

Structure of Alkaloids :-

Alkaloids mostly have complex molecular structure. The structure of alkaloids determination as following -

- (i) Determination of molecular formula - The molecular formula of the given unknown alkaloid is determined.
- (ii) Detection of Groups - The presence of various functional groups in the molecule is ascertained by applying specific tests.
 - (A) Nature of Oxygen functions :- oxygen is present in alcohol, phenol carbonyl, alkoxy or, ester group.
 - (a) Hydroxyl group OH :- The alkaloid is reacted with anhydride, acetyl chloride or, benzoyl chloride to detect the presence of hydroxyl group. The -OH group may be phenolic or alcoholic. It is phenolic if the alkaloid
 - (i) Gives a colouration with ferric chloride.
 - (ii) Is soluble in sodium hydroxide and is reprecipitated by CO_2 .
 - If the above tests are given in negative, the -OH group is alcoholic. i.e. alcohol forms esters and oxidation gives a ketone.
 - (b) Carboxyl group (-COOH) :- The presence of Carboxyl group is indicated by the formation of salts and esters, and the evolution of CO_2 with sodium bicarbonate solution.
 - (c) Methoxy group (-OCH₃) :- This group produces molybdate blue on heating with hydroiodic acid.

$$-\text{OCH}_3 + \text{HI} \longrightarrow -\text{OH} + \text{CH}_3\text{I}$$
 - (d) Carbonyl group (C=O) :- The presence of carbonyl group is detected by the formation of oxime and hydrazone.
 - (e) Ester group (-COOR) :- The alkaloid containing the ester group gives an acid and an alcohol on hydrolysis.
- (B) Nature of Nitrogen functions :-
- (C) Amino group (-NH₂) :- The alkaloids containing an amino group form salts with acids. The nature of the amino group is decided on the basis of the following reactions -

- (ii) Aliphatic (-NH₂) group reacts with nitrous acid to give a primary alcohol with the evolution of nitrogen.
- (iii) Aromatic (-NH₂) group forms diazonium salts and dyes by coupling reaction.
- (iv) Secondary amino group (-NH-), reacts with nitrous acid to form nitrosamines.

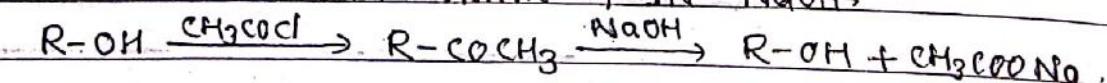
(b) Amide group (-CONH₂) :- Upon hydrolysis, the alkaloids containing an amide group yield the corresponding carboxylic acid and ammonia.

(c) Presence of Unsaturation :-

Alkaloids react with bromine water or, dilute alkaline KMnO₄ to indicate unsaturation of alkaloids. Reduction with Sodium amalgam, sodium and ethanol, hydriodic acid or Hg and hydrochloric acid also show the presence of unsaturation.

(3) Estimation of groups :- The estimation of various functional group is following.

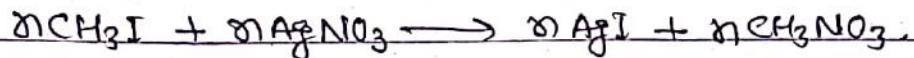
(a) Hydroxy groups :- The number of hydroxy groups is determined by acetylation of the alkaloid and hydrolysing the acetyl derivative with a known volume of 3N-NaOH.



The excess of alkali is estimated by titration with a standard solution of hydrochloric acid. The number of acetyl groups or, hydroxyl groups can be calculated from the volume of alkali used for aldehyde.

(b) Carboxyl groups :- The number of carboxyl groups may be determined volumetrically by titration against a standard barium hydroxide solution using phenolphthalein as indicator or gravimetrically by silver salt method.

(c) Methoxy groups (zeisler's method) :- The number of methoxy groups is estimated by heating the alkaloids with concentrated hydrochloric acid. The methyl iodide evolved is absorbed in ethanolic silver nitrate when silver iodide is precipitated.



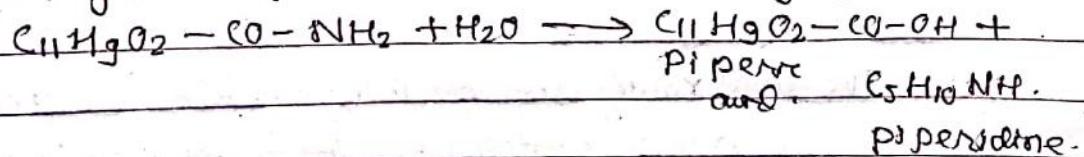
The precipitate of silver iodide is boiled with nitric acid, filtered washed, dried and weighed. From the weigh of the precipitate formed, the number of methoxy groups can be calculated.

(d) $-NH_2 > NH$ and $-NK$. These can be estimated -

(i) By forming the HCl and titrating aqueous solution against $N/10\ KOH$ using phenolphthalein as indicator and (ii) By the platinichloride method. In this method chloroplatinic acid (H_2PtCl_6) reacts with alkaloids to form precipitation of platinum and other complex substances of basic nature.

(e). Degradation :- The alkaloid is decomposed by treating with suitable reagents to give simpler compounds which can be identified easily.

(i) Hydrolysis - An alkaloid is decomposed by treating with suitable reagents to give simpler compound by hydrolysis.



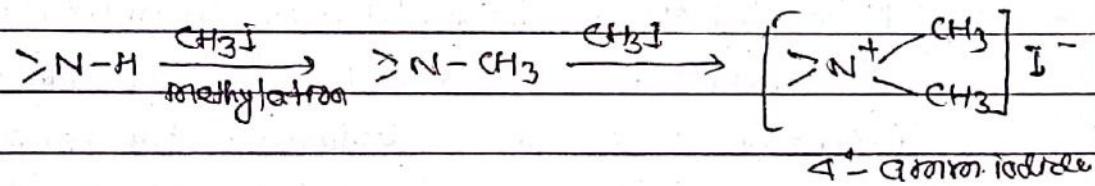
From this we infer that piperine is an amide of piperic acid.

(ii) Oxidation - Oxidation of alkaloid with K_2MnO_4 , $K_2Cr_2O_7$ + H_2O_2 can bring about several change. Thus with K_2MnO_4 the molecule may be oxidised away leaving a -COOH group at the root -

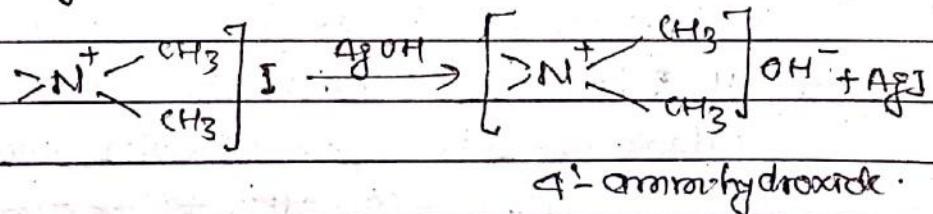
(iii) Distillation with zinc dust :- When distilled with zinc dust many alkaloids yield the parent compound or are dehydrogenated! Thus morphine on distillation with zinc dust gives phenanthrene

indicating the presence of the latter as the basic skeleton in the molecule. Heating yields emetine by the loss of a molecule of hydrogen.

- (iv) Exhaustive methylation - This is an important method used to find a recognisable molecule in an unknown alkaloid. This is accomplished by degradation of the alkaloid by the following steps.
- The tetracyclic ring of the alkaloid is reduced if unsaturated.
 - The alkaloid is reacted with excess of methyl iodide when the $>\text{NH}$ of the ring system is quaternized and then converted to the respective quaternary ammonium iodide.



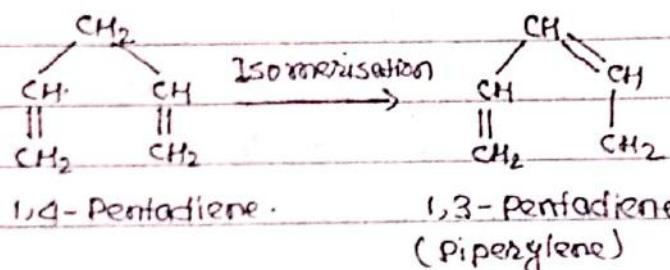
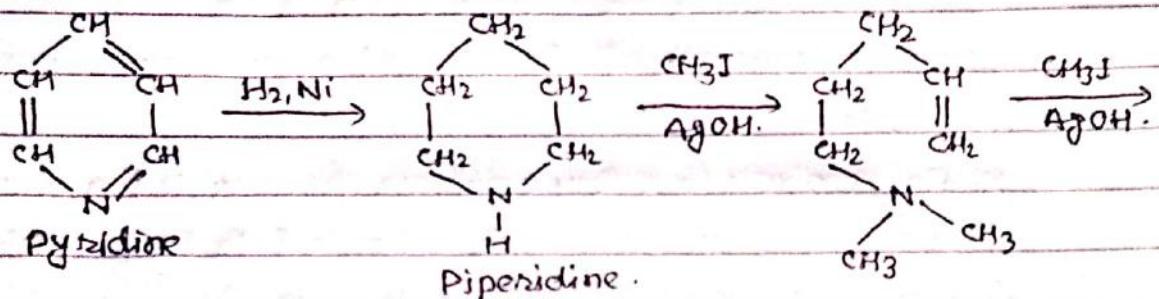
- The quaternary ammonium iodide is changed to the corresponding hydroxide by reaction with moist silver oxide (AgOH)



- The quaternary ammonium hydroxide on pyrolysis splits out a molecule of water the OH group extracting a H atom from the β -position with respect to N-atom. As a result the C-N bond on the side of the β -hydrogen converted ruptures giving an open chain unsaturated amine.

- The above sequence of reaction listed in steps a, b, c & d are repeated with excess of CH_3I . When rupture of the second C-N bond occurs and atom is eliminated as $(\text{CH}_3)_3\text{N}$. The unsaturated hydrocarbon left behind, which often isomerizes to a conjugated diene, is identified by the usual analytical methods.

The overall process mentioned in the steps above repeated methylation to get the degradation end-products is called Exhaustive Methylation. The nature of these products helps in arriving at the structure of the parent alkaloid. This may be illustrated by taking example of pyridine ring system.



According to Hofmann's exhaustive methylation method is applicable as long as β -hydrogen is available for elimination of H_2O , otherwise it fails. Thus it does not apply in case of quinoline and isoquinoline derivatives.

5. The analytical procedure discussed above will project the tentative structure for the alkaloid under investigation. Because of the aforesaid physical methods, which are sure and accurate, the confirmation of the structure by synthesis of the alkaloid is no longer that important. Nevertheless, synthesis will ever remain a fruitful method for confirming the proposed structure as it might as well provide a newer way of obtaining an alkaloid rather than depending only on a natural source.
6. Newer physical methods:- In conjunction with the chemical methods mentioned earlier more recent and sophisticated techniques are now

frequently used to elucidate the earlier more recent structure of alkaloids. In fact, in some cases the structure of alkaloid has been given even without carrying out any chemical work.

- I. Infrared spectra are used to detect the presence of many functional group-
- II. Ultraviolet spectra are employed so as to predict the possible type of structures of the alkaloid accurately present in the molecule.
- III. X-Ray Analysis - X-Ray analysis has provided a means to fit in the various structural units indicated to be present in the molecule thus giving a sure procedure to give the final structure of the alkaloid accurately.
- IV. NMR Spectroscopy - It is more recent and sophisticated method for detecting many functional groups such as alkene protons, N-, O-, and C-methyl group. The presence of heterocyclic ring system e.g. pyrrole, pyridine, quinoline, isoquinoline, indole etc. is clearly proved by NMR spectroscopic method.

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