Alkaloids

Plan

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- The term "**alkaloid**" was proposed by the pharmacist W. Meissner in 1819 to cover a group of natural substances, which were "**vegetable alkalis**".
- An alkaloid may be defined as a naturally occurring organic base containing one or more heterocyclic nitrogen atoms in its molecule. Alkaloids possess pharmacological activity and have economic importance as clinical agents.

Nomenclature

- The name of all alkaloids should end with the suffix '***-ine***'.
- The names of the alkaloids are obtained in various ways:

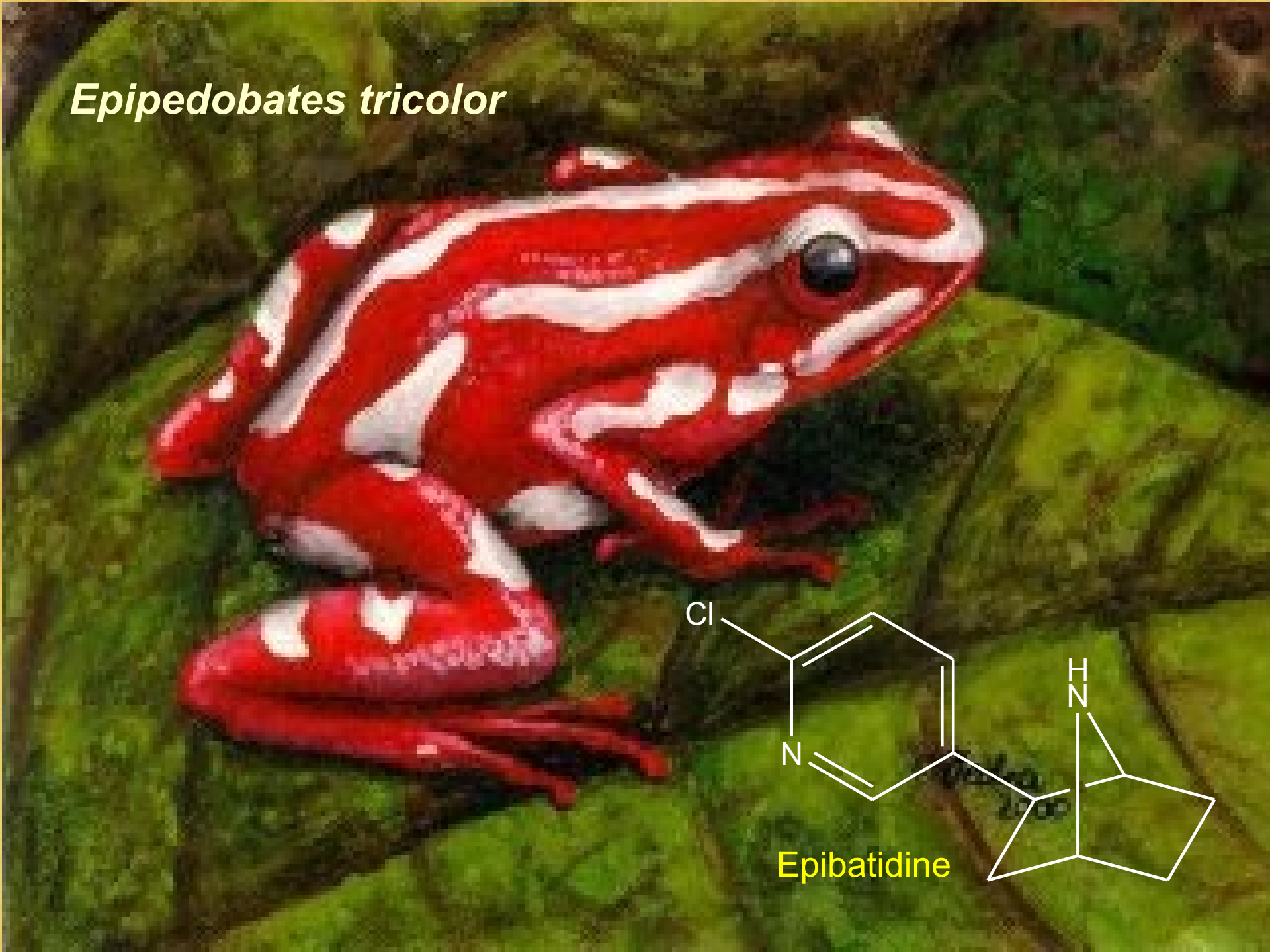
1. From the generic name of the plant yielding them, e.g. *atropine*.
2. From the specific name of the plant yielding them, e.g. *cocaine*.
3. From the common name of the drug yielding them, e.g. *ergotamine*.
4. From their physiologic activity, e.g. *emetine*.
5. From the discoverer, e.g. *pelletierine*.

Distribution in plant kingdom

- Alkaloids are not found in all plants and appear to be present in only about 10 - 15 % of vascular plants. Although they are present in some fungi (eg, *Claviceps* [ergot], *Penicillum),* they are mainly known from dicotyledonous plants and particularly from certain families such as Apocynaceae (eg, *Rauwolfia, Catharanlhus),* Fabaceae (eg, *Physostigma),* Loganiaceae (eg, *Strychnos),* Papaveraceae (eg. *Papaver),* Rubiaceae (eg, *Cinchona),* Solanaceae (eg, *Atropa, Nicotiana).*

- Within a particular organ they may be concentrated in one tissue (eg, *Atropa* leaf—epidermis, nerves).
- The contents of alkaloids in plants are small and ranges from thousandth shares of percent to some percents.
- For example, the bark of cinchona contains 15-20% of alkaloids. The content of alkaloids in medicinal plant raw material often ranges from 0,1 to 2%.
- Alkaloids are dissolved in cellular juices in plants and they form **salts** with organic acids: malic acid, citric acid, oxalic acid; in some plants they combine with specific acids, for example with meconic acid in papaver, with quinic acid in cinchona.

Epipedobates tricolor



Epibatidine

Accumulation of alkaloids

- Accumulation of alkaloids depends on age and phase of development of plant and on factors of outside environment (Light, soil, climate conditions, geography factor etc). In over-ground organs the largest number of alkaloids are accumulated in the phase of flowering: and in autumn their contents is decreased. The largest number of alkaloids are accumulated in southern regions, in northern ones their contents is decreased.

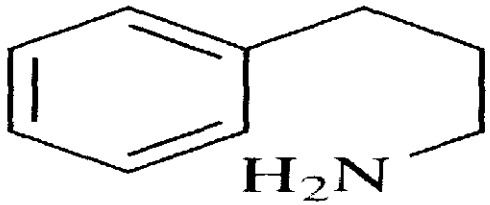
Functions of alkaloids in plants

- There are several speculations about the advantages of their presence in plants, including:

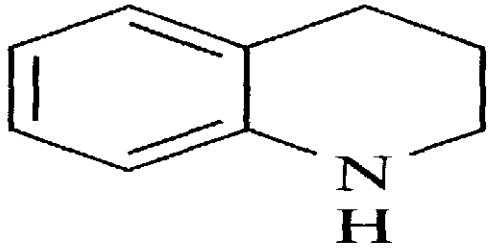
1. Poisonous agents protecting the plant against insects and herbivores "Animals that feed chiefly on plants".
2. End products of detoxification reactions.
3. Regulatory growth factors.
4. Reserve substances capable of supplying nitrogen or other elements necessary to the plant's economy.

Physico-chemical properties

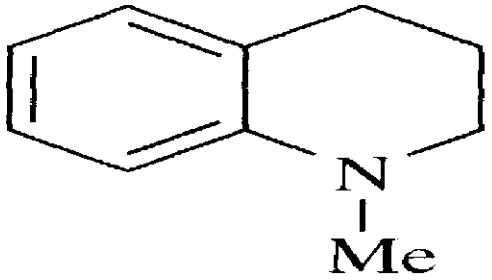
- Most alkaloids are well-defined crystalline substances which unite with acids to form salts.
- In the plant they may exist in the free state, as salts or as *N*-oxides.
- In addition to the elements carbon, hydrogen and nitrogen, most alkaloids contain oxygen.
- A few, such as coniine from hemlock and nicotine from tobacco, are *oxygen-free and are liquids*.
- Although colored alkaloids are relatively rare, berberine, for example, is yellow and the salts of sanguinarine are copper-red.



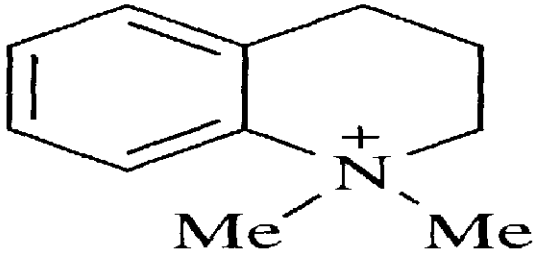
Primary amine
(basic)



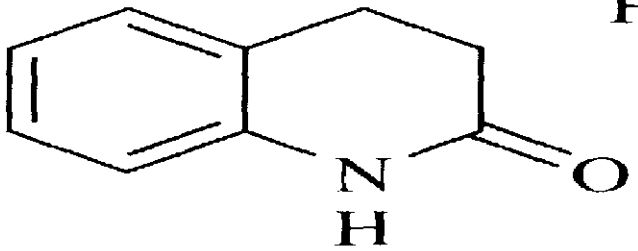
Secondary amine
(basic)



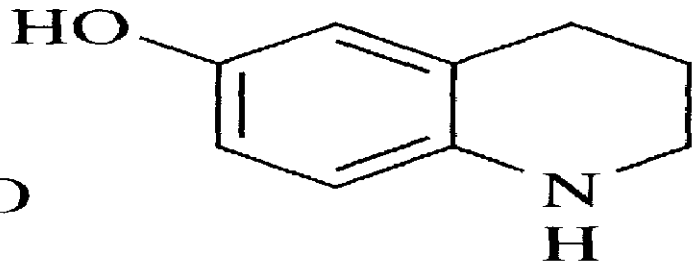
Tertiary amine
(basic)



Quaternary amine
(neutral)



Amide alkaloid
(neutral)



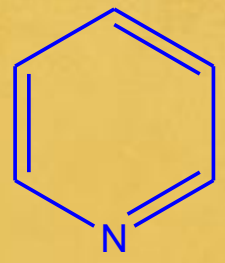
Phenolic alkaloid
(acidic and basic)

- As a general rule, alkaloids as bases are not soluble or are sparingly soluble in water, soluble in apolar organic solvents.

- The basicity of alkaloids varies greatly, since this property depends entirely on the availability of the lone pair of electrons on the nitrogen atom:

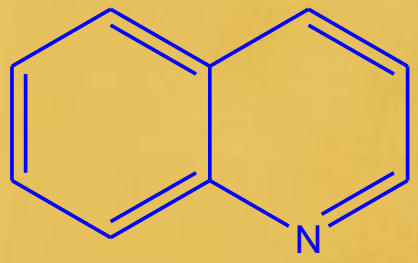
1. ***Electron-withdrawing*** groups in close proximity to the nitrogen atom decrease the basicity, whereas
2. ***Electron-donating*** groups enhance the basicity.

- *The basic character of the heterocyclic ring itself varies:*

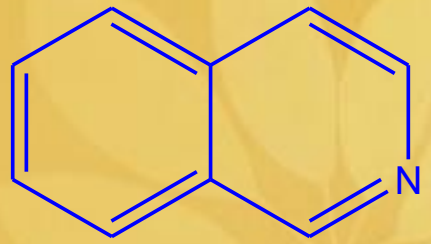


Pyridine

- in the molecule of ***pyridine***, with 6 π electrons, and in the case of *quinoline* and *isoquinoline*, the lone pair of electrons on the nitrogen atom is available and the basicity is clear.



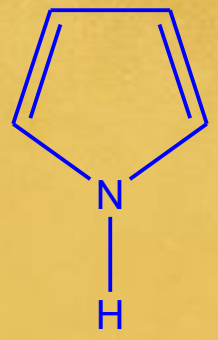
Quinoline



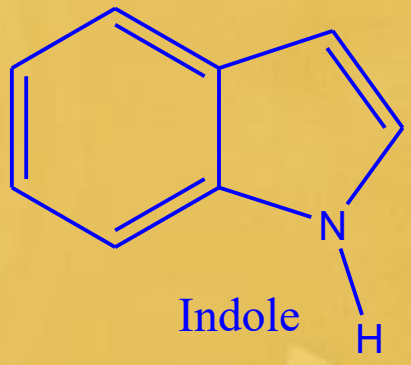
Isoquinoline

- In the case of ***pyrrole*** or *indole,* the lone pair of electrons on the nitrogen atom plays a role in the aromatic character, and the compounds are not basic (they are acidic).

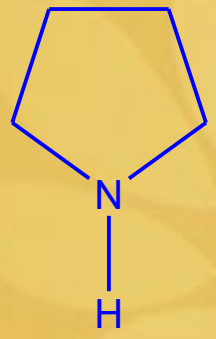
- Another example is ***pyrrolidine,*** which is saturated, and is a strong base.



Pyrrole



Indole



Pyrrolidine

Biosynthetic origin

- **Alkaloids** are formed from amino acids, but other precursors, e.g. terpenes or steroids, are often also built into the final alkaloidal skeleton.
- The amino acids that most often serve as alkaloidal precursors include:

  phenylalanine (*epedrin*), tyrosine (*isoquinolin*), tryptophan (*indole, quinolin*), histidine (*imidazole*), anthranilic acid, lysine (*piperidin, chinolizidin*) and ornithine (*pyrrolidin, tropane, pyrolyzidin*).

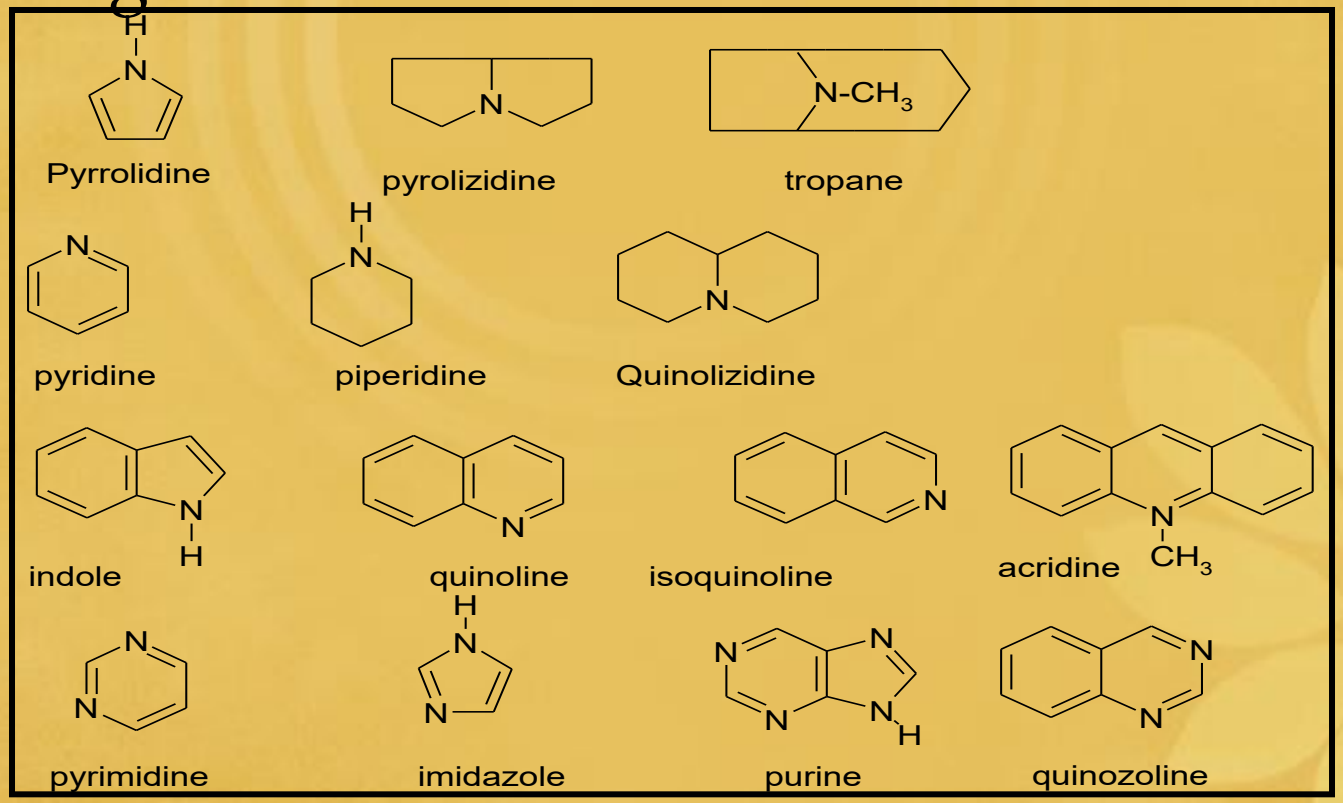
Classification

Alkaloids are usually classified according to the nature of the basic chemical structures from which they derive.

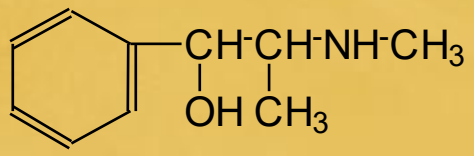
Generally, there are 3 broad divisions:

1. **Typical alkaloids**.
2. **Protoalkaloids**
3. **Pseudoalkaloids**

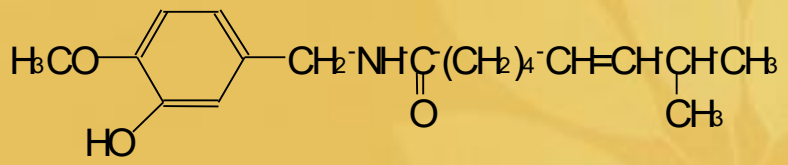
- ***Typical alkaloids*** are derived from amino acid precursors, they are basic, they contain one or more nitrogen atoms (usually in a heterocyclic ring) and they usually have a marked physiological action on man or other animals. Typical alkaloids or heterocyclic, divided into ***14 groups*** according to their ring structure.



- The name ***'proto-alkaloid'*** or 'biological amines' is sometimes applied to compounds such as capsaicin, ephedrine and colchicine which lack one or more of the properties of typical alkaloids.
- The alkaloids in this group do not contain heterocyclic nitrogen atoms. Many are simple derivatives of phenylethylamine and as such, are derived from the common amino acids, phenylalanine or tyrosine.



ephedrine

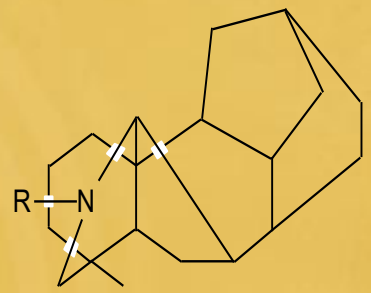


capsaicin

The term *'pseudoalkaloid'* has been introduced to cover alkaloids, which are formed from terpenes.

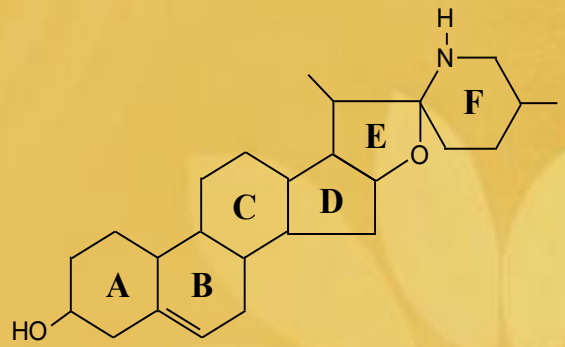
They divide into 2 groups:

- 1. **Diterpenoid** alkaloids. These alkaloids are contained in Aconitum. These alkaloids are: aconitine, lyctonine.



Aconitin

- 2. **Steroidal** alkaloids. The steroidal alkaloids are characterized by the cyclopentenoperhydrophenantherene nucleus. Solasodine, veratrum, alkamine esters and their glycosides are the main alkaloids of this group. They occur in genus: Solanum, Veratrum.



Solasodine

Extraction of alkaloids

- There are several methods that can be used for the extraction of the alkaloids from plant materials. However, the common procedures are largely based on: **(1)** the basic nature of most alkaloids; **(2)** the subsequent ability to form salts with acids; **(3)** the ease by which the free bases can be liberated from their salts by alkalinization and finally **(4)** the relative solubility of the alkaloids and their salts in water and various organic solvents.
- The conventional process involved in the alkaloids separation and isolation may be divided as follows:

Method 1

1. Preparation of the sample.
2. Liberation of the free alkaloidal base, by treating the dried material with suitable alkali.
3. Extraction of the **alkaloidal base** with an organic solvent.
4. Purification of the alkaloidal extract.

Method 2

1. Preparation of the sample.
2. Convertion all alkaloids in salts, by treating the dried material with suitable acid.
3. Extraction of the **alkaloidal salts** with a water.
4. Purification of the alkaloidal extract.

Qualitative identification

- There are several general reagents, which may be used to test the presence of alkaloids or to help their identification. This includes the alkaloidal precipitating reagents and the alkaloidal coloring reagents. In addition, there are some special reagent that can be used for recognizing and confirming the identity of each alkaloid.
- ***Alkaloidal precipitating reagents*:**

1. **Mayer's reagent** (potassiomercuric iodide solution)
2. **Wagner's and Bushard's reagent** (solution of iodine in potassium iodide)
3. **Dragendorff s reagent** (potassium bismuth iodide)
4. **Marme reagent** (solution of iodide of cadmium in potassium iodide)
5. **Tannins solution**

- ***Alkaloidal coloring reagents*:**

1. **Marqui's reagent** (Formaldehyde-sulfuric acid)
2. **Mandalin's reagent** (sulphovanadic acid)
3. **Erdmann's reagent** (Nitric acid-sulfuric acid)

- ***Alkaloidal specific reagents*:**

1. **VitaliMorin reagent** (for tropanes),
2. **p-dimethytaminobenzaldehyde** (for indoles).

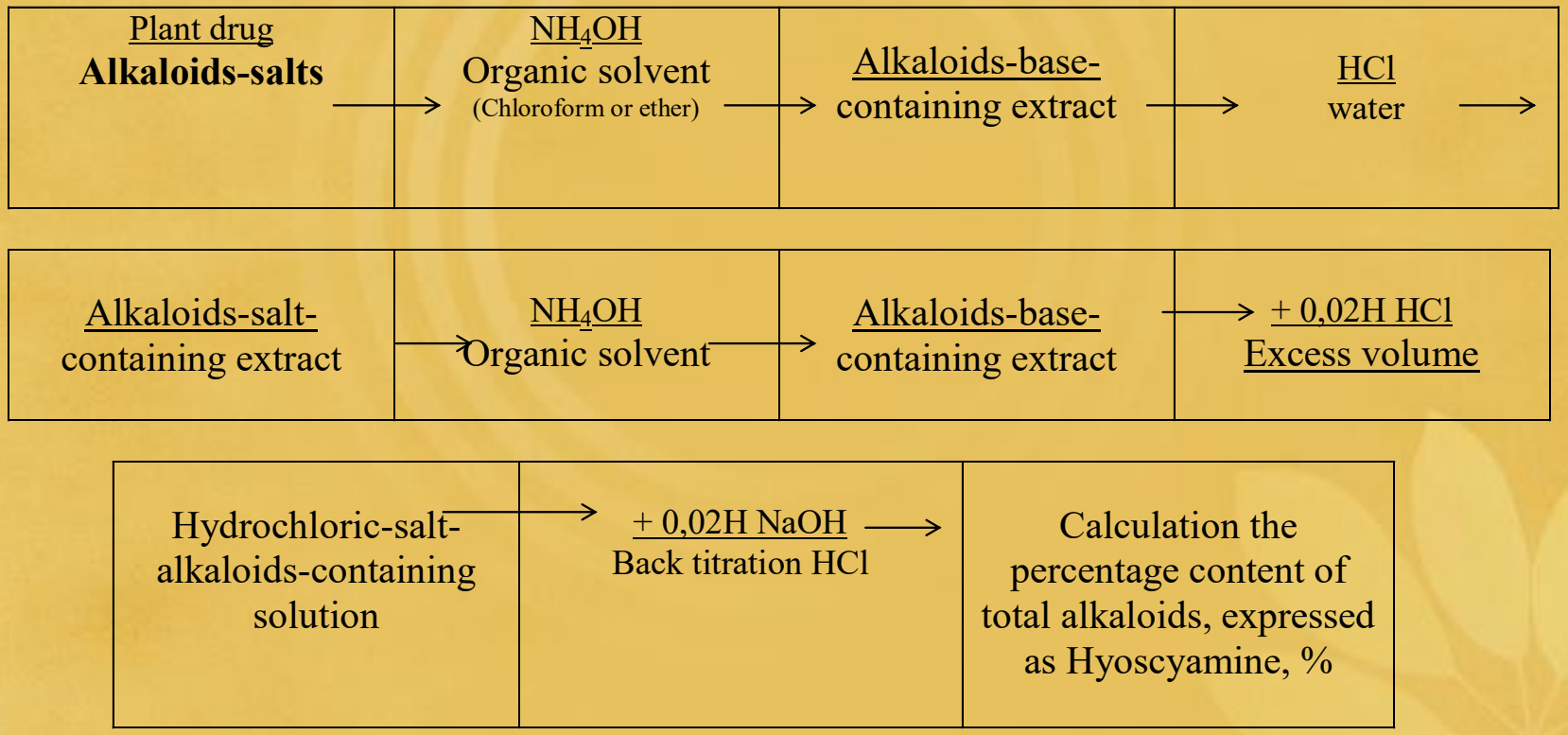
QUANTITATIVE IDENTIFICATION

For quantitative identification of alkaloids volumetric, gravimetric and physico-chemical methods of analysis are used.

All method of quantitative test has 3 steps:

1. Extraction of alkaloids
2. Purification of alkaloids
3. Test of alkaloids

Quantitative test for tropane-containing plant drug



Pharmacological activity and uses

- *Alkaloids are particularly interesting substances because of their multiple pharmacological activities*:

1. on the CNS, whether they are

depressants (**morphine**) or

stimulants (**caffeine**);

on the autonomic nervous system:

sympathomimetics (**ephedrine**) or

sympatholytics (**yohimbine**, certain ergot alkaloids),

parasympathomimetic (pilocarpine),

In addition, alkaloids include

- *local anesthetics* (**cocaine**),
- *agents to treat fibrillation* (**quinidine**),
- *antitumor agents*(**vinblastine**)
- *antimalarials* (**quinine**),
- *antibacterials* (**berberine**),
- *amebicides* (**emetine**).
- *anti cholinergics* (**atropine**, hyoscyamine),
- or *ganglioplegics* (nicotine).

Drying and storage of alkaloid containing crude drugs

Alkaloid containing crude drugs must be stored according to the list requirements: ***B list*** (these drug substances require *caution* in handling, storage and use)**.**

An exception to the rule are:

- **Colchicum corm (*Bulbotuber Colchici)***
- **Nux vomica seeds *Semen Strychni***

These drug must be stored according to the **list A (poisonous drug substances)**

Pure alkaloids must be stored according to the **list A.**

tincture, extracts - according to the ***B list***

- **In order to keep crude drugs as long as possible:**

It is necessary to store them in a dry condition in carefully closed containers.

It is also advisable to exclude light, because - even if it does not affect the active constituents - it almost always causes changes in the appearance of the drug, especially loss of color.

It is also necessary to protect the drug against insect attack.