Alkaloids

1. Alkaloids are alkaloid-like.
2. History of the discovery of alkaloids.
3. Distribution in nature.
4. Classification of alkaloids.
5. Physical and chemical properties of alkaloids.
6. Dynamics of alkaloid formation.
7. Methods of isolation and analysis of alkaloids.
8. Harvesting of medicinal raw materials, containing alkaloids.

- Alkaloids are nitrogen-containing compounds that have the properties of bases, i.e. they can form salts with acids.

- The name "alkaloids" comes from two words: Arabic "alcali" - alkaline and Greek "eidos" - similar.

- However, the simplest amines, amino acids, cannot be classed as alkaloids because they do not possess the corresponding biological properties.

Alkaloids are produced by plants, less commonly by animals. Most alkaloids are cyclic compounds.

The discovery of the first alkaloid was preceded by achievements of French pharmacists at the end of the 18th century, when in 1792 a resinous substance containing an entire group of alkaloids was obtained from cinchona bark and in 1797 a crystal salt, which represented an crude alkaloid - narcotin, was obtained from opium. In 1802, Deron also obtained an opium salt including a mixture of narcotine and morphine, and in 1804 Séguin obtained morphine from opium and studied its properties, but did not give it a name. This was done in 1806 by the German pharmacist Sertürner, who proved its therapeutic effect, characterised by its sedative effect.

Later, pharmacists and chemists discovered a number of the most important alkaloids in long-known medicinal plants.

The systematic study of alkaloid bearing plants began in our country in 1928, when in Moscow the Department of Chemistry of Alkaloids was headed by Academician A.P. Orekhov (1881-1939). As a result of systematic expeditions to various regions of the country more than 1500 wild plants have been studied, among which more than 200 alkaloid bearing plants have been identified. Their study has led to the creation of valuable medicines.

The main problem in the study of alkaloids was to establish their structure and develop methods of isolation. In Russia there was no industrial isolation of alkaloids until the end of 1915. In the same year, Rodionov organised the first production of opium alkaloids.

Significant progress in the study of alkaloids was made by domestic chemists and pharmacists. Thus in the 20 years before 1950, 400 new alkaloids had been identified throughout the world, including about 120 isolated in our country.

V.S. Sokolov proposed to divide the families containing alkaloid-bearing species into **3 groups:**

1.The first group is a group of families with at least 20% of genus containing alkaloids. These families are called highly alkaloid-bearing families.

For example, *Berberidaceae, Ranunculaceae, Fabaceae, Papaveraceae, Loganiaceae, Solanaceae*, etc.

2. The second group contains between 10% and 20% of the genus with alkaloid-bearing species. These families have been termed medium alkaloid-bearing.

3. The third group contains families with between 1% and 10% of genus with alkaloid-bearing species. They are called low alkaloid-bearing. For example, the families *Asteraceae*.

The alkaloids are present in very small quantities (tenths or hundredths of a percent). If the raw material contains between 1 and 3 % alkaloids, it is already considered alkaloid-rich.

Most plants contain several alkaloids. In a number of plants found 20 - 35 alkaloids: poppy, ergot, cinchona, etc., while some - about 50 alkaloids (snake rauwolfia, periwinkle).

The alkaloids can be found either in the whole plant or in parts of it (leaves, underground organs).

In plants, alkaloids are mostly in the form of salts and dissolved in the cell sap.

Alkaloids can form stable bonds with tannins such as tannin. The dynamics of accumulation fluctuate greatly depending on the conditions, and they vary from plant to plant. Their amount increases during the flowering phase and decreases towards autumn.

The role of alkaloids

The theories of Clothrue (1900) and Thunman (1914) are that alkaloids are produced by plants for protection against pests.

Pictet's theory (1905) is that alkaloids are the waste products of the organism. They are formed from proteins and are the end products of metabolism, corresponding to the urea of the living organism.

N. N. Ivanov and A. A. Kuzmenko (1932-1940) believe that alkaloids are stored nutrients. The theory is based on experiments where protein substances are formed from alkaloids.

Chiamichien and Raven's (1917) theory - alkaloids are essential and active substances in plant biosynthesis. Most often they are hormone biocatalysts.

Alkaloids are widely used in plants as an oxygen transporter via 'N-oxide' forms. The alkaloids are thought to be oxidised during plant respiration into peroxide, then into N-oxide and active oxygen, which is used for further phytochemical processes. The underground parts regulate metabolism and plant growth.

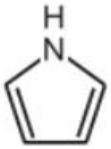
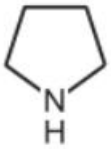
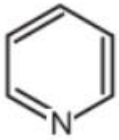
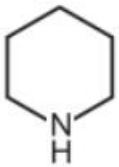
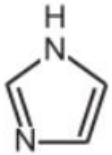
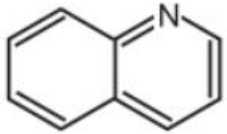
Functions:

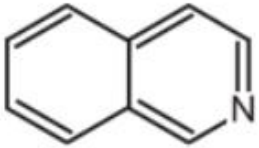
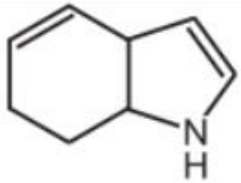
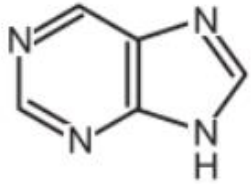
- They are end products of the metabolism of waste products.
- They are storage reservoirs of nitrogen for protein synthesis.
- They act as a protective agent for the plants against attack by predators (parasites or herbivores).
- They act as plants stimulants and regulators in activities such as growth, metabolism, and reproduction.
- They act as a detoxification agent, which renders harmless certain substances, accumulation of which might cause damage to the plant.

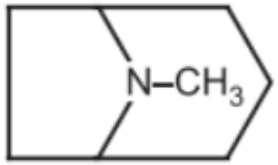
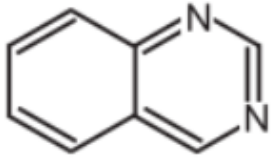
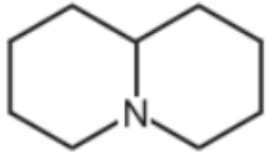
Classification of alkaloids.

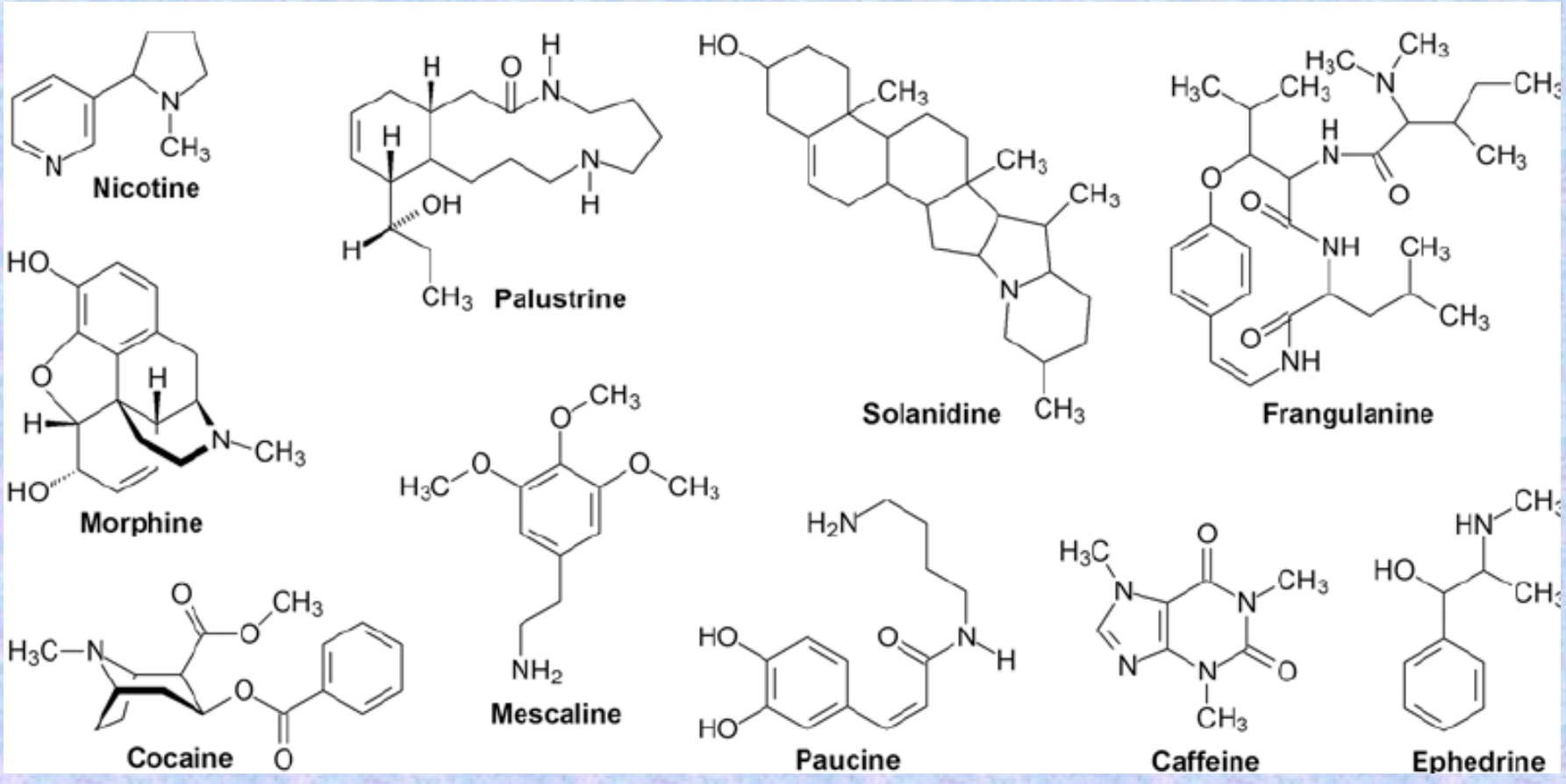
1. Acyclic alkaloids and alkaloids with nitrogen in the side chain.
2. Pyrrolidine and pyrrolizidine alkaloids.
3. Pyridine and piperidine alkaloids.
4. Alkaloids with condensed pyrrolidine and piperidine rings.
5. Quinolizidine alkaloids.
6. Quinoline alkaloids.

7. Isoquinoline alkaloids.
8. Indole alkaloids.
9. Imidazole derived alkaloids.
10. Quinazoline alkaloids.
11. Purine alkaloids.
12. Diterpene alkaloids.
13. Steroid alkaloids.

Types of alkaloids	Structure	Example	Biological source and Family	Uses
Pyrrole		Hygrine from Coca	*Erythroxylum coca* Family: Erythroxylaceae	Analgesic
Pyrrolidine		Nicotine from Tobacco	*Nicotiana tabacum* Family: Solanaceae	Stimulant
Pyridine		Lobeline from Lobelia	*Lobelia inflate* Family: Campanulaceae	Use in Asthma
Piperidine		Piperine from Black pepper	*Piper nigrum* Family: Piperaceae	Anti-inflammatory activity
Imidazole		Pilocarpine from Pilocarpus	*Pilocarpus microphyllus* Family: Rutaceae	Treating glaucoma
Quinoline		Quinine from Cinchona	*Cinchona officinalis* Family: Rubiaceae	Antimalarial

Isoquinoline		Morphine from Opium	*Papaver somniferum* Family: Papveraceae	Analgesic
Indole		Reserpine from Rauwolfia	*Rauwolfia serpentine* Family: Apocyanaceae	Antihypertensive
Purine		Caffeine from Tea	*Thea sinensis* Family: Theaceae	CNS stimulant

Types of alkaloids	Structure	Example	Biological source and Family	Uses
Tropane		Atropine from Datura	*Datura metel* Family: Solanaceae	Depressant
Quinazolin		Vasicine from Vasaka	*Adhatoda vasica* Family: Acanthaceae	Antitussive
Norlupinane		Lupanine from Lupine	*Lupinus albus* Family: Fabaceae	Carminative, Diuretic


Nicotine
Palustrine
Solanidine
Frangulanine
Morphine
Mescaline
Cocaine
Paucine
Caffeine
Ephedrine

Physico-chemical properties.

Most alkaloids contain carbon, hydrogen, nitrogen and oxygen. In addition, some alkaloids also contain sulphur (the alkaloids of yellow pond lily).

Alkaloids that contain oxygen are usually crystalline.

Some alkaloids do not contain oxygen and are mostly volatile oily liquids.

Most alkaloids are optically active, odourless, bitter-tasting, with a distinct melting or boiling point.

The great majority of alkaloids are colourless substances, but a small number of coloured alkaloids are known, such as berberine, serpentine, heleritrin, which have a yellow colour; sanguinarine has an orange colour. A number of alkaloids have a characteristic luminescence in UV light.

The salts of alkaloids are generally well soluble in water and ethyl alcohol (especially diluted when heated). They are poorly or not at all soluble in most organic solvents (chloroform, ethyl ether, dichloroethane, etc.).

But salts of some alkaloids are known to be poorly soluble in water (quinine sulphate, taspin sulphate), as well as salts of alkaloids that are soluble in organic solvents. For example, scopolamine hydrobromide is soluble in chloroform.

Alkaloid bases are mostly well soluble in organic solvents and insoluble or poorly soluble in water.

However, there are alkaloids that are well soluble not only in organic solvents but also in water. For example, cytisine, methylcytisine, caffeine and some others.

- Alkaloids are naturally occurring organic compounds.
- They mostly contain basic lone pair electrons on nitrogen, hence they are basic (Some compounds like theobromine, theophylline are amphoteric).
- Alkaloids react with acids to form salts. These salts are usually freely soluble in water (Example: Quinine sulfate is water-soluble but Quinine mono-sulphate is insoluble in water) and alcohol but poorly soluble in most organic solvents (Exceptional: Scopolamine hydrobromide is soluble in organic solvents). Strong bases form a salt with weak acid and vice versa. Very weak bases form unstable salts like Caffeine, nicotine, etc.
- They form a precipitate with heavy metal iodides.
- Naturally, alkaloids exist either in a free state (as amine) or as salt with acid or alkaloid N-oxides.
- They contain one or more nitrogen in their structure and form primary amines ($R\text{-}NH_2$; Example: Norephedrine), Secondary amines ($R_2\text{-}NH$; Example: Ephedrine), Tertiary amines ($R_3\text{-}N$; Example: Atropine), and Quaternary ammonium salt ($R_4\text{-}N$; Example: d-Tubocurarine).
- They decomposed by heat but some are undergoing sublimation (E.g. Caffeine, Strychnine).
- They decomposed at a temperature above 70°C for a long time.

Analysis of medicinal plant material containing alkaloids.

General precipitation reactions are carried out to detect alkaloids.

Specific (colour) reactions, chromatographic, luminescent and spectroscopic analyses are carried out to detect a specific group of alkaloids as well as to identify individual alkaloids.

General ("precipitation") reactions for alkaloids:

1. Mayer's reagent (solution of mercury dichloride and potassium iodide).
2. Dragendorf's reagent (solution of bismuth nitrate basic and potassium iodide with addition of acetic acid).
3. Wagner and Bouchard reagent (iodine and potassium iodide solution).
4. Marmet reagent (cadmium iodide and potassium iodide solution).
5. Sonenstein's reagent.
6. Phosphoric-molybdenum acid solution
7. Phosphoric-tungstic acid solution
8. Silica-tungstic acid solution
9. Picric acid solution

Specific reactions.

To discover individual alkaloids or groups of alkaloids (ergot indole alkaloids). Reactions are performed with pure (individual) alkaloids or with purified extracts.

The pharmacological analysis uses specific qualitative reactions for raw materials of hellebore, ergot and barberry (normative documents for the mentioned types of raw materials).

Chromatographic analysis.

This method of analysis is widely used for the detection, identification and separation of alkaloids.

Chromatographic analysis involves several stages:

1. Extraction.
2. Separation in solvent system.
3. Chromatogram detection.

Spectral analysis.

Spectral analysis is used to identify alkaloids and to establish their structure.

UV-, IR- and PMR-spectra are determined. Other characteristics such as melting point, specific gravity, gross formula and molecular weight are determined for the purpose of identification.

Determination of the alkaloid content of herbal raw materials.

In most cases the process of determining the content of alkaloids in raw materials is divided into 3 main stages:

I) extraction (extraction) of alkaloids from plant raw materials;

2) purification of the extracts;

3) the actual quantification of alkaloids.

Quantification of alkaloids

1. Gravimetric.
2. Titrimetric.
   А. Reverse titration method.
   Б. Direct titration method.
3. Photo-electro-colorimetric (PEC) method.
4. Spectrophotometric (SP).
5. Polarography.

Harvesting. When harvesting, remember that alkaloids are **poisonous** and harvesting should be done with caution and in strict accordance with the instructions for each plant. The collection should be carried out in special clothing. For example, wear a respirator when harvesting thermopsis. Do not touch the mucous membranes during harvesting and analysis of herbal products containing alkaloids, do not drink, smoke, eat, because many alkaloids are absorbed through the mucous membranes. Pregnant women and children should be excluded from harvesting.

The alkaloid content is influenced by local conditions and the geographical location of the area.

The soil has an impact.

Warm weather increases the alkaloid content of the plants, while cold weather inhibits this process.

The intensity of exposure to sunlight affects the amount of alkaloids.

The effect of altitude also affects the alkaloid content of the plants. There are certain optimums for each species.

Storage. All alkaloid-containing raw materials are stored under list B because they are classified as highly potent.

Seeds of Chilibukha, corms of the ageless flower and rhizome of Scopolia carnioli are stored under list A. Poppy capsules and ephedra are stored as narcotics with special caution.

Pure alkaloids are stored under Schedule A; compound preparations containing them are stored under list B.

- Store raw materials containing alkaloids separately! The room should be dry, without direct sunlight, with bars on the windows and an upholstered metal door with good locks. The bags must be clearly labelled with the word "toxic". A list of raw materials containing alkaloids must be available in the warehouse. Raw materials on list A must have a security alarm.

Use of raw materials containing alkaloids.

Pharmacies receive thermopsis lanceolate herb and celandine herb for infusions.

Herbs for the processing of medicinal plant raw materials are supplied to processing plants for tinctures, extracts: Passiflora herb, grass and leaves of mottle, Thermopsis lanceolatum herb, rhizomes and roots of hellebore, fruits of chilli pepper.

- The bulk of the raw materials containing alkaloids are supplied to chemical-pharmaceutical factories and used to produce preparations.
- "Ephedrine hydrochloride" is from ephedra horsetail herb; "Glaucine hydrochloride" is from macchia herb yellow; "Platyphylline hydrotartrate" is from the herb and rhizomes with roots of crossbush;

"Ergotal", "Ergometrine maleate" - from ergot horns; "Codeine", "Codeine phosphate", "Morphine hydrochloride", "Omnopon" - from poppy capsules; "Raunatin", "Rutherpin". "Aymalin, from the roots of rauwolfia serpenta; Berberine bisulphate, from the roots of common barberry; Strychnine nitrate, from the seeds of chilibukha; Pachycarpine hydroiodide, from the herb Sophora thickifolia; Scopolomina hydrobromide, from the fruit and seeds of Indian durman.

Thanks for your attention