

ALKALOIDS

§1. **Definition of an alkaloid.** Originally the name **alkaloid** (which means alkali-like) was given to *all organic bases isolated from plants*. This definition covers an extraordinary wide variety of compounds, and as the study of "alkaloids" progressed, so the definition changed. Königs (1880) suggested that alkaloids should be defined as naturally occurring organic bases which contain a pyridine ring. This definition, however, embraces only a limited number of compounds, and so the definition was again modified a little later by Ladenburg, who proposed to define alkaloids as natural plant compounds having a basic character and containing at least one nitrogen atom in a heterocyclic ring. Ladenburg's definition excludes any synthetic compounds and any compounds obtained from animal sources. One must admit that even today it is still difficult to define an alkaloid. The term is generally limited to organic bases formed in plants. Not all authors do this, and so they specify those alkaloids obtained from plants as *plant alkaloids* (or *vegetable alkaloids*). On the whole, alkaloids are very poisonous, but are used medicinally in very small quantities. Thus we find that the basic properties, physiological action and plant origin are the main characters which define plant alkaloids. Even so, the class of compounds known as the *purines* (Ch. XVI), which possess the above characters, are not usually included under the heading of alkaloids (some purines are also obtained from animal sources).

It is interesting to note in this connection that Sertürner (1806) isolated a basic compound from opium. Up to that time it was believed that plants produced only acids or neutral compounds.

§2. **Extraction of alkaloids.** In general, the plant is finely powdered and extracted with ethanol. The solvent is then distilled off, and the residue treated with dilute inorganic acids, whereupon the bases are extracted as their soluble salts. The free bases are liberated by the addition of sodium carbonate and extracted with various solvents, *e.g.*, ether, chloroform, etc. The mixtures of bases thus obtained are then separated by various methods into the individual compounds. More recent methods of extraction involve the use of chromatography. Lee (1960) has converted plant alkaloids into their reineckates, dissolved these in acetone, and passed this solution through an ion-exchange column, and thereby obtained the alkaloids in a high state of purity. (Reinecke's solution is $\text{H}[\text{Cr}(\text{NH}_3)_2(\text{SCN})_4]$.)

§3. **General properties.** The alkaloids are usually colourless, crystalline, non-volatile solids which are insoluble in water, but are soluble in ethanol, ether, chloroform, etc. Some alkaloids are liquids which are soluble in water, *e.g.*, coniine and nicotine, and a few are coloured, *e.g.*, berberine is yellow. Most alkaloids have a bitter taste and are optically active. They are generally tertiary nitrogen compounds and contain one or two nitrogen atoms usually in the tertiary state in a ring system; most of the alkaloids also contain oxygen. The optically active alkaloids are very useful for resolving racemic acids. The alkaloids form insoluble precipitates with solutions of phosphotungstic acid, phosphomolybdic acid, picric acid, potassium mercuri-iodide, etc. Many of these precipitates have definite crystalline shapes and so may be used to help in the identification of an alkaloid.

§4. General methods for determining structure.

(i) After a pure specimen has been obtained it is subjected to qualitative analysis (invariably the alkaloid contains (carbon), hydrogen and nitrogen; most alkaloids also contain oxygen). This is then followed by quantitative analysis and thus the empirical formula is obtained; determination of the molecular weight finally leads to the molecular formula. If the alkaloid is optically active, its specific rotation is also measured.

(ii) When an alkaloid contains oxygen, the functional nature of this element is determined:

(a) *Hydroxyl group*. The presence of this group may be ascertained by the action of acetic anhydride, acetyl chloride or benzoyl chloride on the alkaloid (acylation must usually be considered in conjunction with the nature of the nitrogen also present in the molecule; see **iii**). When it has been ascertained that hydroxyl groups are present, then their number is also estimated (by acetylation, etc.). The next problem is to decide whether the hydroxyl group is alcoholic or phenolic. It is phenolic if the alkaloid is soluble in sodium hydroxide and reprecipitated by carbon dioxide; also a coloration with ferric chloride will indicate the presence of a phenolic group. If the compound does not behave as a phenol, then the hydroxyl group may be assumed to be alcoholic, and this assumption may be verified by the action of dehydrating agents (most alkaloids containing an alcoholic group are readily dehydrated by sulphuric acid or phosphorus pentoxide). The behaviour of the compound towards oxidising agents will also disclose the presence of an alcoholic group.

(b) *Carboxyl group*. The solubility of the alkaloid in aqueous sodium carbonate or ammonia indicates the presence of a carboxyl group. The formation of esters also shows the presence of a carboxyl group.

(c) *Oxo group*. The presence of an oxo group is readily ascertained by the formation of an oxime, semicarbazone and phenylhydrazone.

(d) Hydrolysis of the alkaloid and an examination of the products lead to information that the compound is an ester, lactone, amide, lactam or a betaine.

(e) The *Zerewitinoff active hydrogen determination* may be applied to the alkaloid (see Vol. I).

(f) *Methoxyl group*. The presence of methoxyl groups and their number may be determined by the *Zeisel method*. The alkaloid is heated with concentrated hydriodic acid at its boiling point (126°); the methoxyl groups are thereby converted into methyl iodide, which is then absorbed by ethanolic silver nitrate and the silver iodide is weighed. Only methoxyl groups have been found in natural alkaloids.

(g) *Methylenedioxy group* ($-\text{O}\cdot\text{CH}_2\cdot\text{O}-$). The presence of this group is indicated by the formation of formaldehyde when the alkaloid is heated with hydrochloric or sulphuric acid.

(iii) *The functional nature of the nitrogen.*

(a) The general reactions of the alkaloid with acetic anhydride, methyl iodide and nitrous acid often show the nature of the nitrogen.

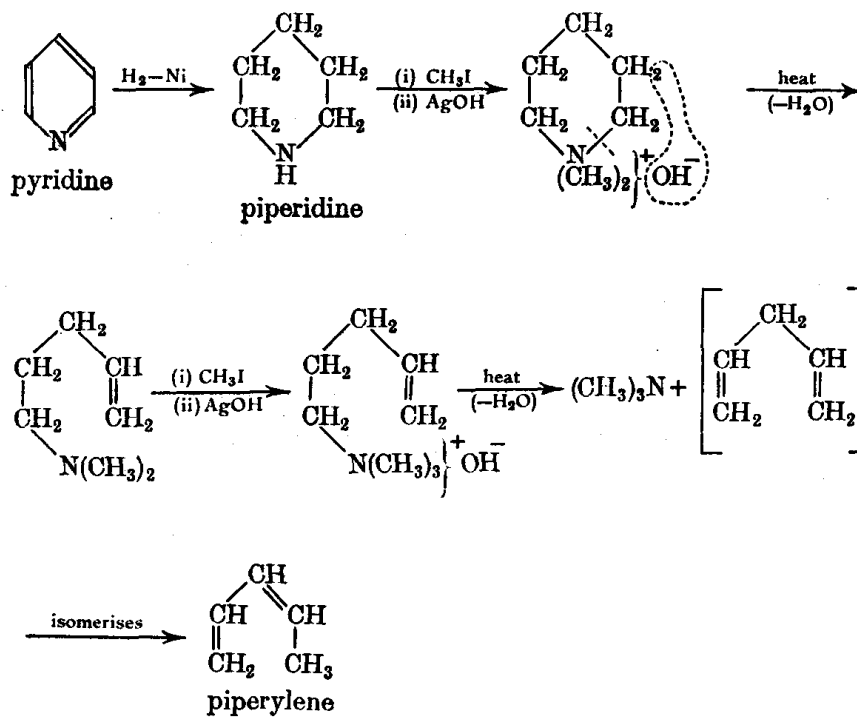
(b) Distillation of an alkaloid with aqueous potassium hydroxide usually leads to information regarding the nature and number of alkyl groups attached to nitrogen. The formation (in the volatile products) of methylamine, dimethylamine or trimethylamine indicates respectively the attachment of one, two or three methyl groups to a nitrogen atom; the formation of ammonia shows the presence of an amino group. Only *N*-methyl groups have been shown to be present in alkaloids with one exception, *viz.*, aconitine, which contains an *N*-ethyl group.

(c) The presence of *N*-methyl groups and their number may be determined by means of the *Herzig-Meyer method*. When the alkaloid is heated

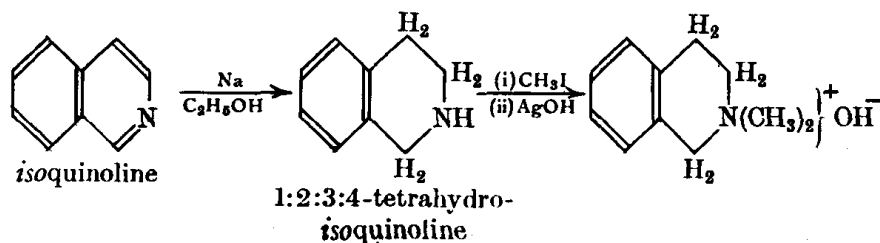
with hydriodic acid at 150–300° under pressure, *N*-methyl groups are converted into methyl iodide (*cf.* the Zeisel method, *ii*f).

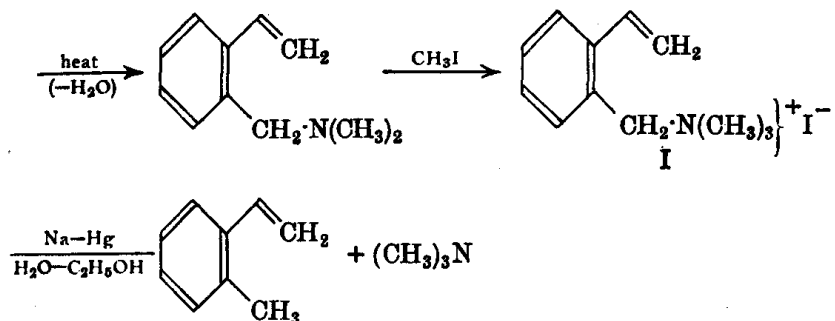
(*d*) The results of hydrolysis will show the presence of an amide, lactam or betaine (*cf.* *ii*d).

(*e*) *Hofmann's exhaustive methylation method* (1881) is a very important process in alkaloid chemistry, since by its means heterocyclic rings are opened with the elimination of nitrogen, and the nature of the carbon skeleton is thereby obtained. The general procedure is to hydrogenate the heterocyclic ring (if this is unsaturated), then convert this compound to the quaternary methylammonium hydroxide which is then heated. In this last stage a molecule of water is eliminated, a hydrogen atom *in the β-position* with respect to the nitrogen atom combining with the hydroxyl group, and the ring is opened at the nitrogen atom on the *same* side as the *β*-hydrogen atom eliminated. The process is then repeated on the product; this results in the complete removal of the nitrogen atom from the molecule, leaving an unsaturated hydrocarbon which, in general, isomerises to a *conjugated diene* (see also Vol. I); *e.g.*,



Hofmann's method fails if there is no *β*-hydrogen atom available for elimination as water; in such cases the Emde modification (1909, 1912) may be used. In this method the quaternary ammonium halide is reduced with sodium amalgam in aqueous ethanol or catalytically hydrogenated, *e.g.*,

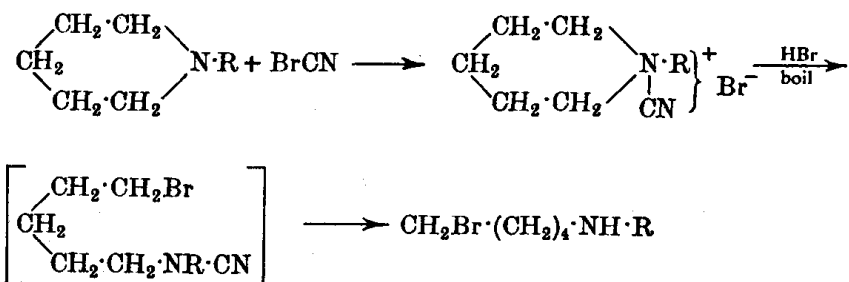




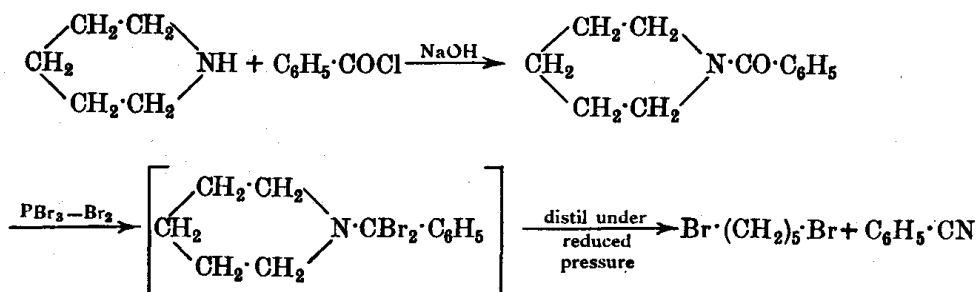
Examination of I shows that β -hydrogen is absent; hence Hofmann's method cannot be used.

Other methods for opening heterocyclic rings containing nitrogen are:

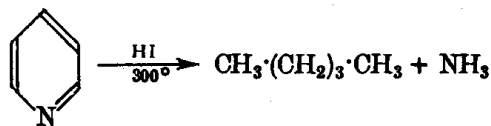
(i) *Von Braun's method* for tertiary cyclic amines (see also Vol. I); e.g.,



(ii) *Von Braun's method* for secondary cyclic amines (see also Vol. I); e.g.,



(iii) In a number of cases the ring may be opened by heating with hydriodic acid at 300° , e.g.,



(iv) The presence of unsaturation in an alkaloid may be ascertained by the addition of bromine and halogen acids, or by the ability to be hydroxylated with dilute alkaline permanganate. Reduction by means of sodium amalgam, sodium and ethanol, tin and hydrochloric acid, hydriodic acid, etc., also may be used to show the presence of unsaturation. In some cases, reduction may decompose the molecule. This often happens when catalytic reduction is used (ring cleavage occurs), and hence milder methods of reduction are desirable. Two particularly mild reducing reagents are lithium aluminium hydride and sodium borohydride. Sodium in liquid ammonia gives the Emde type of degradations (see iii).

(v) *Oxidation*. This is one of the most valuable means of determining

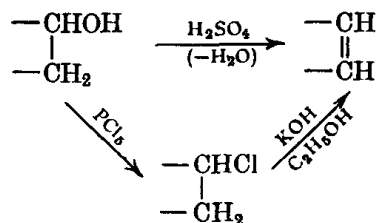
the structure of alkaloids (*cf.* terpenes, §3. VIII). By varying the "strength" of the oxidising agent, it is possible to obtain a variety of products:

(a) Mild oxidation is usually effected with hydrogen peroxide, ozone, iodine in ethanolic solution, or alkaline potassium ferricyanide.

(b) Moderate oxidation may be carried out by means of acid or alkaline potassium permanganate, or chromium trioxide in acetic acid.

(c) Vigorous oxidation is usually effected by potassium dichromate-sulphuric acid, chromium trioxide-sulphuric acid, concentrated nitric acid, or manganese dioxide-sulphuric acid.

This classification is by no means rigid; the "strength" of an oxidising agent depends to some extent on the nature of the compound being oxidised. In those cases where it can be done, better results are sometimes achieved by first dehydrating the compound and then oxidising the unsaturated compound thus obtained; oxidation is readily effected at a double bond.



More recently, mercuric acetate has been used to dehydrogenate certain alkaloids, thereby introducing olefinic bonds.

(vi) Fusion of an alkaloid with solid potassium hydroxide often produces relatively simple fragments, the nature of which will give information on the type of nuclei present in the molecule (*cf.* **iiib**).

(vii) *Zinc dust distillation*. This usually gives the same products as (vi), except that when the alkaloid contains oxygen the oxygen is removed.

(viii) Physical methods are also now being used, in conjunction with chemical methods, to elucidate structure, *e.g.*, infra-red spectra studies are used to identify many functional groups; ultraviolet spectra are used to indicate the likely type of structure present; and X-ray analysis has offered a means of distinguishing between alternative structures that appear to fit equally well the alkaloid in question.

(ix) *Synthesis*. The foregoing analytical work will ultimately lead to the proposal of a tentative structure (or structures) for the alkaloid under consideration. The final proof of structure, however, depends on an unambiguous synthesis of the alkaloid.

§5. Classification of the alkaloids. Long before the constitutions of the alkaloids were known, the source of the alkaloid was considered the most important characteristic of the compound. Thus there could not be a rational classification. Even today, with the structures of so many known, the classification of the alkaloids is still somewhat arbitrary owing to the difficulty of classifying into distinct groups. Even so, it is probably most satisfactory (chemically) to classify the alkaloids according to the nature of the nucleus present in the molecule. Members of the following groups are described in this book:

- (i) Phenylethylamine group.
- (ii) Pyrrolidine group.
- (iii) Pyridine group.
- (iv) Pyrrolidine-pyridine group.
- (v) Quinoline group.
- (vi) *iso*Quinoline group.
- (vii) Phenanthrene group.