Pharmacognosy and Phytochemistry

Alkaloids-Part 1

B. Pharm. Semester-1

Course Code: 0510221; Session: 2022-2023

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Learning Outcomes

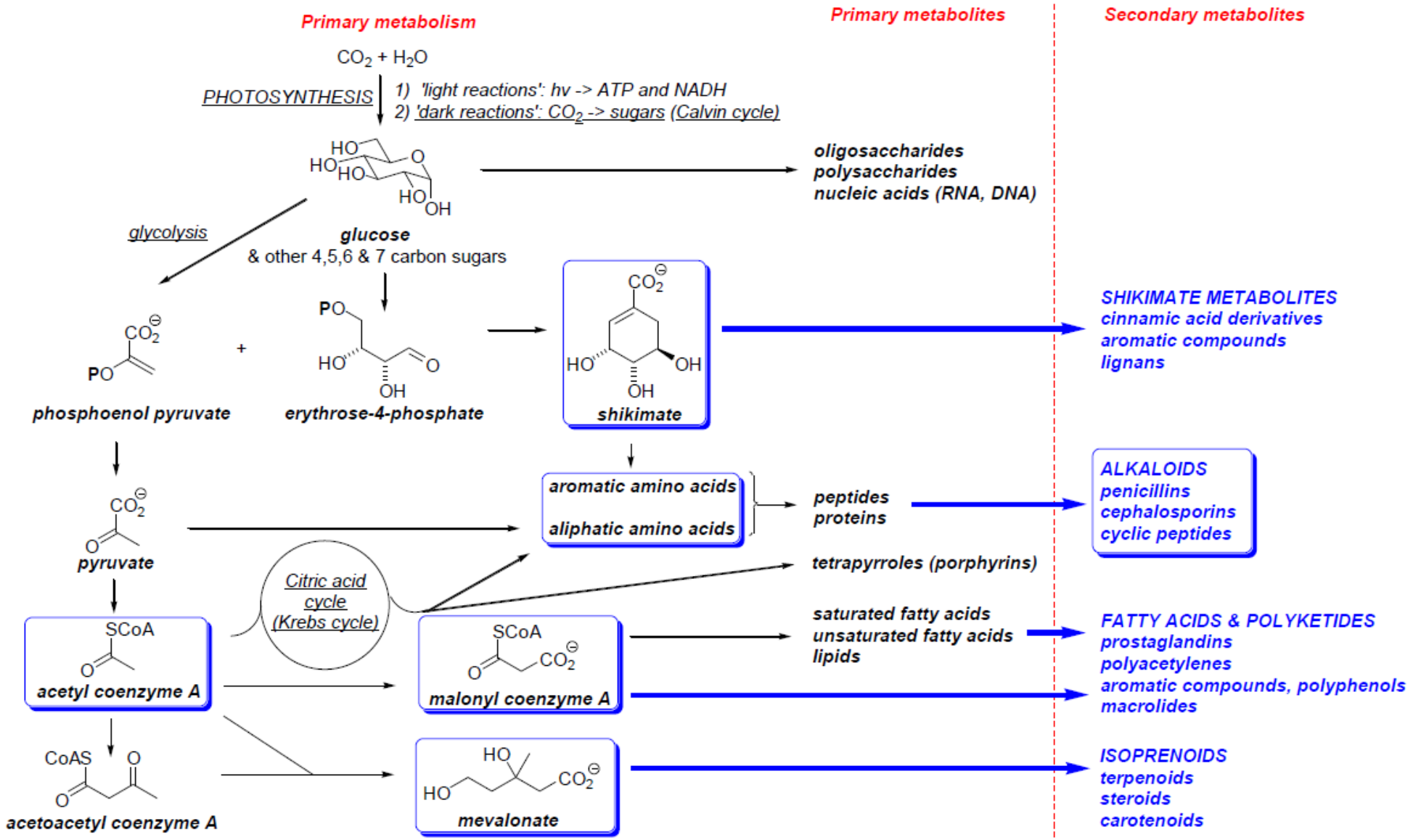
At the end of this lesson, students will be able to explain

- **Primary Metabolism-Overview**
- **Definition and Functions of alkaloids**
- **Occurrence and Classification of alkaloids**
- **Properties of alkaloids**
- **Chemical tests to identify alkaloids**
- **Chemical classification based on structures**
- **Extraction of alkaloids**
- **Biosynthesis of alkaloids**

Objective

The objective of this course is to give to the students of pharmacy the basic knowledge about the alkaloids as major phytoconstituents.

Primary Metabolism-Overview



Alkaloids: Definition and Functions

Definition of Alkaloids:-

Alkaloids are derived from plant sources, 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.

Functions of Alkaloids in plants:-

- Converting toxic substances into alkaloids that are less toxic (detoxification of the poisonous substances produced during metabolism),
- As a reservoir of nutrients, e.g. storing nitrogen.
- To secure protection against grazing animals due to the bitter taste and inherent toxicity.

Alkaloids: Occurrence and Classification

Occurrence of Alkaloids:-

- ✓Over 27,000 alkaloids are known - majority (21,000) occur in flowering plants.
- ✓Most alkaloids occur in dicotyledons (flowering plants with two embryonic leaves) in a number of families, the richest are Apocynaceae, Papaveraceae, and Fabaceae.
- ✓Increasing number of alkaloids have been isolated from animals, fungi, insects and microorganisms.

Three major classes of Alkaloids:-

1. True Alkaloids
2. Proto Alkaloids
3. Pseudo Alkaloids

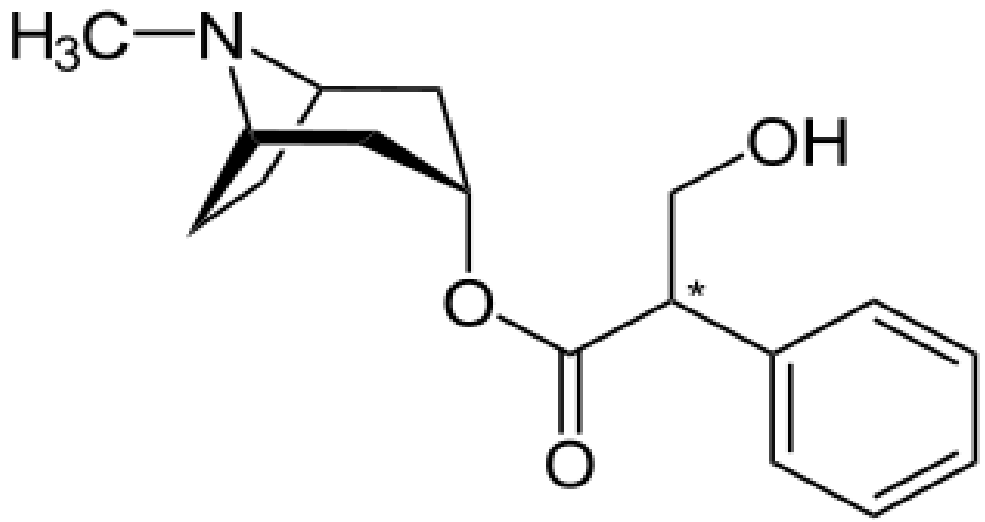
1. True Alkaloids

- ✓True alkaloids derived from **amino acid** and they share a heterocyclic ring with nitrogen.
- ✓These alkaloids are highly reactive substances with biological activity even in low doses.
- ✓All true alkaloids have a bitter taste and appear as a white solid, with the exception of nicotine which has a brown liquid.
- ✓True alkaloids form water-soluble salts. Moreover, most of them are well-defined crystalline substances which unite with acids to form salts.
- ✓True alkaloids may occur in plants (1) in the free state, (2) as salts and (3) as N-oxides.

1. True Alkaloids

- ✓The primary precursors of true alkaloids are amino acids such as
- ✓L-ornithine, L-lysine, L-phenylalanine/L-tyrosine, L-tryptophan and L-histidine.
- ✓Examples of true alkaloids include such biologically active alkaloids as **cocaine, quinine, dopamine** and **morphine.**

Atropine



2. Proto Alkaloids

- Protoalkaloids are compounds, in which the Nitrogen atom derived from an amino acid **is not a part of the heterocyclic**.
- Such kinds of alkaloid include compounds derived from L-tyrosine and L-tryptophan.
- Protoalkaloids are those with a closed ring, being perfect but structurally simple alkaloids.
- They form a minority of all alkaloids.
- **Hordenine, mescaline and yohimbine** are good examples of proto alkaloids.

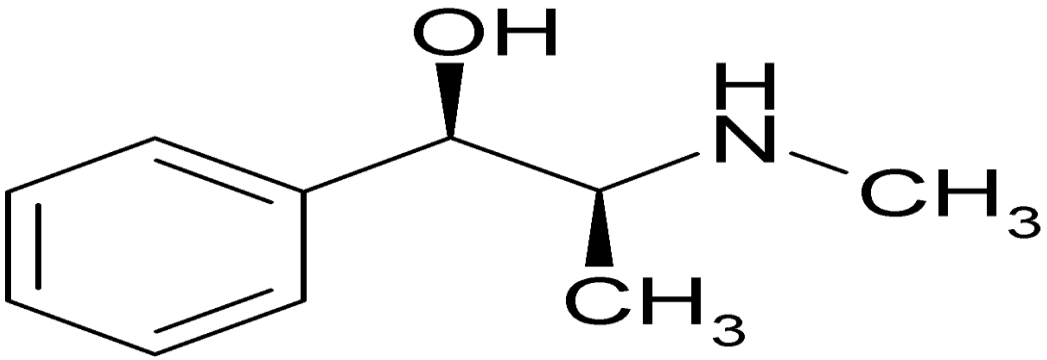
3. Pseudo Alkaloids

- Pseudoalkaloids are compounds, the basic carbon skeletons of which are **not derived from amino acids**.
- pseudoalkaloids are connected with amino acid pathways.
- They are derived from the precursors or post-cursors of amino acids.
- They can also result from the amination and trans-amination reactions of the different pathways connected with precursors or post-cursors of amino acids.
- These alkaloids can also be derived from non-aminoacid precursors.
- Nitrogen atom is inserted into the molecule at a relatively late stage.
- **Coniine, capsaicin, ephedrine, solanidine, caffeine** and **theobromine** are the good examples of pseudo alkaloids.

Structures and examples

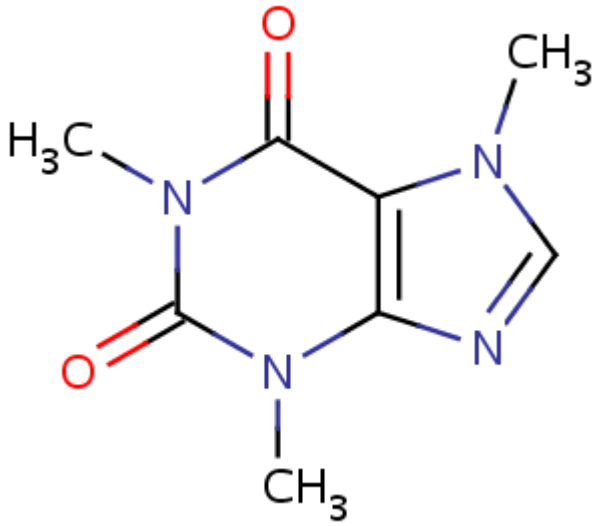
Proto alkaloids

Ephedrine



Pseudo alkaloids

Caffeine



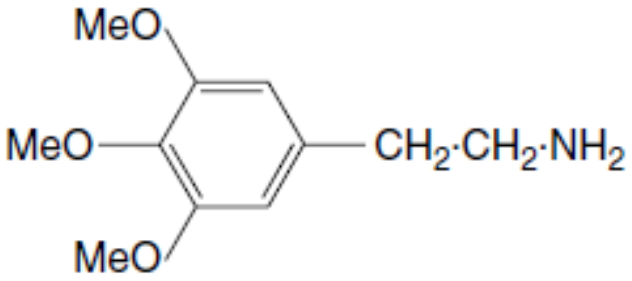
Properties of Alkaloids

- Alkaloids are colourless, crystalline solids which are basic, have a ring structure, bitter taste and have definite melting points.
- Some alkaloids are not basic and others are brightly coloured (betanidine, berberine, sanguinarine) or liquid (nicotine).
- Most alkaloids are also chiral molecules, present as isomers that have different chemical properties.
- One isomer have physiological function, while the other does not
- Free bases of alkaloids are soluble in organic solvents and insoluble in water, where as alkaloidal salts are soluble in water.
- Strychnine hydrochloride is much more soluble in water than strychnine as a base.

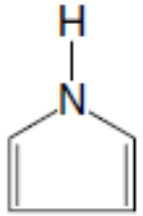
Chemical tests for Alkaloids

- **Dragendorff's Test**: Drug solution + Dragendroff 's reagent (Potassium Bismuth Iodide), formation of Orangish red colour.
- **Mayer's Test**: Drug solution + few drops of Mayer's reagent (potassium mercuric iodide), formation of creamy-white precipitant.
- **Hager's Test**: Drug solution + few drops of Hagers reagent (Saturated aq. Solution of Picric acid), formation of crystalline yellow precipitate.
- **Wagner's Test**: Drug solution + few drops of Wagner's reagent (dilute Iodine solution), formulation of reddish-brown precipitate.
- **Tannic Acid Test**: Drug solution + few drops of tannic acid solution, formation of buff coloured precipitate.

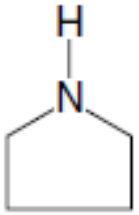
Chemical classification of Alkaloids



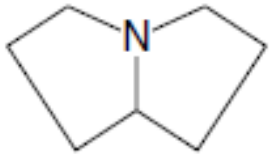
I, Mescaline



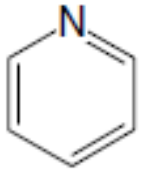
II,1 Pyrrole



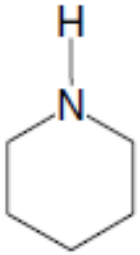
II,1 Pyrrolidine



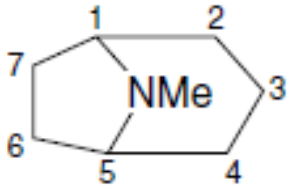
II,2 Pyrrolizidine



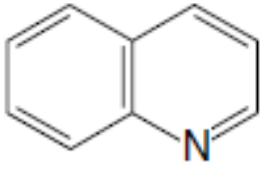
II,3 Pyridine



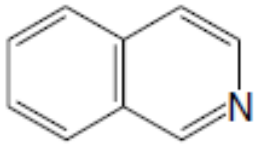
II,3 Piperidine



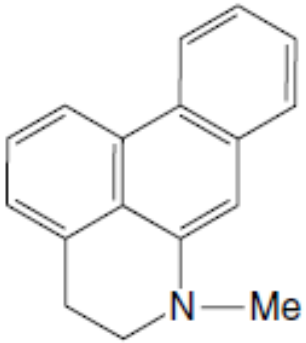
II,4 Tropane



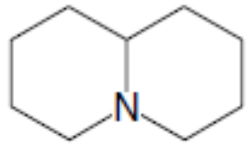
II,5 Quinoline



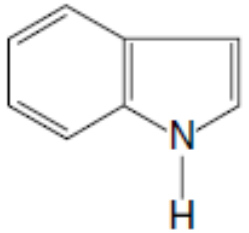
II,6 Isoquinoline



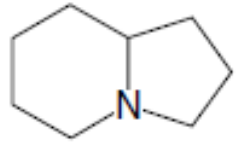
II,7 Aporphine



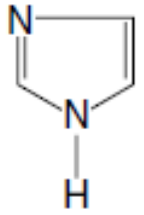
II,8 Quinolizidine



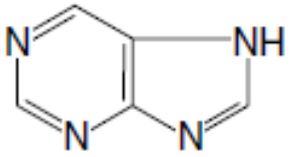
II,9 Indole



II,10 Indolizidine



II,11 Imidazole



II,12 Purine

Extraction of Alkaloids

- The extraction of alkaloids is based on basic character and solubility profiles.
- Generally alkaloids are extracted mainly using two methods.

Process A.

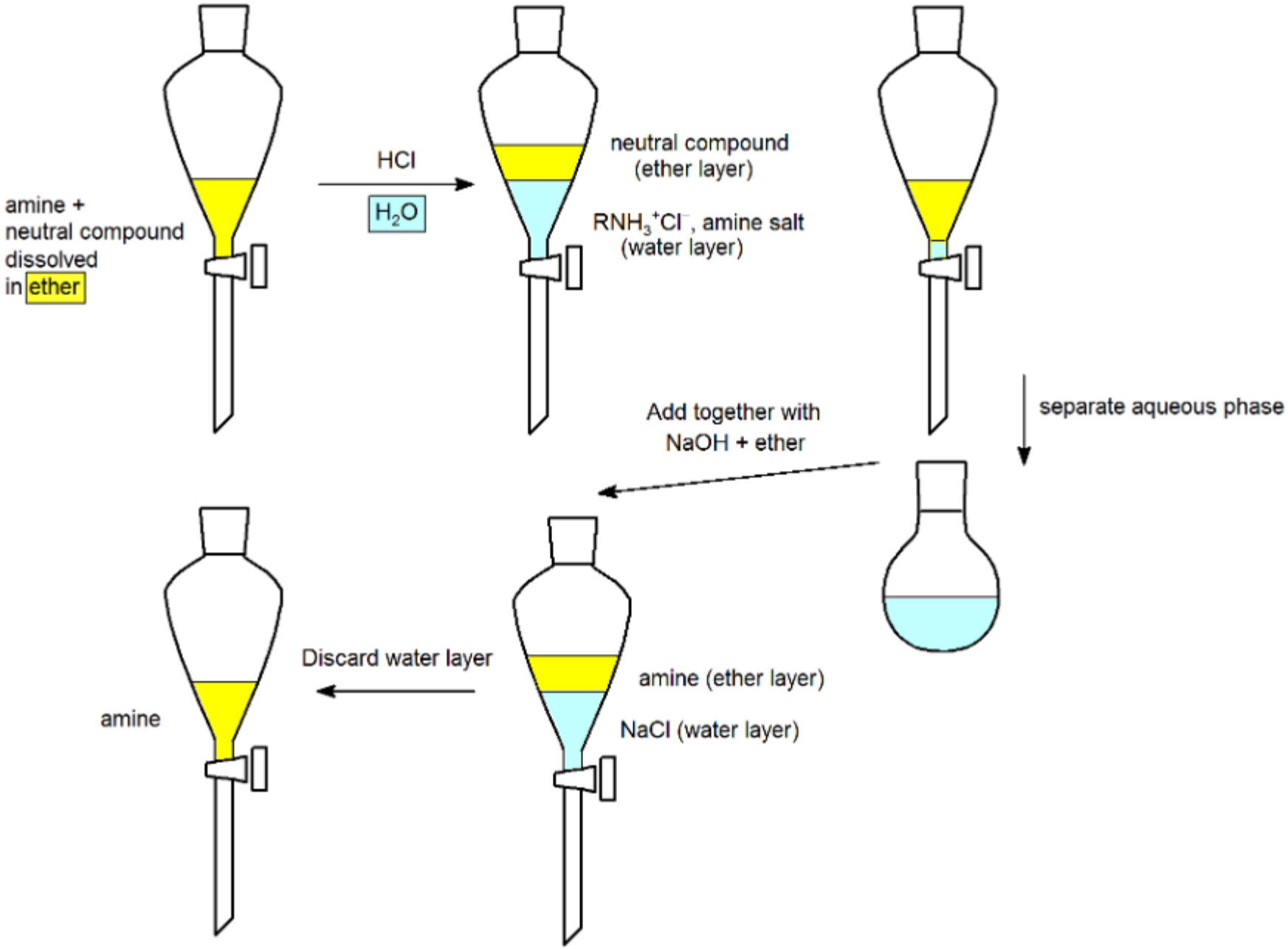
- The powdered material is moistened with water and mixed with lime which combines with acids, tannins and other phenolic substances and sets free the alkaloids (if they exist in the plant as salts).
- Extraction is then carried out with organic solvents such as ether or petroleum spirit.
- The concentrated organic liquid is then shaken with aqueous acid and allowed to separate.
- Alkaloid salts are now in the aqueous liquid, while many impurities remain behind in the organic liquid.

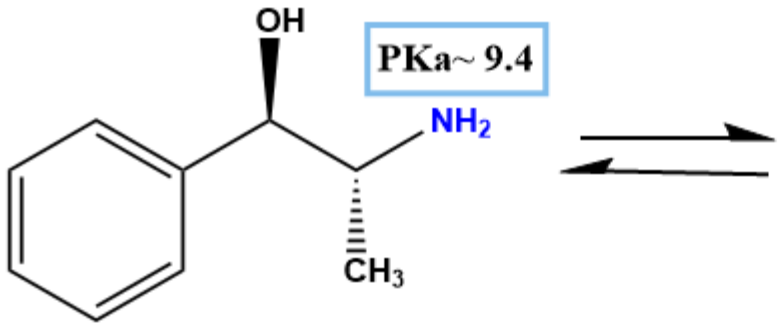
Extraction of Alkaloids

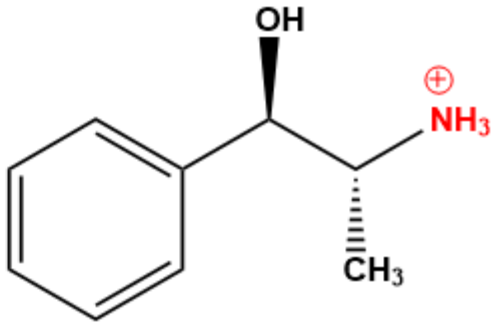
Process B.

- The powdered material is extracted with water or aqueous alcohol containing dilute acid.
- Pigments and other unwanted materials are removed by shaking with chloroform or other organic solvents.
- The free alkaloids are then precipitated by the addition of excess sodium bicarbonate or ammonia and separated by filtration or by extraction with organic solvents.

Extraction of Alkaloids





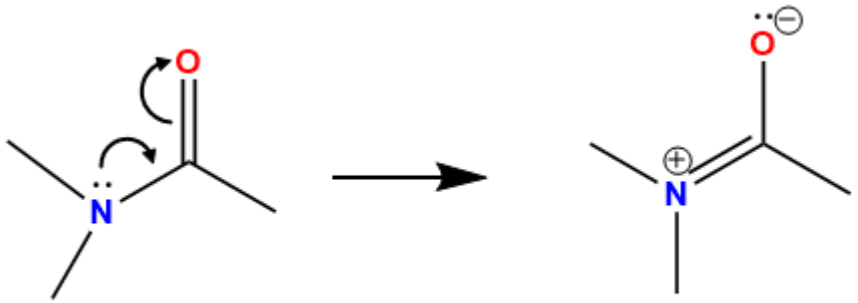


Neutral
Undissociated
Unionized

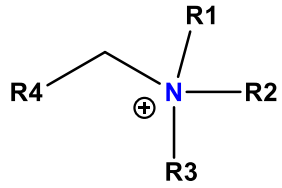
Positively charged
Ionized

Less Polar
Dissolve in organic phase

Very polar can dissolve in water

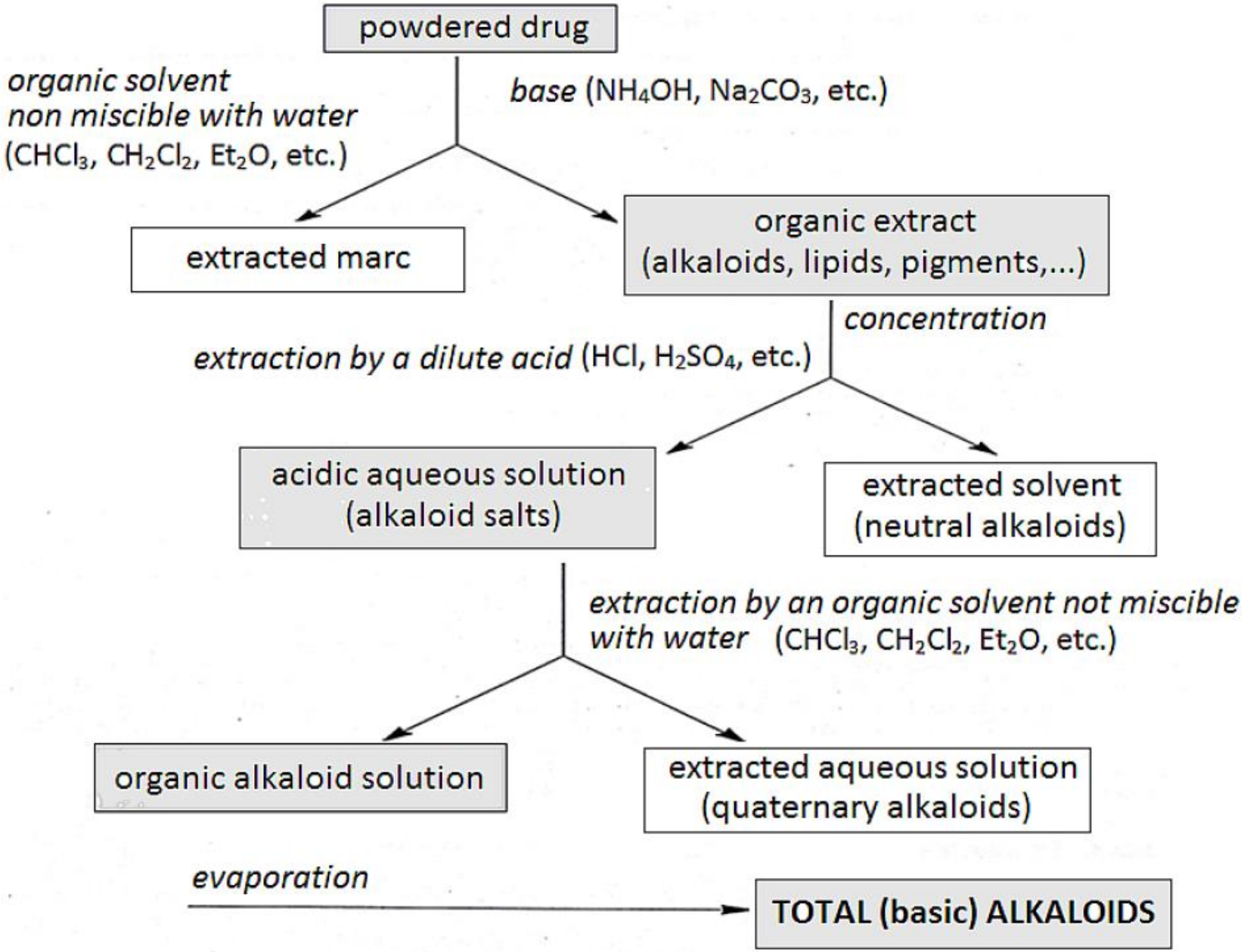


Neutral amide functional group



Quaternary ammonium stable charge

Extraction of Alkaloids in Alkaline Medium



Extraction of Alkaloids in Acidic Medium

Two approaches are possible: the pulverized drug is extracted with

- a. , acidified water
- b., an acidified alcoholic or hydroalcoholic solution.
- In the latter case, the extraction is followed by a distillation under vacuum which eliminates the alcohol and leaves behind an acidic aqueous solution of alkaloid salts.

In both cases, the result is an **aqueous solution of alkaloid salts requiring purification**. This can be accomplished by

1. alkalinizing the solution and extracting the bases with an immiscible organic solvent, which leads back to the above step;
2. selectively adsorbing the alkaloids contained in the solution on an ion-exchange resin, then eluting them with a strong acid;
3. precipitating the alkaloids as iodomercurates. The resulting complex is recovered by filtration, dissolved in a mixture of water, alcohol, and acetone, and decomposed by passing it through an ion-exchange resin. This technique can be used to extract quaternary ammonium salts.

Biosynthesis of Alkaloids

The most common amino acids that act as precursor in biosynthesis of alkaloids (true alkaloids) are:

i. Ornithine

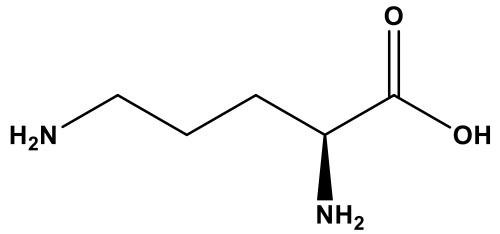
ii. Lysine

iii. Phenylalanine

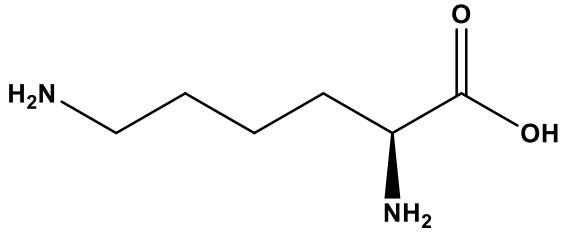
iv. Tyrosine

v. Methionine

vi Trytophan



ornithin



lysine

Biosynthesis of Alkaloids

The formation of alkaloids require the involvement of:

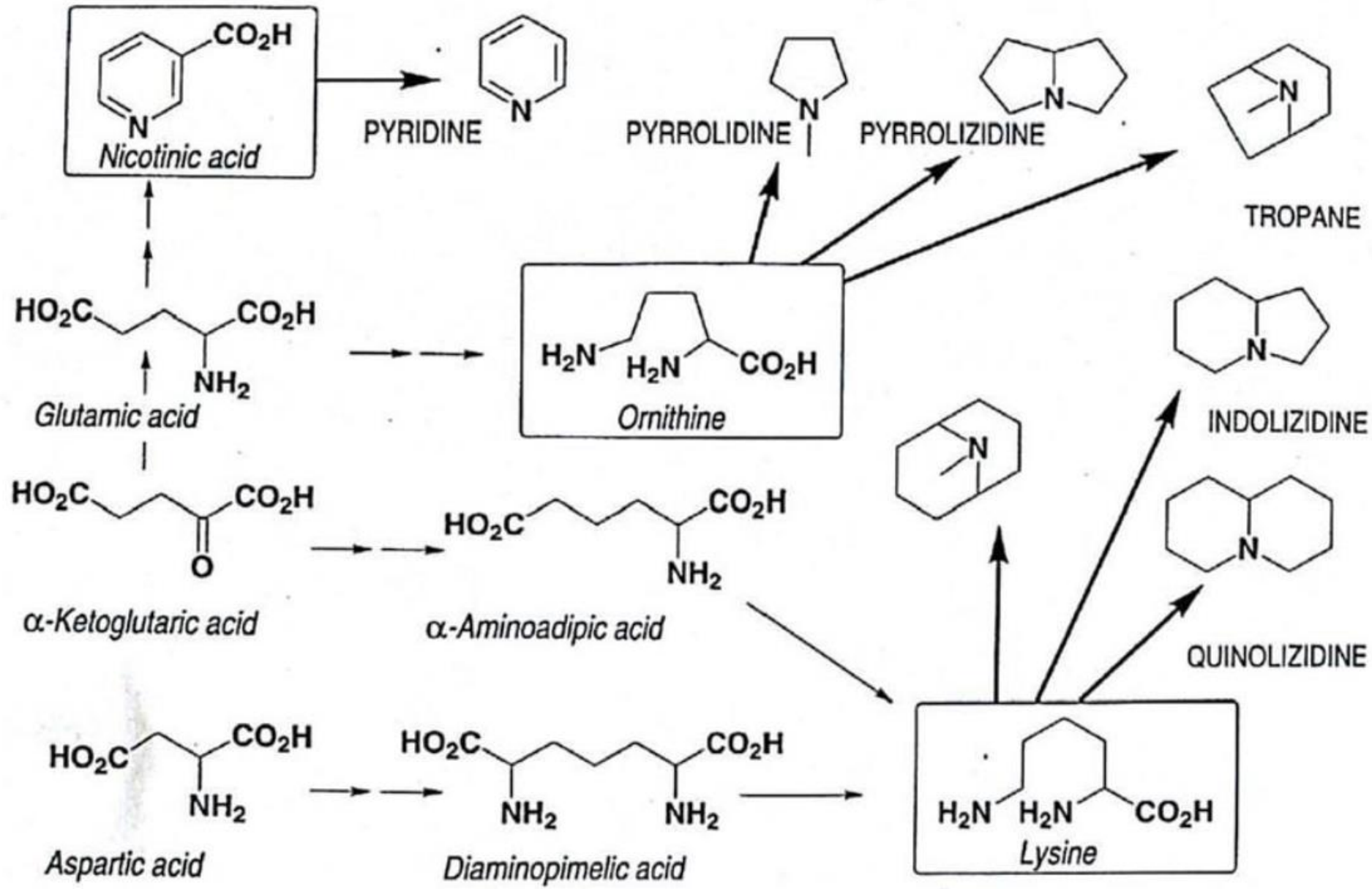
i. One molecule of amino acid (or)
ii. Two molecules of same amino acids (or)
iii. Less commonly 2 different amino acids (or)
iv. Several molecules of acids.

The mechanism of formation of heterocyclic systems may be the intra- or inter-molecular reactions: Schiff base or Mannich reactions.

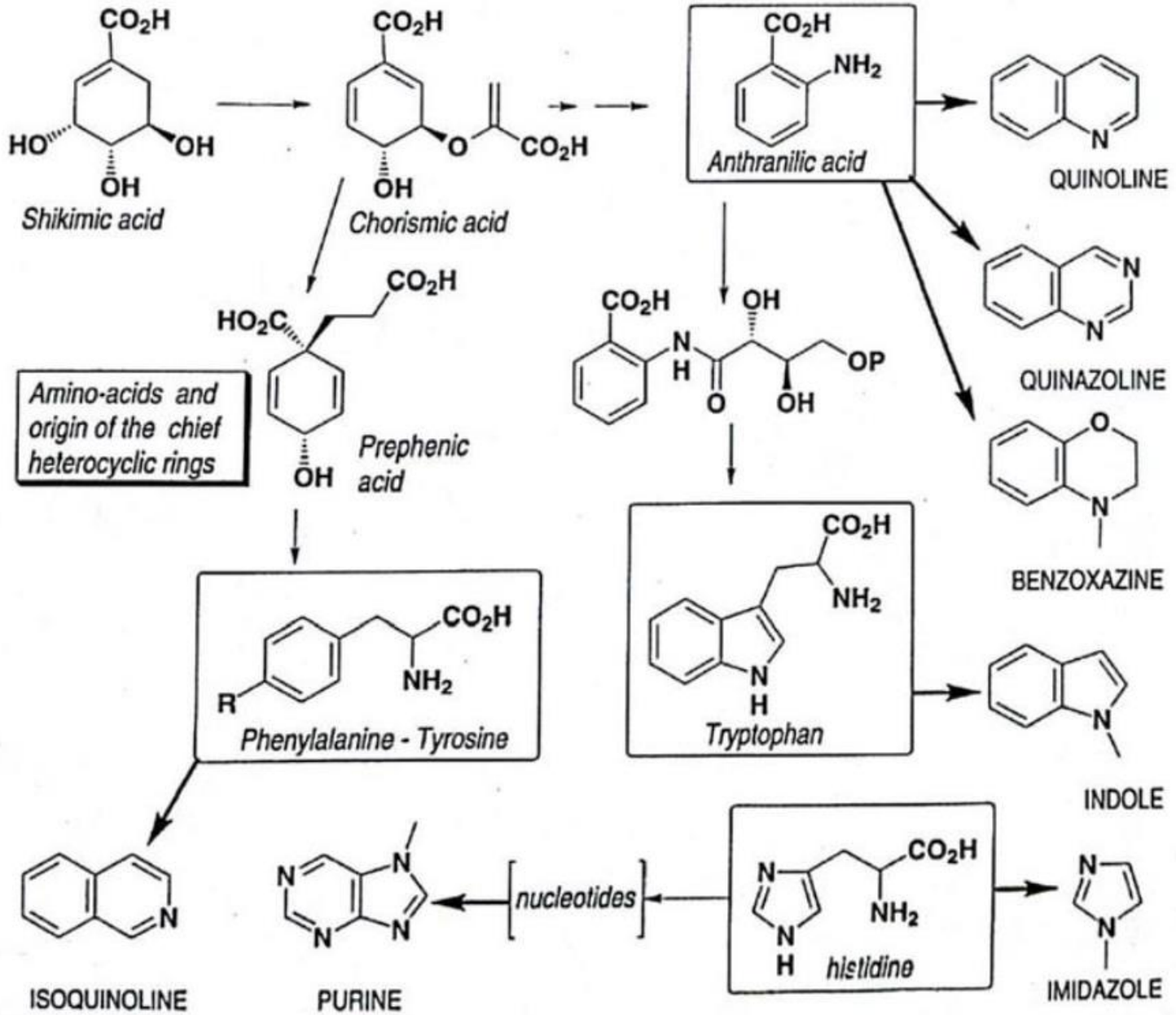
Additional carbons come from:-

(1) Intermediates having major role in other metabolic pathways. Ex: Acetate pathway (tropane) **[or]**
(2) Intermediates from specific group of plants.

Amino acids and origin of the chief heterocyclic rings I.



Amino acids and origin of the chief heterocyclic rings II.



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2. **Textbook of Pharmacognosy and Phytochemistry 2nd Edition, 2019, Authors: B. Shah, A. N. Kalia, Publisher: Elsevier, ISBN: 978-978-9386217738.**
3. **Medicinal Natural Products: A Biosynthetic Approach, 2nd Edition, 2002, Author: Paul M Dewick, Publisher: John Wiley and Sons Ltd, ISBN: 0471496405.**

Supplementary book:

Fundamentals of Pharmacognosy and Phytotherapy. A Guide for Health Care Professionals by Carol A. Newal, Linda A. Anderson and J. David Phillipson. (2010). the Pharmaceutical Press, London, UK; ISBN: 0 85369-474-5.