **Type of amino group:**
  - **Nitrogen in alkaloids exists in the form of amine.**
  - **It may be:**
  - **A primary amino group e.g. nor-pseudoephedrine**
  - **A secondary amino group e.g. ephedrine.**
  - **A tertiary amino group e.g. nicotine and atropine.**
  - **A quaternary ammonium ion e.g. tubocurarine.**

(cont…)

Chemical properties

Basicity:

The basicity of alkaloids is due to the presence of a lone pair of electrons on the amino nitrogen atom. Amines and, consequently, alkaloids resemble ammonia in chemical characters. They form salts with acids without liberation of water.

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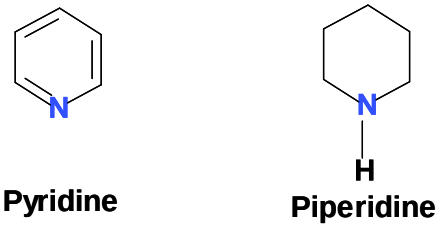
Factors influencing the degree of basicity

- **Unsaturation decreases the basicity e.g. piperidine alkaloids are more basic than the pyridine alkaloids.**



Pyridine Piperidine

- **The presence and position of other substituents and functional groups e.g.:**
  - **The electron releasing groups, such as alkyl groups, increase the basicity.**
  - **The electron withdrawing groups, such as the carbonyl groups, decrease the basicity.**
  - **Alkaloids may therefore, be neutral or slightly acidic, as the electron availability on the amino nitrogen atom decreases.**
  - **An example of acidic alkaloid is ricinine.**
- **Some alkaloids are amphoteric due to the presence of acidic groups in their molecule. Examples are:**
  - **The phenolic alkaloids such as morphine, psychotrine, and cephaline.**
  - **The alkaloids containing a carboxylic group, such as narceine.**

Pharmacological activity…

Alkaloidals exhibit a wide range of pharmacological activities.

They can be used as:

- **Analgesic and narcotics:** **e.g. morphine and strychnine**
- **CNS stimulants:** **e.g. caffeine and strychnine**
- **Anticancers:** **e.g. vincristine, vinblastine and taxol**
- **Mydriatics:** **e.g. atropine**
- **Myotics:** **e.g. eserine and pilocarpine.**
- **Anti-asthmatics:** **e.g. ephedrine**
- **Antitussives:** **e.g. codeine.**
- **Expectorants:** **e.g. lobeline.**
- **Anti-hypertensives:** **e.g. reserpine**
- **Smooth muscle relaxants:** **e.g. atropine and papaverine**
- **Skeletal muscle relaxants:** **e.g. tubocurarine.**
- **Anthelmintics:** **e.g. pelletierine and arecoline.**
- **Antiparasitics:** **e.g. quinine and emetine.**