CHAPTER 2

NATURE OF SELECTED HETEROCYCLES
Heterocyclic compounds are a major class of organic chemical compounds, characterized by the fact that the atoms in their molecules are joined into rings or circles containing at least one atom of an element other than carbon. Substitution of one or more of the ring carbon atoms in the molecules of a carbocyclic compound with a heteroatom gives a heterocyclic compound. These compounds are of great importance because many of the biochemical materials essential to life belong to this class.

In the present work pyrazoline (chapter III), isoxazole & isoxazoline (chapter IV), imidazolin-5-one (chapter V) and 1,4-dihydropyridine (chapter VI) groups were selected for the study. A brief history, synthetic methods, physical and chemical properties of the selected heterocycles are dealt in this chapter.

**PYRAZOLINE GROUP**

Pyrazole\(^1\textsuperscript{-5}\) was first described by Buchner\(^6\) in 1889, who discovered it during the decomposition of pyrazole 3, 4, 5-tricarboxylic acid and later by Balbiano\(^7\) who condensed epichlorohydrin with hydrazine hydrate in the presence of zinc chloride. The interest in pyrazoles stemmed from their applications in drugs, dyes and anaesthetics. Pyrazoles have also been used in medical and agricultural fields. Orisul is an example of a pyrazole sulfonamide. In the present work dihydropyrazoles or pyrazolines were synthesised.

Pyrazoline is a colourless liquid with boiling point 144°C. The pyrazolines are less stable than pyrazoles and are more like unsaturated compounds. Three types of structures are possible depending on the position of the double bond. They are 1-pyrazoline (I), 2-pyrazoline (II) and 1, 3-pyrazoline (III). Out of these three structures 1, 3-pyrazoline (III) is the most common.
Synthetic methods:

1. The hydrazones (IV) of α, β-unsaturated aldehydes and ketones are isomerised to pyrazolines (V) when warmed with acetic acid or hydrogen chloride in ethanol.

$$\text{CH}_2=\text{CH}-\text{CHO} + \text{C}_6\text{H}_5\text{NH}.\text{NH}_2 \rightarrow \text{CH}_2=\text{CH}-\text{CH} = \text{C}_6\text{H}_5\text{NH}-\text{N} \rightarrow \text{N}_\text{C}_6\text{H}_5$$

(IV)  
(V)

Pyrazolines are often formed by the direct action of hydrazine\(^8\) or its primary derivatives on the unsaturated carbonyl compounds or on progenitors of these, such as mannich bases\(^9-10\). Pyrazoline acids or esters are similarly obtained\(^11\) (VI).

$$\text{CH}_3\text{O}--\text{C-CH}=\text{CH}-\text{C}-\text{CH}_3 + \text{NH}_2.\text{NH}_2 \rightarrow \text{H}_3\text{COOC}-\text{HC} \equiv \text{N} \equiv \text{C}-\text{CH}_3$$

(VI)

Chemical Reactions:

The ring system of pyrazole is very stable and inert. In acid medium it exists as the cation.

Reactions with oxidizing and reducing agents: The pyrazole ring is remarkably stable to the action of oxidizing agents, but the side chain may be oxidized to the carboxylic function (VII). The oxidation proceeds well in alkaline potassium permanaganate.
The catalytic reduction of 1-phenyl pyrazole yields both phenyl pyrazoline (VIII) and 1-phenyl pyrazolidine (IX).

**Photochemical reactions:** The most important photochemical reaction of pyrazole is its conversion to imidazole (X). The transformation can be accounted in terms of the ring-opening to produce an azirine and subsequent ring closure.

**ISOXAZOLE GROUP**

Isoxazoles (XI) are unique in their chemical behaviour not only among heterocyclic compounds in general but also among related azoles. This is because isoxazole possesses the typical properties of the aromatic system, which are in fact rather pronounced in these derivatives, together with high liability of the ring under certain
conditions, particularly at the nitrogen oxygen bond. Isoxazole can be considered as an analog of pyridine.

The labile five membered ring undergoes electrophilic substitution reactions, owing to the high instability of ring towards the nucleophilic reagents\(^\text{12}\). Isoxazole was first prepared in 1903\(^\text{13}\). It resembles pyridine in odour\(^\text{14}\). The dimensions and resonance energies of isoxazoles have not been measured, but chemical properties show that the compounds are best considered as resonance hybrid to which the charged structure contribute\(^\text{15}\).

![Structural formula of isoxazole](image)

\((\text{XI})\)

Ioxazole is a colourless weakly basic liquid and boils at 96°C. It is a 1, 2-di hetero compound. Isoxazoles are not soluble in dilute mineral acids and in general don't give definite salts which can be isolated by treatment with acids. Chlorourate and chloroplatinate salts of isoxazole have been reported. Isoxazoles give crystalline addition products with cadmium and mercuric salts.

Reactivity of isoxazoles and its derivatives can be explained mainly due to the dissymmetry of its nucleus for having two heteroatoms located in a conjugated system, which allows displacement of electrons from oxygen to nitrogen. A differentiation of three carbon atoms and this lead to marked differences in physical and chemical properties of the isoxazole derivatives.
Synthetic methods:

1. From Diketones: The most general method for the synthesis of isoxazoles involves the condensation-cyclization of an $\alpha$, $\beta$-diketone with hydroxylamine$^{16,17}$. The reaction involves an initial attack of hydroxylamine on the carbonyl carbon which on subsequent cyclization yields a mixture of isomeric isoxazoles (XII, XIII).

\[
\begin{array}{ccc}
\text{R}_1 & \text{CH} & \text{CH}_2 \\
\text{O} & \text{C} & \text{R}_2 \\
\text{H}_2\text{NOH} & \rightarrow & \text{R}_1 \\
\text{C} & \text{CH} & \text{N} \\
\text{O} & \text{R}_2 & \text{R}_1 \\
\end{array}
\]

(XII) (XIII)

2. Isoxazolines (XIV) are synthesised by the action of hydroxylamine on $\alpha$, $\beta$-unsaturated ketones or on $\beta$-halogeno ketones$^{18}$.

\[
\begin{array}{ccc}
\text{C}_6\text{H}_5\text{CH} & \text{CH} & \text{C} & \text{C}_6\text{H}_5 \\
\text{O} & \rightarrow & \text{C}_6\text{H}_5\text{CH} & \text{CH} & \text{C} & \text{C}_6\text{H}_5 \\
& & & & \text{HO} & \text{N} \\
\end{array}
\]

(XIV)

Chemical reactions:

1. The electrophilic substitution attacks readily at C-4 and frequently fails if this position is occupied. Both the heteroatoms influence the rate of electrophilic substitution in the isoxazole ring. Nitration of 5-methyl isoxazole gives 5-methyl-4-nitroisoxazole (XV) according to the following mechanism$^{19}$. 
2. Condensation involving methyl group: 3, 5-dimethyl isoxazole (XVI) condenses with benzaldehyde to give 3-methyl-4-(benzoylmethyl) isoxazole\(^{20}\) (XVII).

\[
\begin{align*}
\text{(XVI)} & \quad + \quad \text{C}_6\text{H}_5\text{CHO} & \quad \text{(i) NaNH}_2 \\
& \quad \text{(ii) H}_2\text{O} & \quad \text{(XVII)}
\end{align*}
\]

**IMIDAZOLE GROUP**

Imidazole\(^{21-23}\) (XVIII) is an azapyrazole, the two nitrogen atoms being separated by one carbon atom. The compound was earlier called as glyoxaline as it was first prepared in 1858 from glyoxal and ammonia.

The imino nitrogen is assigned position-1, while the tertiary nitrogen atom position-3. The imidazole nucleus is found in a number of naturally occurring compounds, such as histamine, histidine, pilocarpine and allantoin. Since imidazole exists
in tautomeric forms, either of the nitrogen atom can bear the hydrogen atom and the two nitrogen atoms become complex for monosubstituted imidazoles. Depending on the position of the double bond, the dihydroimidazoles are referred to as imidazolines and three of them are possible. These are 2-imidazoline (XIX), 3-imidazoline (XX), and 4-imidazoline (XXI). The 2-imidazolines are most common. These are mono acidic bases and form monohydrogen halide salts.

\[
\begin{align*}
\text{(XIX)} & \\
\text{(XX)} & \\
\text{(XXI)} & 
\end{align*}
\]

Imidazole is a colourless liquid, b.p. 256°C and is high boiling than all other five membered heterocyclic compounds. Imidazole shows amphoteric properties and behaves as an acid. The introduction of alkyl group into the ring increases the basicity. It is a aromatic compound with resonance energy 14.2 k cal/mole.

**Synthetic methods**

1. The Radiszewski synthesis: It consists of condensing a dicarbonyl compound such as glyoxal (XXII), \(\alpha\)-keto aldehydes or \(\alpha\)-diketones with an aldehyde in the presence of ammonia to form the imidazole derivative (XXIII).

\[
\begin{align*}
\text{H}_5\text{C}_6\text{C}=\text{O} & + \text{H}_2\text{NH} \\
\text{H}_5\text{C}_6\text{C}=\text{O} & + \text{H}_2\text{NH} \\
\text{H}_2\text{NH} & \rightarrow \text{H}_5\text{C}_6\text{C}=\text{O} \\
\text{H}_2\text{NH} & \rightarrow \text{H}_5\text{C}_6\text{C}=\text{O} \\
\text{H}_2\text{NH} & \rightarrow \text{H}_5\text{C}_6\text{C}=\text{O} \\
\end{align*}
\]

\[
\text{(XXII)}
\]
2. 1-aryl-2-imidazolines\textsuperscript{25-26} (XXV) are formed from (a) N-allyl-acetamide or N-allyl-benzamide (XXIV) when heated with an arylamine hydrochloride; (b) N-2-chloroethyl carboxyamides (XXVI) when heated with PCl\textsubscript{5} in presence of arylamine gave 1-aryl-2-imidazolines (XXVII).

\begin{align*}
\text{(XXIV)} & \quad \xrightarrow{C_6H_5NH_2, HCl} \quad \text{(XXV)} \\
\text{(XXVI)} & \quad \xrightarrow{PCl_5} \quad \xrightarrow{C_6H_5NH_2} \\
\text{(XXVII)} \\
\end{align*}

**Chemical Reactions**

1. Reaction with acids: Imidazole is a monoacidic base and forms crystalline salts with acids. It also possesses weakly acidic properties.
2. Quaternization of imidazoles at the nitrogen atom is normally achieved by the reaction of alkyl halides or dialkyl sulfates under strongly basic conditions in an organic solvent. Imidazoles on treatment with ethylchloroformate\textsuperscript{27} obtained 1-carboethoxyimidazoles (XXVIII).

\[
\begin{align*}
\text{imidazole} & \xrightarrow{\text{H}^+} \text{imidazolium} & \text{imidazolium} & \xrightarrow{\text{H}^+} \text{imidazole} \\
\text{imidazole} & \xrightarrow{\text{CICO\text{R}}} \text{imidazole} & \text{imidazole} & \xrightarrow{170^\circ \text{C}} \text{imidazolium}
\end{align*}
\]

(XXVIII)

**PYRIDINE GROUP**

Pyridine (XXIX) was first discovered by Anderson from bone oil\textsuperscript{28}. Later it was isolated from coal tar\textsuperscript{29}, shale oil, petroleum, peat, commercial amyl alcohol and roasted coffee. Certain naturally occurring substances such as nicotine and vitamin B\textsubscript{6} are pyridine derivatives and yielded pyridine or its simple derivatives on distillation with zinc dust. The main source of pyridine is coal tar in which they occur to the extent of nearly 0.2\%\textsuperscript{30}.

The nitrogen atom in pyridine is assigned position-1. The presence of this atom introduces an element of asymmetry into the aromatic ring and as a consequence there are three monosubstituted pyridines.
There are three reduced pyridines (i.e.) dihydropyridines (XXX), tetrahydropyridines (XXXI), hexahydropyridines (XXXII)

Pyridine is a colourless liquid with boiling point 115°C and freezing point −42°C.

Pyridine is completely soluble in water and most organic solvents. It has a characteristic unpleasant odour.

**Synthetic methods**

1. The Hantzsch synthesis: It involves the condensation of an aldehyde with two moles of a β-dicarbonyl compound and ammonia\(^{31}\) to form a 1, 4-dihydropyridine (XXXIII).

\[
2\text{CH}_3\text{COOCH}_2\text{COCH}_3 + \text{HCHO} + \text{NH}_3 \rightarrow \text{H}_3\text{COCOOC}_2\text{H}_4\text{N}_3
\]

(XXXIII)

2. From other ring systems: The 2-acetylfurans react with ammonia/ammonium chloride at high temperatures to give 3-hydroxypyridines\(^{32}\) (XXXIV).
Chemical Reactions

1. Reaction with acids: Pyridine forms crystalline salts with most protic acids. With HCl it forms pyridinium chloride (XXXV).

\[
\begin{align*}
\text{NH}_3, \text{NH}_4\text{Cl} & \quad \xrightarrow{\text{HCl}} \\
\text{OH} & \quad \text{(XXXIV)}
\end{align*}
\]

(XXXV)

2. Halogenation: Bromination of pyridine is carried by using bromine in oleum. Vapour phase (300°C) chlorination or bromination of pyridine gives a complex mixture of products (XXXVI).

\[
\begin{align*}
\text{Br}_2, \text{Oleum} & \quad \text{Pyridine} \quad 130^\circ\text{C} \\
\text{Br} & \quad \text{(XXXVI)}
\end{align*}
\]

Problem undertaken and work done

Research in the field of pharmaceuticals has its most important task in the development of new and better drugs and their successful introduction into clinical practice. Central to these efforts, accordingly stand the search for pharmaceutical substances and preparations which are new and original. In addition to these objectives we may search for drug which exhibit a clear advantage over a drug already known. Such
advantage may be qualitative or quantitative improvement in activity, the absence of undesirable side effects, a lower toxicity, improved stability or decreased cost.

It is important at the outset to note that the drug discovery is not an unambiguous term in the pharmaceutical R&D world. ex. it can be defined using either programmatic or organizational approaches (or both), with several options on each category. Hence, it is important first to understand this variability and to adopt a specific definition for the purpose of this discussion.

Taking in view of the applicability of heterocyclic compounds, an attempt has been made to prepare the 1, 3, 5-trisubstituted pyrazolines(20), 3, 5-disubstituted isoxazoles/isoaxolines(20), Imidazolin-5-ones(10), 1,4-dihydropyridines(10) derivatives. The placement of a wide variety of substituents on these nuclei have been designed in order to evaluate the synthesised products for their biological profile against different strains of bacteria, fungi, helminthes and insects. All the synthesised compounds were characterised by using spectroscopic techniques like IR and $^1$H-NMR and by elemental analysis. The purity of the compounds were checked by T.L.C.

**Biological Studies:**

The synthesized compounds were evaluated for their biological studies like

(i) **Antimicrobial activity:** Antibacterial and Antifungal activity was carried out by using filter paper disc diffusion plate method. The activity was determined by using 4% and 2% solutions of prepared pyrazolines, isoxazoles & isoxazolines, imidazolin-5-one, dihydropyridines. Greseofulvin (for fungi) and Streptomycin (for bacteria) were also prepared in the same concentrations. The activities of the synthesized compounds are compared with the standard substances under same conditions. The filter paper discs were soaked in the synthesized compounds solutions and the activity was determined by placing them on the cultured medium. A clear zone of growth of inhibition was found
around the disc. The activity was moderate to good. Overall the methoxy and chloro derivatives are more potent than the rest of the derivatives.

(ii) *Anthelmintic activity:* 4% and 2% solutions of synthesized compounds were prepared in ethylene glycol. Same concentration of standard drug piperazine hydrochloride was also prepared in ethylene glycol. The test sample solutions and standard sample solution were poured in to the petridishes and earthworms are kept in it. The time taken by the earthworm to become motionless was noted as paralytic time. The time of death was noted as lethal time. The chloro and 3-methoxy-4-hydroxy derivatives showed good activity than the rest of the derivatives.

(iii) *Insecticidal activity:* Cockroaches were selected for the study. 4%(W/V) solutions of synthesized compounds of pyrazolines, isoxazole, isoxazoline, imidazolin-5-one, and 1,4-dihydropyridine were prepared in acetone. Cypermethrin 25% E.C is used as a standard. The solutions were injected in to the abdominal region of the cockroach with the help of a microsyringe. The time of death was noted as KD value (Knock down value). Almost all the derivatives exhibited moderate to good activity.

**Summary**

In the present work isoxazole, pyrazole, imidazole and pyridine groups were selected for the study.

The chapter deals with the nature of selected heterocycles like.

(a) History of its discovery.

(b) Different methods of synthesis.

(c) Physical properties like M.P., B.P., etc.

(d) Different types of chemical reactions they undergo.

Finally a brief account of the problems undertakes and workdone is dealt.
References:


7. L. Balbiano, Ber., 23, 1103, 1890.


