PharmacognosyIII

Lec. 1 **3rd stage 2nd semester** **Year 23-24**

Lecturer: Dr. Jamel Fani

ALKALOIDS

Introduction

Alkaloids are extremely difficult to define for they do not represent a homogeneous group of compounds either from the chemical, biochemical, or physiologic viewpoint. Consequently, Alkaloids are all organic nitrogenous compounds. Plants have been a rich source of alkaloids, but some are found in animals, fungi, and bacteria; practically all have been reproduced in the laboratory by chemical synthesis. Most possess basic properties, due to the presence of an amino nitrogen, and many possess marked physiologic activity. In spite of the difficulties attending a precise definition, the term is an extremely useful one, commonly applied to basic nitrogenous compounds of plant origin which are physiologically active.

Distribution:

1. Angiosperms:

   Leguminosae, Papaveraceae, Ranunculaceae, Rubiaceae, Solanaceae, and Berberidaceae.

   -The Labiatae and Rosaceae are almost free of them.

2. The gymnosperms only rarely contain them (Taxaceae).
3. The monocotyledons do not generally produce alkaloids, investigations indicate that the Amaryllidaceae and Liliaceae are two of the most promising families in which to search for alkaloid-yielding plants.

Alkaloids may occur in various parts of the plant:

- In seeds (nux vomica, areca),
- In fruits (black pepper, conium),
- In leaves (belladonna leaf, hyoscyamus),
- In underground stems (sanguinaria, corydalis),
- In roots (aconite, belladonna root),
- In rhizomes and roots (ipecac, hydrastis),
- In barks (cinchona, pomegranate),
- They are also found in the fungi (ergot, Amanita citrina),

The names of the alkaloids are obtained in various ways:

1. from the generic name of the plant yielding them (hydrastine, atropine),
2. from the specific name of the plant yielding them (cocaine, belladonnine),
3. from the common name of the drug yielding them (ergotamine),
4. from their physiologic activity (emetine, morphine),
5. from the discoverer (pelletierine).

* By agreement, chemical rules designate that the names of all alkaloids should end in “ine”.

History of alkaloids:

Alkaloids are among the most important drugs in human history. The isolation of the alkaloid morphine by Friedrich in 1806 is regarded as the “formal” start of plant secondary metabolism. It is widely accepted that the main role of alkaloids in plants is toxicity against predators and

pathogens. The same toxic properties observed in the plant defense scenario can often be used in prospection for new drugs. For example, a very specific toxicity may be used to fight certain tumor cell types, or also be used to control specific microorganisms or pests.

Toxicity to Humans and Other Vertebrates:

Animal intoxication by alkaloids is mostly caused by accidental ingestion of food contaminated with alkaloid-containing plants. Clearly, the amount of ingested alkaloid and the sensitivity of the targeted animal are the key factors leading to intoxication.

Some alkaloids can be extremely harmful to mammals, which is the case of the steroidal alkaloid cyclopamine in lambs, identified as the compound in *Veratrum californicum* (Fam: Melanthiaceae) responsible for teratogen effects.

The possible functions of alkaloids in plants are as:

1. Poisonous agents protect the plant against insects and herbivores.
2. End products of detoxification reactions represent a metabolic locking-up of compounds, otherwise harmful to the plant.
3. Regulatory growth factors.
4. Reserve substances capable of supplying nitrogen or other necessary elements to the plant's economy.

The pharmacologic action of alkaloids varies widely:

1. some (morphine, codeine) are analgesics and narcotics while others (strychnine, brucine) are central stimulants.
2. Some (atropine, homatropine) are mydriatics whereas others (physostigmine, pilocarpine) are myotics.
3. Some (ephedrine) will cause a rise in blood pressure, but others (reserpine) will produce a fall in excessive hypertension.

In fact, the alkaloids are capable of extensive physiologic activity.

PROPERTIES:

Most alkaloids are well-defined crystalline substances which unite with acids to form salts. In the plant they may exist in the free state, as salts or as N-oxides [N-oxides, also referred to as amine oxides, are organic compounds that contain the functional group N^{+}-O^{-}. Amine oxides are weak bases and highly polar molecules. Small amine oxides are found to be hydrophilic in nature and hence possess excellent water solubility]. ln addition to the elements carbon, hydrogen and nitrogen, most alkaloids contain oxygen, and an additional few, coniine, nicotine, and sparteine, which lack oxygen in their molecules, are liquids. Although colored alkaloids are relatively rare, they are not unknown; berberine for example is yellow and the salts of sanguinarine are copper-red.

Alkaloids usually contain one nitrogen atom, although some like ergotamine may contain up to five. The nitrogen may exist as a primary amine (RNH2), as a secondary amine (R2NH), or as a tertiary amine (R3N).

Since the nitrogen atom bears an unshared pair of electrons, such compounds are basic and resemble ammonia in chemical properties. The degree of basicity varies greatly depending upon the structure of the molecule and the presence and location of other functional groups.

Like ammonia, the alkaloids are converted into their salts by aqueous mineral acids, and when the salt of an alkaloid is treated with a hydroxide ion, nitrogen gives up a hydrogen ion and the free amine is liberated. Quaternary ammonium compounds [$R4N^+$ X^-] such as tubocurarine chloride or muscarine chloride have four organic groups covalently bonded to nitrogen, and the positive charge of this ion is balanced by some negative ion. The quaternary ammonium ion, having no proton to give up, is not affected by hydroxide ion; consequently, quaternary ammonium compounds have chemical properties quite different from those of the amines.

In spite of the difficulty in definitely characterizing alkaloids by definition, they do show a surprising number of physical and chemical properties. For the most part, the alkaloids are insoluble or sparingly so in water, but the salts formed upon reacting with acids are usually freely soluble. The free alkaloids are usually soluble in ether or chloroform or other relatively nonpolar, immiscible solvents in which, however, the alkaloidal salts are insoluble. This permits a ready means for the isolation and purification of the alkaloids as well as for their quantitative estimation.

Tests for alkaloids:

Most alkaloids are precipitated from neutral or slightly acid solution by:

- Mayer's reagent (potassium mercuric iodide solution),
- Wagner's reagent (solution of iodine in potassium iodide),
- Solution of tannic acid,
- Hager's reagent (a saturated solution of picric acid),
- Dragendorff's reagent (solution of potassium bismuth iodide).

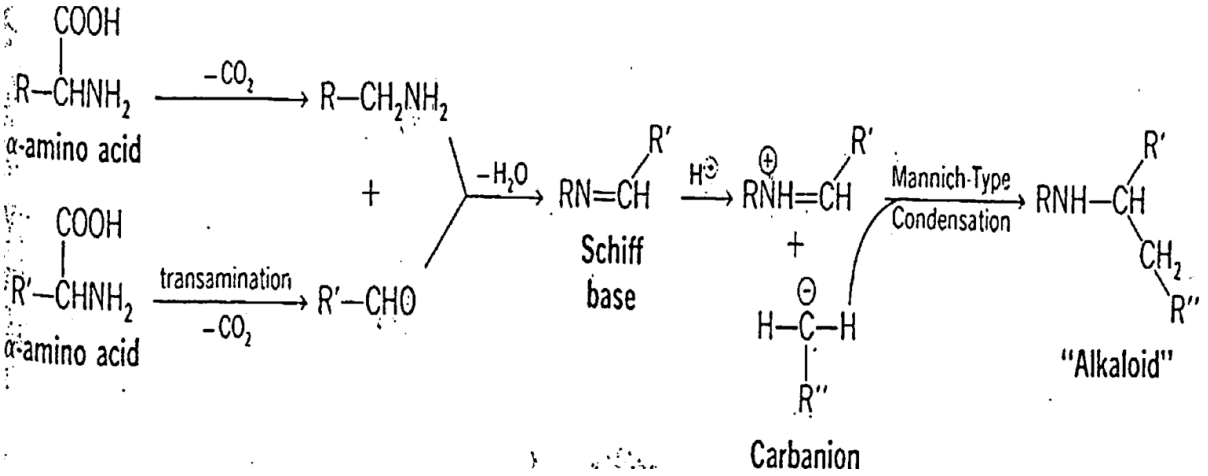
These precipitates may be amorphous or crystalline and are of various colors: cream (Mayer's), yellow (Hager's), reddish-brown (Wagner's and Dragendorff's).

Care must be taken in the application of these alkaloidal tests:

1. The reagents also give precipitates with proteins. During the extraction of alkaloids from the plant and subsequent evaporation, some proteins will not be extracted and others will be made insoluble (denatured) by the evaporation process and may be filtered out.
2. Caffeine, and other purine derivatives, do not precipitate like most alkaloids. It is usually detected by mixing with a very small amount of potassium chlorate and a drop of hydrochloric acid, evaporating to dryness and exposing the residue to ammonia vapor. A purple color is produced, this is known as the murexide test.

Biosynthesis of alkaloids

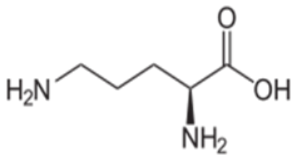
- The biosynthesis of many alkaloids' structures can be rationalized through simple chemical reactions that involve amino acids.
- The general reactions that are of particular importance include the decarboxylation and transamination of the amino acids to yield the corresponding amine or aldehyde respectively.
- These can react to form a Schiff base which in turn, can react with a carbanion in a Mannich type of condensation.



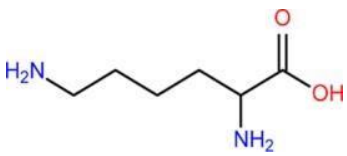
General reactions in alkaloid biosynthesis

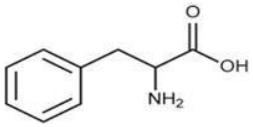
The more amino acids involved in the biosynthesis of alkaloids are:

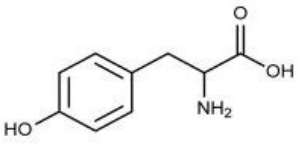
1- Ornithine



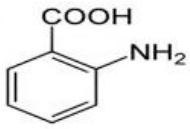
2- Lysine

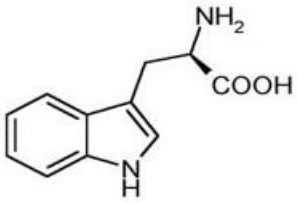


3- Phenylalanine 

4- Tyrosine 

5- Anthranilic acid

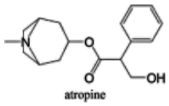
It differs from other amino acids in that the COOH & NH2 groups are not on the same carbon atom. 

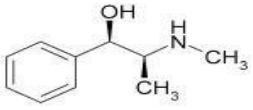
6- Tryptophan 

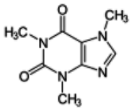
Classification:

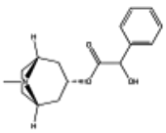
Various schemes for the classification of alkaloids have been suggested:

1. **Due to Hegnauer:**

True (Typical) alkaloids that are derived from amino acids and have nitrogen in a heterocyclic ring. e.g Atropine. 

Proto alkaloids that are derived from amino acids and do not have nitrogen in a heterocyclic ring. e.g Ephedrine. 

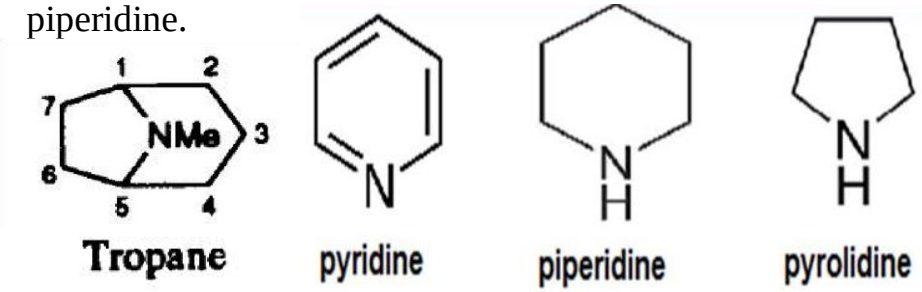
Pseudo alkaloids that are not derived from amino acids but have nitrogen in a heterocyclic ring. e.g Caffeine. 

False alkaloids are non alkaloids give false positive reaction with alkaloidal reagents. e.g. homatropine. 

2. **The following plan is based on the ring structure or nucleus of the chief alkaloid group in the plant drug:**
   (1) Pyridine-piperidine combined.
   (2) Tropane.
   (3) Quinoline.
   (4) Isoquinoline.
   (5) Indole.
   (6) Imidazole.
   (7) Steroid.
   (8) Lupinane.
   (9) Alkaloidal amine.
   (10) Purine.

3. **Alkaloids that classified according to the nature of the basic chemical structures from which they derive:**

1. Arecoline, pelletierine, lobeline, coniine, and nicotine are derivatives of pyridine and piperidine.
2. Atropine, hyoscyamine, and hyoscine are derived from tropane, a consensus on the product of pyrrolidine and piperidine.

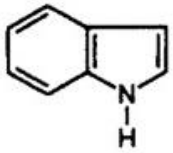


Tropane pyridine piperidine pyrolidine

3. The cinchona alkaloids; quinine, quinidine, cinchonine, and cinchonidine contain quinoline as the principal nucleus; hydrastine, d-tubocurarine, emetine, and certain of the opium alkaloids are characterised by the isoquinoline nucleus.

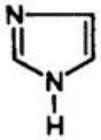
Quinoline Isoquinoline

4. Ergonovine, reserpine, and strychnine which derive from the indole ring.



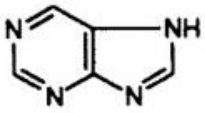
Indole

5. Pilocarpine having the imidazole ring.



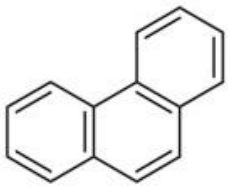
Imidazole

6. Caffeine and theobromine which are purine bases.

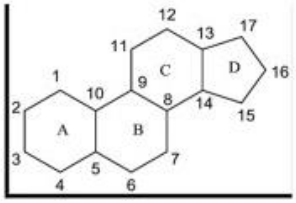


Purine

7. Morphine and codeine possessing the phenanthrene ring, and aconitine and protoveratrine which contains a steroidal structure.



phenanthrene



cyclopentanoperhydrophenanthrene

Extraction of alkaloids:

The extraction by fractional extraction (From less Polar to more Polar):

1. Defeating by non-polar solvents (Petroleum ether, benzene, alkane, etc.), to get rid of Chlorophyll, Wax, Volatile oil and Fixed oil.
2. Filtration, for marc use methanol or ethanol 95% Evaporate by rotary evaporator (to concentrate).
3. Add Tartaric acid 2% and Ethyl acetate will separate into two layers:
   - Organic layer (for weak or neutral alkaloids).
   - Aqueous layer (acidic layer, tartaric acid) which have alkaloidal salt.

To break the salt, add NH3 or Sodium bicarbonate, then add ethyl acetate again so it will separate into two layers again:

- Aqueous layer (Quaternary alkaloids 4º)
- Organic layer (For basic alkaloid 1^0,2º,3º).

Large-scale extractions based on the above principles and the crude mixtures of alkaloids afterwards sent to a factory for separation and purification. This has been done for both cinchona and coca alkaloids by fractional precipitation or by fractional crystallization of salts such as oxalates, tartrates or picrates.

Purification of the extract:

- **Direct crystallization:**

The simplest procedure, but it is seldom successful when a crude mixture is involved.

The extract is evaporated to dryness and the residue is dissolved in a crystallizing solvent, which may be either a single organic solvent or a mixture of two solvents.

In general, order of increasing solubility of most alkaloids is as follows:

Hexane, benzene, ether, ethyl acetate, methanol, acetone, chloroform and dioxane.

- **Steam distillation:**

It is used in rare cases, for liquid alkaloids e.g. coniine, nicotine and sparteine.

- **Crystallization of sparingly soluble salts:**

The choice of acid is unlimited, but HCl, HBr, oxalic, picric, perchloric, sulfuric, maleic, and tartaric acids are among the widely used acids.

The general procedure for hydrohalides involves dissolving the crude base in methanol or acetone and adding an ethereal solution of the acid.

Oxalates, picrates and perchlorates are usually formed by mixing methanolic solutions of the base and the acid.

Distribution between immiscible solvents:

The alkaloids are taken up in a dilute acid solution. From this, it may be possible to recover the alkaloids by the addition of ammonium hydroxide solution and extract with water immiscible organic solvent. The choice of organic solvent for this method is usually limited to benzene, chloroform or ether.