College of pharmacy /Al-Nahrain University

3rd stage/ 2nd coarse

Alkaloids

Pharmacognosy III -Lecture 1

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Objectives

- Introduction: Alkaloid's definition and history
- Occurrence of alkaloids
- Chemical properties of alkaloids
- Nomenclature
- Hegnauer Classification of alkaloids
- Pharmacological actions of alkaloids
- Extraction & isolation of alkaloids
- Classification of alkaloids
- Biosynthesis of alkaloids

Introduction: Alkaloid's definition and history

- Alkaloids are organic **nitrogen** containing compounds **generally** in a **heterocyclic** ring, they are basic, so alkaloids can be defined as basic organic compounds **containing one or more nitrogen atom** usually in a hetero cyclic ring, most of them have a marked **physiological action** on human beings or animals and are derived from **a natural source**. The general structure is **R-N.**
- **History:** The name alkaloids is derived from alkali, this was proposed by a pharmacist in 1819.
- The first isolation was reported when percolation method was introduced as a method of extraction in the beginning of the 19th century, so we can say that the **first alkaloid isolated in 1803 by a French apothecary** & it was found to be **narcotine**. Then comes **Serturner** who isolated **morphine** from opium. Then a group of scientists, headed by Pelletier isolated **strychnine.**

Occurrence of alkaloids

- Alkaloids are found in natural products like **plants , animals and fungus.**
- Alkaloids are **very toxic** and are found **in very small percentage** in plant. Alkaloids could be found in any part of the plant.
- Alkaloids are found in the plants as **a protection**, **growth factor** & **nitrogen nature source (nitrogen storage)**.
- Generally, most of the **higher plants** (Angiospermae) & flowering contain alkaloids.
- **Microorganisms** also contain alkaloids, e.g., ergot which is a fungus rich in alkaloids.
- Some animals **(Ecuadorian frog)** produce alkaloids as a defense.



Chemical properties of alkaloids

- **Alkaloids are basic compounds**, contain up to five nitrogen atoms.
- However, **not all nitrogen containing compounds are alkaloids** for example proteins and carbohydrates.
- Also, **not all alkaloids are basics** since , Sometimes nitrogen is found as **an amide which has no basicity.**
- Degree of basicity depends on structure and functional groups

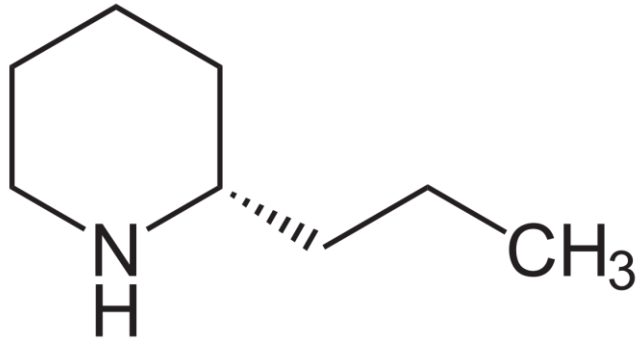
1) Amide nitrogens are less basic than the corresponding amines.
This is due to delocalization of the lone pair of the nitrogen.



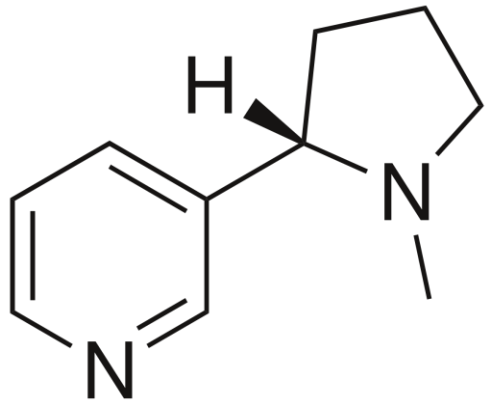
resonance delocalization of nitrogen lone pair

Physical properties of alkaloids

- Most alkaloids are colorless with some exceptions e.g. **berberine** **which is yellow, &** **salt of sanguinarine** **which is red.**
- They are amorphous or crystalline & some are liquids.
- **If an alkaloid does NOT contain oxygen then it is a liquid, Nicotine & coniine are liquid alkaloids.**



Coniine



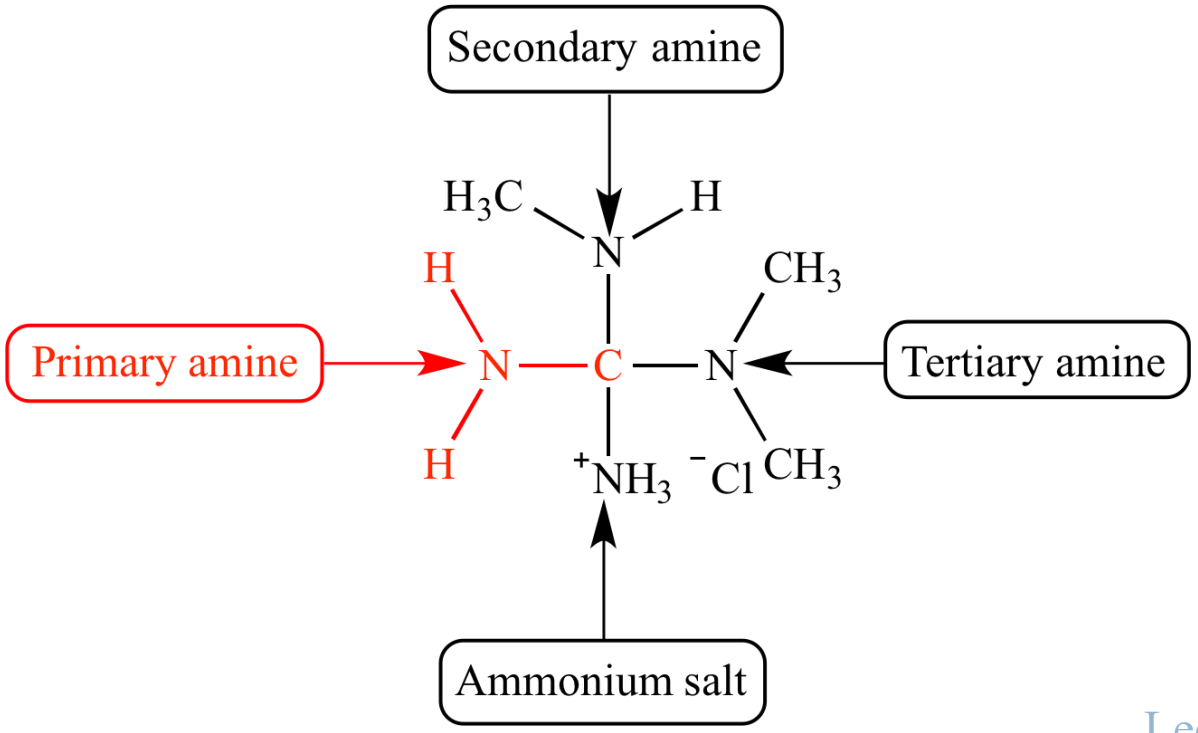
Nicotine

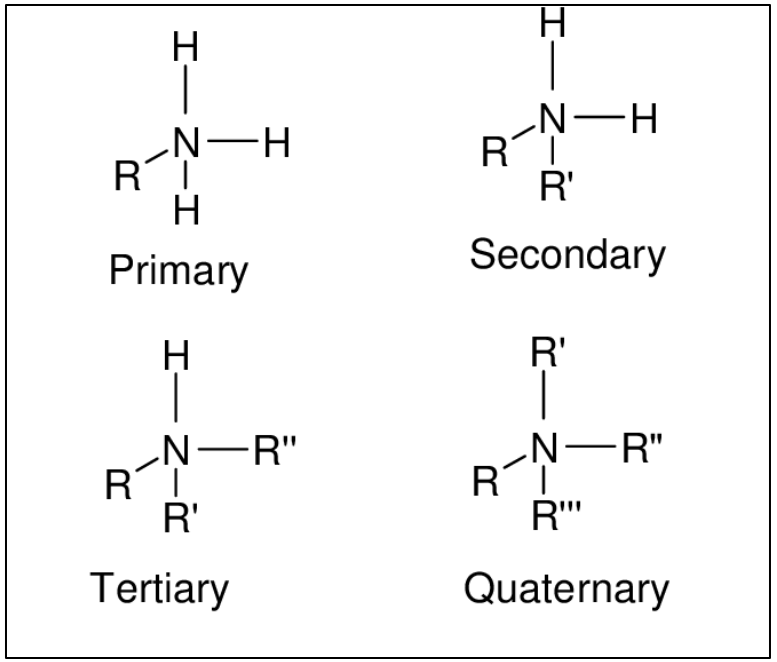




Chemical properties of alkaloids

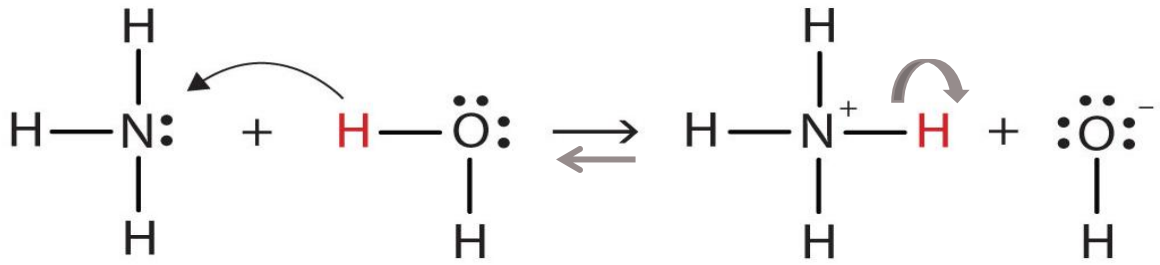
- The nitrogen may exist as a primary amine (RNH2), or as a secondary amine (R2NH), or as a tertiary amine (R3N) & quaternary amine.





Chemical properties of alkaloids

- The degree of basicity varies greatly, depending on the structure of the molecule & presence & location of other functional groups.
- Alkaloids are found in two forms namely, **free state (free base)** & **salt form**.
- Just like **ammonia the alkaloids are converted into their salts by aqueous mineral acids .**
- **when the salt of an alkaloid is treated with hydroxide ion (base), nitrogen gives up a hydrogen ion, and the free amine (free base) is liberated.**

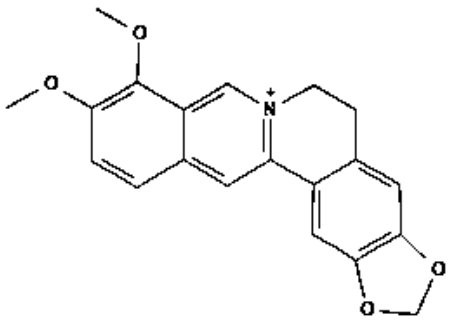


Hydrogen ion acceptor: B-L base

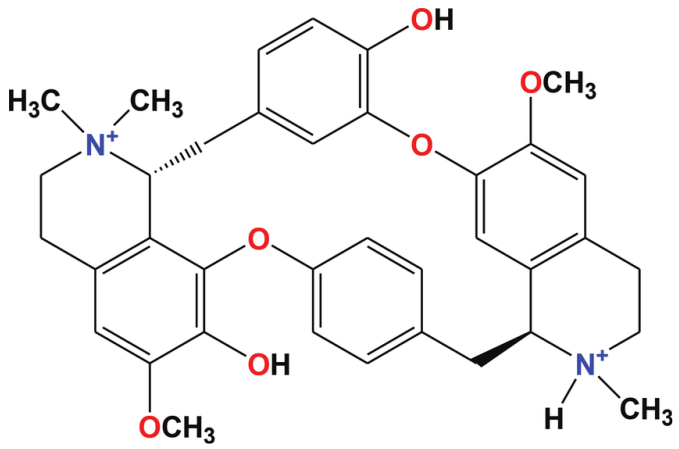
Hydrogen ion donor: B-L acid

Chemical properties of alkaloids

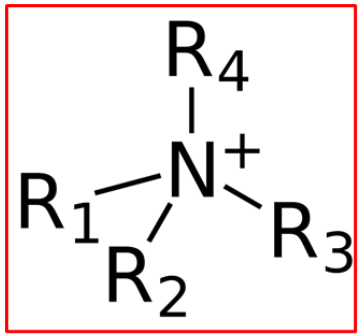
- **Quaternary ammonium compounds** (quaternary alkaloids), such as **tubocurarine chloride**, **berberine chloride**,
- Have four organic groups covalently bonded nitrogen, & the **positive charge** of this ion is balanced by some negative ion. The **quaternary ammonium ion, have no proton to give up, is not affected by hydroxide ion. Quaternary ammonium compounds have chemical properties quite different from those of amines.**



Berberine chloride



Tubocurarine chloride



- Always charged
- Cannot lose proton
- Different properties

Chemical properties of alkaloids

- **Alkaloids free base are insoluble in water**, but with acids, **salts are freely soluble in water.**
- **The free alkaloids are usually soluble in ether, chloroform, or other relatively nonpolar water immiscible solvents** in which the alkaloids salts are insoluble. This permits a ready means of the isolation & purification of the alkaloids.
- **There are certain exceptions for the solubility**
- **Caffeine,** a free alkaloid base, is **soluble in water.**
- **Quinine sulfate** salt, is **soluble in organic solvents**.
- **Alkaloids, form double salts with compounds of mercury, gold, platinum & other heavy metals**. **These double salts are usually obtained as precipitates.**

Chemical properties of alkaloids

- This makes the basis for alkaloids reagents:
- **Mayer's reagent** (**potassium mercuric iodide solution**),
- **Wagner's reagent** (solution of **iodine in potassium iodide**),
- **Hager's reagent** saturated **solution of picric acid**),
- **Dragendorff's reagent** (solution of **potassium bismuth iodide**).
- The precipitates obtained are amorphous or crystalline of various colors e.g., **cream (Mayer)**, **yellow (Hager's), reddish-brown (Wagner's & Dragendorff's).**
- **Pseudoalkaloids like Caffeine & some other alkaloids do not give precipitates**
- Care must be taken in the application of these alkaloid's tests, **as the reagents also give precipitates with proteins.**

Nomenclature

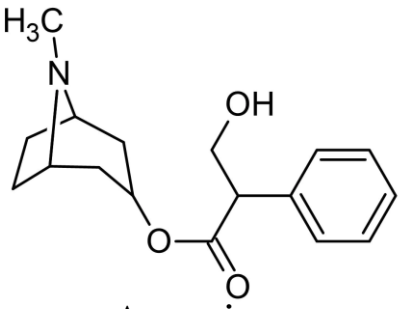
- There are several methods for the nomenclature of alkaloids:

1. According to the **genus** e.g., Atropa belladonna which contains **atropine**.
2. According to the **species** e.g., Atropa belladonna which contains **belladonine.**
3. According to the **name of the drug** e.g., ergot which contains **ergotamine & ergometrine.**
4. According to the **pharmacological activity** e.g., **emetine** which causes emesis.
5. According to the name of **the scientist** e.g., **pelletierine** according to the scientist Pelletier.

Hegnauer Classification of alkaloids

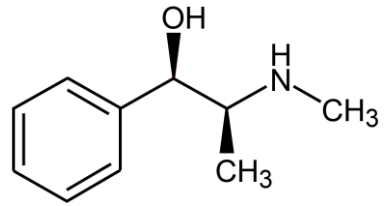
One of the classifications (due to Hegnauer), groups the alkaloids as:

1) **True alkaloids**: they show a wide range of physiological activity; they are basic & normally **containing a nitrogen in a heterocyclic ring**; they are **derived from amino acids** & they normally occur in the plants as **the salt** of an organic acid (atropine)



Atropine

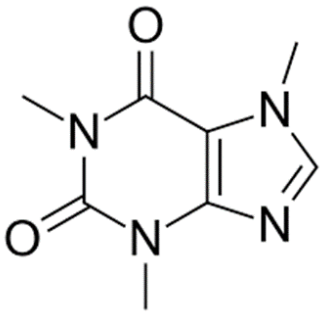
2) **Proto alkaloids**: they are relatively simple amines in which the **nitrogen is not in a heterocyclic ring**. They are **biosynthesized from amino acids & are basic**.



Ephedrine

The term "**biological amines**" is often used for this group of compounds e.g., ephedrine.

3) **Pseudo alkaloids**: those are **not derived from amino acids**. They are usually basic and **the nitrogen in a heterocyclic ring**. There are two important series of alkaloids in this class, the **steroidal alkaloids & the purine bases** e.g., caffeine



caffeine

Pharmacological actions of alkaloids

- Alkaloids are capable of extensive pharmacological activities e.g.
- 1. Morphine and Codeine: are **analgesics & narcotics**.
- 2. Strychnine and Brucine are **central stimulants**.
- 3. Atropine and Homatropine are **mydriatics**, while Physostigmine and pilocarpine are **myotics.**
- 4. Ephedrine: **(hypertensive agent)/ decongestant**
- 5. Reserpine: fall in excessive hypertension (**hypotensive agent**)











Extraction & isolation of alkaloids

- Alkaloid extraction is based on **one main principle**: alkaloids are **weak bases**, so we can move them between organic and aqueous layers by **changing pH** (converting alkaloids between salt and free base forms using **acid–base treatment**)

➢ Using organic solvents for **extraction** mainly **ethanol.**

➢ **Convert alkaloids to salt using acid**: Add an **acid** to **change the free alkaloid base to salts**,

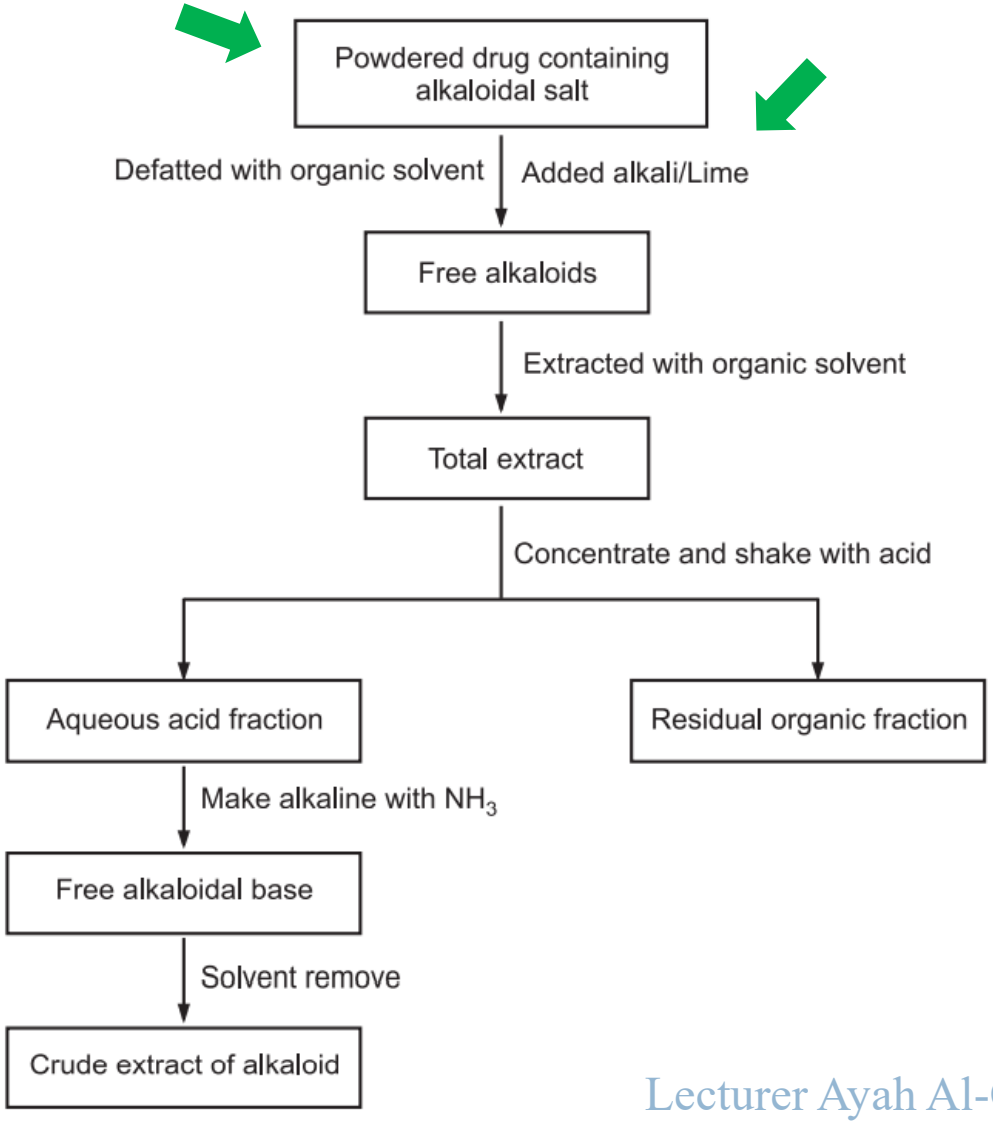
➢ Addition of **base-**(ammonia) **to turn it back to a free base**

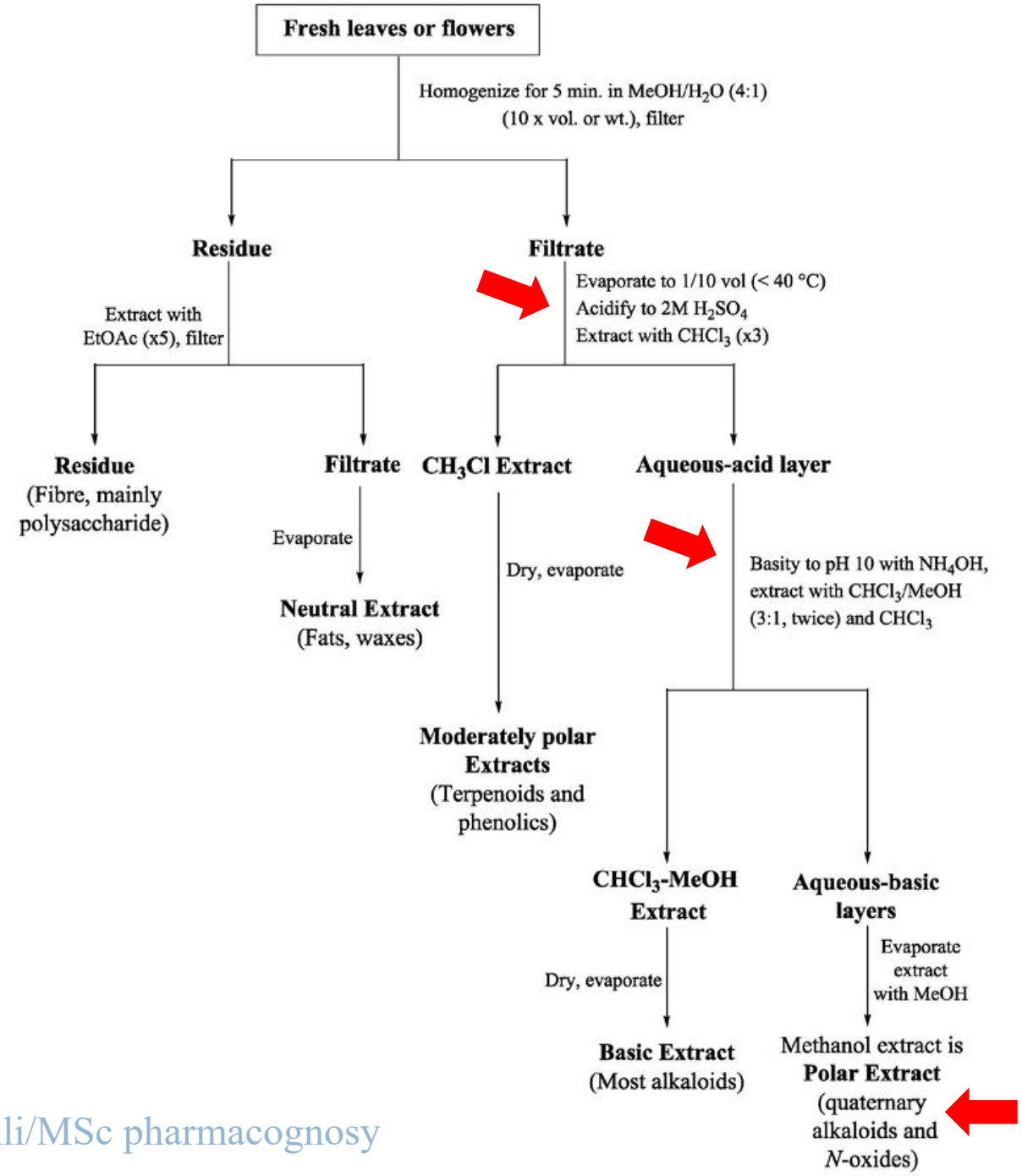
➢ Then the **free alkaloidal base is isolated by an immiscible organic solvent (partition).**

➢ **Separate and purify**

- If the plants is already rich with **alkaloidal salts, treat with ammonia first** (**we turn it to free base by maceration in ammonia)**
- **Quaternary alkaloids are always charged, so acid or base does not change their solubility.** That's why they remain in the aqueous layer and require polar solvents like methanol."

General procedure of alkaloid extraction





Classification of alkaloids

There are many classification procedures:

1. Depending on the pharmacological activities; e.g., central stimulant, narcotics.

2. Depending on the biosynthetic precursors (amino acid precursor):

- **Ornithine-derived alkaloids** like tropane, pyrrolizidine alkaloids.
- **Lysine-derived alkaloids like** lobelia, pomegranate, pepper.

3. Depending on the basic ring structure (nucleus) as:

- 1. Pyridine-piperidine-pyrrolidine alkaloids
- 2. Tropane alkaloids
- 3. Quinoline alkaloids
- 4. Iso-quinoline alkaloids
- 5. Indole alkaloids
- 6. Imidazole alkaloids
- 7. Lupinane alkaloids
- 8. Steroidal alkaloids
- 9. Alkaloidal amines
- 10. Purine bases

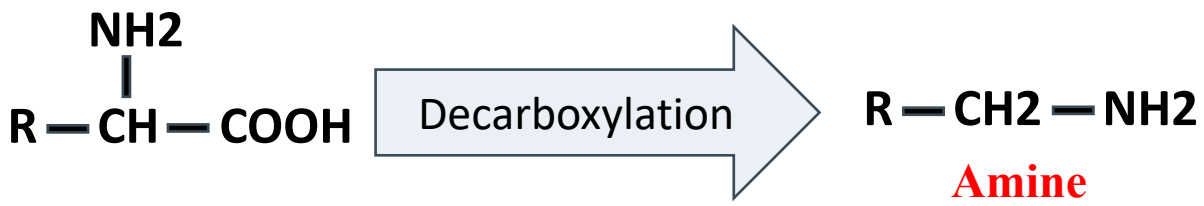
Biosynthesis of alkaloids

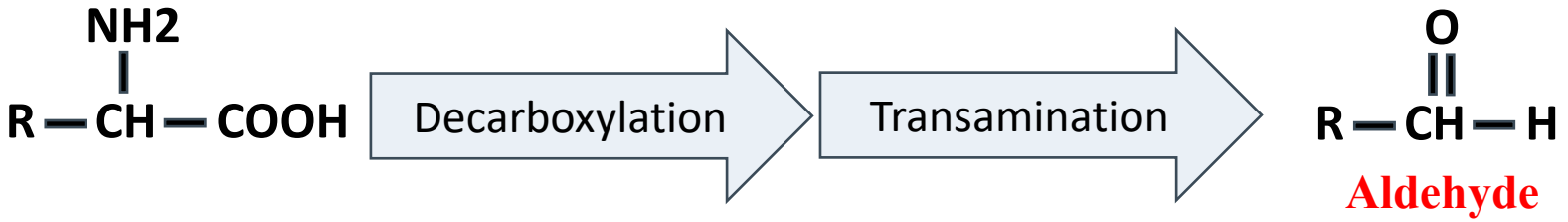
- The biosynthesis of many alkaloid structures is through simple chemical reactions that **involve amino acids.**
- The general reactions that are of particular importance include the **decarboxylation** & **transamination** of the amino acids to yield the corresponding **amine** or **aldehyde**, respectively.
- These can react to form a **Schiff base** which in turn, can react with a compound containing **carbonyl** group in a **Mannich type of condensation.**
- **What reacts?**

1. Amine (from amino acid)
2. Carbonyl compound
3. Formation of Schiff base
4. Reaction with another carbonyl compound
5. Formation of β-aminocarbonyl compound.

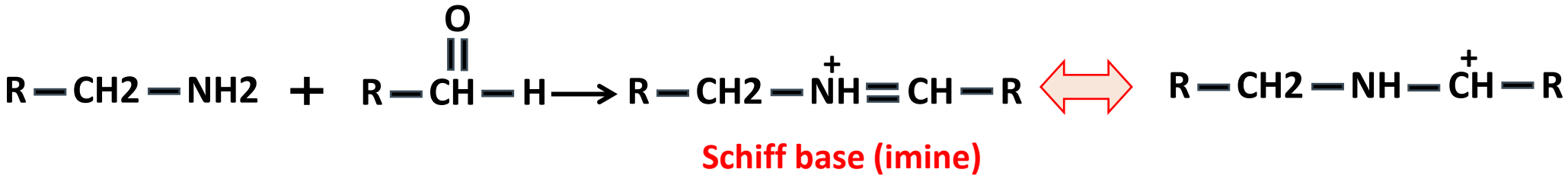
- Cyclization + modifications =ALKALOID

Alkaloids originate from amino acids which are converted into amines or aldehydes

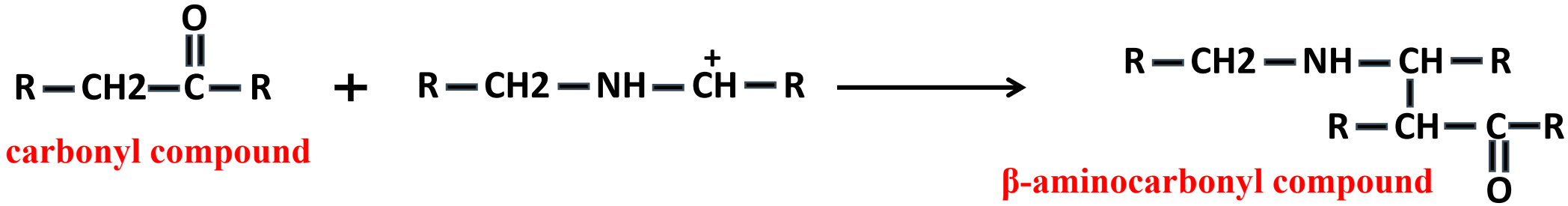




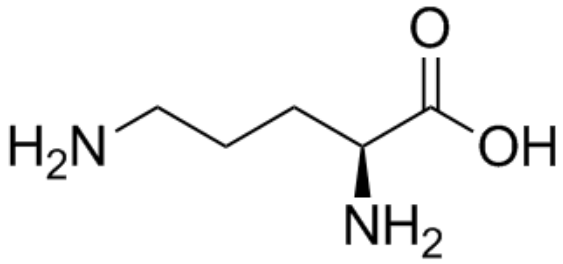
This step activates nitrogen for incorporation into alkaloid skeleton



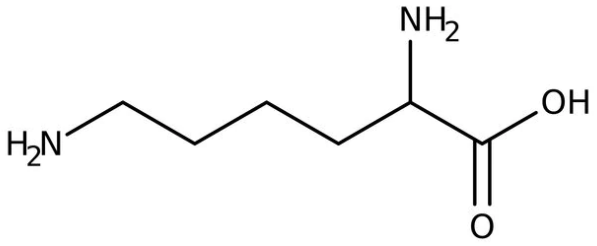
Mannich type of condensation



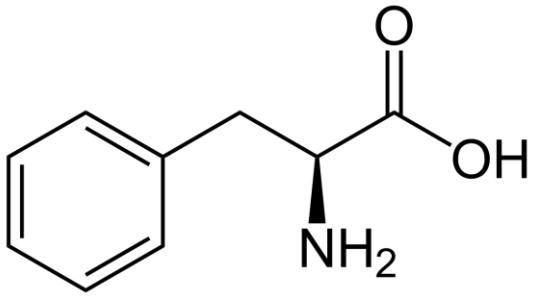
The major amino acids involved in the biosynthesis of alkaloids are:



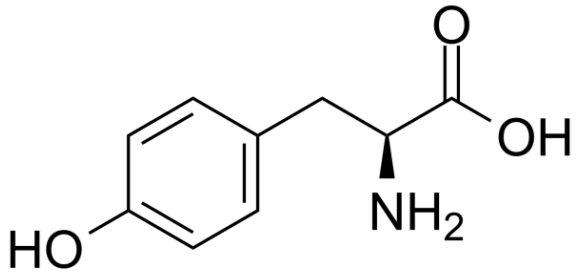
1-Ornithine



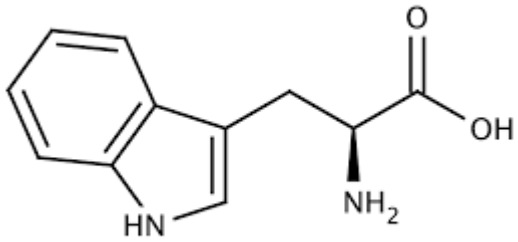
2- Lysine



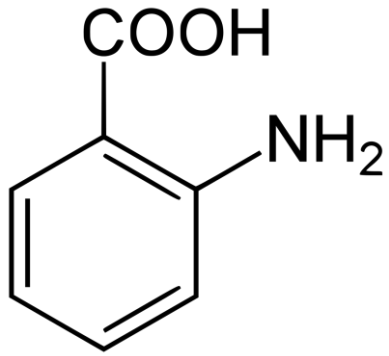
3. Phenylalanine



4. Tyrosine



5- Tryptophan



6- Anthranilic acid

It differs from other A.A that COOH group and NH2 are not on the same carbon atom

THE END