CHAPTER I

Introduction
INSTRUCTION

A heterocyclic compound is one which possesses a cyclic structure with at least two different type of atoms in the ring. The most common type of heterocyclic compounds comprise mainly carbon atoms along with the hetero atom/atoms. The heteroatoms are usually nitrogen, oxygen or sulphur in the heterocyclic ligands but many other elements including even bromine are also known to be part of the ring. The heterocyclic compounds are widely distributed in nature and are essential to life in various ways. Pyridine, pyrole, furan and thiophene are aromatic heterocycles that can be extracted from coal tar. Several of the other naturally occurring and synthetically important compounds also contain heterocyclic rings eg. the members of vitamin B complex group, the alkaloids, some antibiotics, haemin, chlorophyll, other plant pigments, amino acids, dyes, drugs, enzymes and genetic materials like DNA etc.

Pyrole is specially important among all the five membered heterocyclic compounds because its nucleus occurs in several important natural products.

Another heterocyclic molecule indol owes its importance to its presence in plant growth hormone heteroauxine, in the α amino acids (Tryptophan) and in some alkaloids (viz ergot alkaloids, strychnine and reserpine) found in plants. (1-2)
Pyridine and piperidine heterocycles are found to be present in numerous important natural products. Nicotinamide and Nicotinic acid are among the important constituents of Vitamin B complex. Nicotinamide adenine dinucleotide (NAD) and its phosphate (NADP) form the prosthetic part (coenzymes) of many enzymes which are involved in oxidation-reduction processes in living organisms. Sulphapyridine was the most famous drug of the last quarter century. It is particularly effective against pneumococci but has adverse side effects. Nicotindiethylamide is a powerful cardiac or circulatory failure drug and is also used in carbon-monoxide poisoning. The drug does not possess any undesirable after effects. Isoniazid has been used in the treatment of tuberculosis. Various alkaloids also possess the pyridine nucleus eg. coniine, ricinine and nicotine.\(^{3-5}\) Recently it has been shown that presence of planar ligands like pyridine in trans \([\text{PtCl}_2(\text{py})_2]\) greatly enhances the cytotoxicity of this compound and it is at least equivalent if not superior to cisplatin in treatment of certain kinds of tumour eg. murine tumour.\(^{6}\)

Quinoline molecule is obtained by the fusion of benzene and a pyridine ring and thus it bears the same relationship to pyridine as napthalene does to benzene. Quinoline nucleus is found in various types of organic compounds viz cinchona alkaloids, chemotherapeutic agents and analytical reagents. Cinchona alkaloids are quinoline derivatives which occur in cinchona bark. Two important cinchona alkaloids are quinine
and cinchonine. 8-hydroxy-quinoline is also a good antiseptic. Various commercially valuable dyestuffs possess the quinoline nucleus but these dyes are more important as photographic sensitisers due to their instability to light than as dyes for fabrics. Quinoline yellow is used as dye for textiles. Quinoline blue ethyl red dye, pseudocyanine dyes and sensitol red dye are some other more important ones which are widely used. Isoquinoline is isomeric with quinoline and is always present with quinoline in coal tar and bone oil. The isoquinoline nucleus is found in a large number of alkaloids eg. papeverine, landanosine, narcotine, barbituric acid and emetine, benzoquinoline or dibenzopyridine known as acridines. Acridine is found to be the parent substance of a number of dyes and antiseptics.

Imidazole, pyrazole, benzimidazole and benzopyrazole heterocycles have their importance in biological applications. Imidazole nucleus is found in a variety of natural products viz amino acids and peptides in purines and alkaloids. Histidine (α-amino-β-imidazyl propionic acid), histamine (β-imidazyl ethylaminc) and dipeptides carnosine and anserine are other examples of natural products possessing imidazole ring.

Histamine is found in the fresh nucleus membrane of the small intestine. It is formed from histidine by bacterial putrefaction and is believed to be responsible for certain
allergic reactions such as Asthma. Histamine is also found to be present in ergol preparation, where it is believed to be concerned with the activity of the drug. The alkaloid pilocarpine present in Jaborandi leaves is a derivative of N-methyl-imidazole.

Thio-heterocyclic compounds have the ring composed of carbon oxygen and sulphur like thiazole. Thiazole and their derivatives are found in certain natural products viz Vitamin B$_2$ (thiamine) and the penicillins. Sulphathiazole is also a derivative of thiazole which is used as a drug.

Six membered rings containing two heteroatoms are O-diazine (pyridazine), pyrimidine and pyrazine. Pyridazine compounds are of some importance as these are used as a selective plant growth inhibitor. A few pyrazines are natural products and others are important synthetic drugs eg. sulphapyrazine and chlorocyclizine (Antihistamine drug).

Recently a large number of biologically active pyrimidine derivatives have been synthesized in which pyrazolo pyrimidine exhibits antithrombotic activity.$^{(9)}$ They are used as antimicrobial, antibacterial and antimalarial drugs.$^{(10)}$ Some pyrimidinyl ureas and thioureas have been shown to act as effective herbicides.$^{(11-12)}$ Flourinated pyrimidines are useful in cancer chemotherapy.$^{(13)}$ Several pyrimidines eg. cystosine, uracil and thiamine have been isolated from the nucleic acid hydrolysates. Nucleic acids
are essential constituents of all cells and living matter.

Cystosine is found to be present in both types of nucleic acid eg. ribonucleic acid (RNA) and deoxyribonucleic acid (DNA) while uracil is present only in RNA and thiamine only in DNA. Pyrimidine ring is also found in vitamine B₁, barbituric acid and its several derivatives eg. veronal which are used as hypnotics. Platinum complex of barbituric acid is used as antitumour agent. The 5,5 substituted derivatives of barbituric acid are also well known chemothe-raptentic agents.

Fused diazine heterocycles are also very important eg. purines and pteridines. The pteridine nucleus occurs in the pigments of butterfly wings such as xanthopterin folic acid (growth factor), vitamin B₂ and coenzyme flavin-adenine-dinucleotide.

Pyridine-2-thiol also known as 2-mercaptopyridine containing the -N(H)-C(C=S)- chromophore belongs to the category of some important biological compounds. Included in this class of compounds are the analogues of purine and pyrimidine base. Since the keto form of pyridine-2-thiol is considered as a model compound for 6-thioguanosin (2-amino-1,2-dihydro-9β-D-ribofuranosyl-6H-purine-6-thione), it finds use in preparing and testing clinically useful drugs.

Many transition metal complexes of pyridine-2-thiol have been reported. Important among them being the [RuCl (PyS)(PySH)(PPh₃)₂] [PySH=Pyridine-2-thiol and PyS=deproto-
ated pyridine-2-thiol] which was reported by Gilbert and Wilkinson (16) and formulated as a dimer. Some other ruthenium derivatives eg. \([\text{Ru(PyS)}_2(C_8H_{12})] \) \((C_8H_{12}-\text{cyclo-octa-15 diene})\) \(\text{Ru(PyS)(PPh}_3)_2\) have also been prepared recently. (17-19) Metal complexes of \(\text{Zn}^{2+}(20-21)\), \(\text{Cd}^{2+}(22)\), \(\text{Hg}^{2+}(23-24)\), \(\text{Ti}^{4+}(25)\), \(\text{Mo}^{6+}(26-27)\), \(\text{W}^{6+}(26)\), \(\text{Fe}^{2+}(28)\), \(\text{Co}^{2+}(29-30)\), \(\text{Ni}^{2+}(31)\), \(\text{Ag}^{+}(32)\), \(\text{Pb}^{2+}(23)\), \(\text{Sn}^{2+}(22)\) and \(\text{Pt}^{4+}(32-33)\) and for at least one \(f\) block metal mainly \(\text{U}^{4+}(34)\) have been reported with \(\text{PySH}\) or \(\text{PyS}\).

Studies of the coordination of \(\text{Cu(I)}\) to neutral thione and deprotonated thiolate give insoluble complexes of the general formula \([\text{CuX}(C_5H_5\text{NS})_n]\) \((X=\text{Cl, Br or I}, n=2 \text{ or } 3)\) and \(\text{Cu}(C_5H_4\text{NS})\) and \([\text{Cu}(C_5H_4\text{NS})(\text{PPh}_3)]\). The complex \([\text{Cu}(C_5H_5\text{NS})_3]^{+}\) has been shown by X-ray crystallographic studies to have a distorted trigonal configuration about the copper centre defined by three \(S\)-donor atoms. The complex cation \([\text{Cu}(C_5H_5\text{NS})_4]^{+}\) has the copper atom tetragonally coordinated by four \(S\)-donor atoms (35) and the complex \([\text{Cu}_2(C_5H_5\text{NS})_6]\text{Cl}_2\) exists as a dimer as a result of two bridging \(C_5H_5\text{NS}\) ligand. The crystal structure of mixed ligand complex \((\text{CuCl}(C_5H_5\text{NS})(\text{PPh}_3)_2\) has also been reported. (36) The \(\text{Fe(II)}\) complexes are however reported to be the tetrahedral \(\text{FeX}_2(LH)_2\) type \((X=\text{Cl, Br})\) where \(\text{PySH}\) is coordinated to iron through the thione \(S\) atom. Since coordination by the thiolato functional group is well documented in \(\text{Fe(II)}\) chemistry, it is rather surprising
that no Fe(II) complex of Py2SH is reported where the ligand is bound to the metal centre through the pyridine N and thiolato S atoms. Tetraethylammonium tris(pyridine-2-thiolato)ferrate(II), which is the first octahedral complex of Fe(II) with all three Py2SH ligands in the bidentate 'thiolate' form has also been prepared.\(^{(37)}\)

During the last few years we have been interested in the study of interaction of organic corrosion inhibitors such as 2-mercaptobenzothiazole and indazole with metallic copper surfaces. The chemistry of these ligands has also shown a vast potential in the field of bioinorganics. Recent developments in copper thiol and copper indazole cluster chemistry provide several new compounds which seem quite interesting.\(^{(38-40)}\) The use of 2-mercaptobenzothiazole as a analytical reagent and of its complexes in industry and medicine has been known for a long time.\(^{(41-44)}\) The
Figure II

Figure III
structure of its complexes with metal ion has been investigated using various physical techniques.

A search of the literature shows that the chemistry of the interaction of 2-mercaptobenzothiazole with transition metal complexes has been studied. The use of mercaptides for separation of the platinum group elements has also been reported. \(^{(45)}\) This compound may exist either in thione or in thiol form (Figure II). However, it is assumed here that in solution it is behaving as a tautomer rather than in any one particular form \(^{(46-47)}\) (Figure III). It is evident that in the ligand molecule there are only two bonding sites, the thiocarbonyl sulphur atom and the nitrogen atom. Since the lone pairs on the sulphur atom present in the skeleton of the ring are involved in the resonating structures of the molecule, it is expected that it should have very weak co-ordinating ability. \(^{(48)}\) It is therefore reasonable to assume that it will not coordinate with the metal ions. Out of the remaining two bonding sites on the ligand molecule only one may coordinate when the ligand acts as monodentate but in some complexes it acts as a bidentate one involving both sites. \(^{(49-51)}\)

The chemistry of Indazole is of great relevance in the field of bioinorganics. \(^{(52-53)}\) Indazole (Figure - IVA) is an isomer of the biologically active molecule benzimidazole (Figure - IVB). \(^{(54)}\) Indazole and its derivatives have been found to be useful in the synthesis of dyes. The coordina-
tion behaviour of indazole and its derivatives with transition metals has been extensively studied in these laboratories.\(^{(55-58)}\)

![Figure IV](image)

Barbituric acid and succinimide are oxygen and nitrogen containing ligands respectively. Barbituric acid is an analogue of pyrimidine, which is having different coordination sites. It exists in two tautomeric forms C and D as given below.

![Figure V](image)
However on the basis of halogenation reactions it has been shown to exist predominantly in the form C.

Fairly good deal of work on indazole, imidazole, pyrazole, indol, 2-mercaptobenzothiazole and their derivatives has been reported from this laboratory in the last two decades. These organyl borates with varying composition have been studied with a view to locating the mode of coordination in the complexes formed and investigating their physicochemical properties. (59-65)

In the past ten years a number of compounds of these heterocyclic systems have been prepared and the formation of chelate compounds from these ligand have been reported. (66-70) There have been many articles detailing the synthesis and characterization of metal complexes bound through novel nitrogen aromatic heterocyclic ligands. (71-73) Ligands with multiple nitrogen sites that are coordinating are utilized in the formation of bi and polymetallic metal-ligand complexes with applications as oligomer metal complexes, (74) as intramolecular energy transfer centers (75-77), or in solvatochromic studies. (78-80)

Recently many papers detailing the synthesis and characterization of metal complexes from novel aromatic nitrogen heterocyclic ligands have appeared. The unusual behaviour of Ru(bpy)$_2^+$ (bpy=bipyridine) as electron transfer catalyst in photo induced reaction has aroused much interest in the chemistry of the complexes of similar biheterocyclic ligands.
with various modification. (81-83)

Many pyrazole derived ligands are of interest. More important among them are N,N'-chelating biheteroaromatic ligands such as 3,5 dimethyl-1-(2-pyridyl)pyrazole (DMPP), 3,5-dimethyl-1-(2-2-pyrimidyl)pyrazole (DMP'P'), 3,5-dimethyl-1(2-pyrazine)pyrazole and (2-pyridyl)triazole (Figure VI) have been recently studied. (84-86) Complexes of a number of related heteroaromatic ligands such as 2-(2-pyridyl)thiazole (Pyth), 2-2' bithiazole (bth), 2-(2-pyridyl)oxazole (Pyox)

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\text{Figure VI}
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![Diagram showing DMPP, DMP'P', DMPZP structures]
2,2'-bipyrazine (bpz) \(^{78,79,91}\), dipyrido(2,3-a,2',3'-h)phenazine (dpop), 4',7'-phenanthrolino-5', 6': 5,6-pyrazine (ppz), 6,7 dimethyl 2,3-bis(2-pyridyl)quinoxaline (ddpq) and 2,3-bis (2-pyridyl)pyrazine (bppz) \(^{92-94}\) (Figure-VII) with transition metal have also been studied.