Chapter-II

Synthesis of Reagents and Their Characterisation

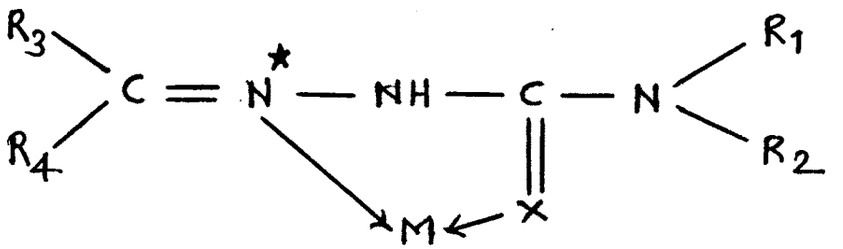
CHAPTER - II

SYNTHESIS OF REAGENTS AND THEIR CHARACTERISATION

PART-A : 5-Methyl Salicylaldehyde Thiosemicarbazone

INTRODUCTION

Thiosemicarbazones (TSC) and Semicarbazones (SC) are a class of compounds obtained by condensing thiosemicarbazide or semicarbazide with suitable aldehydes or ketones. The active grouping for chelation is shown below in structure (I).



(I)

Where X = O , Semicarbazone

X = S , Thiosemicarbazone

Phenylhydrazine ($C_6H_5NHNH_2$) and semicarbazide ($H_2NCONHNH_2$) are related compounds, react with carbonyl group of aldehydes and ketones by addition followed by the elimination of a molecule of water. The C=N bond in products is stabilized by resonance.

Semicarbazide may be considered to be an amide and hydrazide of carbonic acid or the hydrazide of carbamic acid, $H_2N\ CO_2H$(unstable). The name is derived from that of the hydrazine and carbonic acid (carbazide). The nitrogen atoms attached to the carbonyl group in semicarbazide are neutral in aqueous solution, but the $-NH_2$ attached to $>NH$ is basic. Semicarbazones are useful derivatives of aldehydes and ketones and some times are of interest in their own right. These compounds tend to be crystalline compounds and in general, semicarbazones have suitably high melting points. For this purpose they have long been commonly used for identification of individual aldehydes or ketones. Acetone semicarbazone for example melts at 187°C. Although this property is commonly used in all laboratories, the first analytical application of this class of compounds was made by Scott et al.(1) as late as 1945. Since then research activities are gradually growing in this direction and several studies have appeared on photometric determination and gravimetric estimation of metals. The realisation of the importance of thiosemicarbazones as analytical reagents is reflected in gradual increase in the number of papers dealing with their applications in analytical problems. The review of the work on transition metal complexes of thiosemicarbazides and thiosemicarbazones was written by Campbell(2). Singh et al. recently gave a critical review on analytical applications of thiosemicarbazones and semicarbazones (3).

Semicarbazide (aminourea) $NH_2.CO.NH.NH_2$ may be prepared by treating hydrazine sulphate with potassium cynate.

$$H_2N.NH_2.HNCO \longrightarrow NH_2.CO.NH.NH_2$$

It is also prepared by heating urea with hydrazine hydrate.

$$NH_2.CO.NH_2 + N_2H_4.H_2O \longrightarrow NH_2.CO.NH.NH_2 + NH_3 + H_2O$$

A more recent method of its preparation is the electrolytic reduction of nitrourea in H_2SO_4 solution using lead anode.

$$NH_2.CO.NH.NO_2 \xrightarrow{e;\ H^+} NH_2.CO.NH.NH_2 + 2H_2O$$

Semicarbazide is a white crystalline solid. (Melting point = 96°C). It is an important reagent for the identification of carbonyl compounds, with which it forms semicarbazones. It is also used in the Wolff-Kishner reaction.

[Wolff - Kishner - reduction (1912)].

When hydrazones (or semicarbazones) are heated with sodium ethoxide at 180°, nitrogen is eliminated, and a hydrocarbon is obtained, i.e. by this means the carbonyl group is converted into methylene group:

$$>C{:}N.NH_2 \longrightarrow >CH_2 + N_2$$

All the methods of preparation use elevated temperature (180°-200°). But Cram et al.(1962) have shown that the reaction proceeds at room temperature if dimethyl sulphoxide is used as a solvent (4).

The active grouping for chelation in thiosemicarbazones involves bonding through sulphur atom with possible further coordination by the hydrazino nitrogen atom to give a five membered chelating ring. Depending upon the type of aldehydes or ketones used for condensation thiosemicarbazones can act as unidentate, bidentate or multidentate chelating agents for several metal ions producing highly coloured complexes. In case of unidentate ligands, bonding occurs only through the sulphur atom. In most cases the bonding is through sulphur and hydrazinic nitrogen atoms with the metal atom. The earliest report on solid complexation appeared in 1934. However in view of the potential interest in ligands containing S and N donor atoms, the development in structural chemistry, has not been so far considerably significant. The coloured complexes are used in selective and sensitive determination of metal ions. Domagk et al. pioneered pharmaceutical applications of metal thiosemicarbazone for the treatment of tuberculosis (5). Since then a number of papers have appeared on the pharmacology of these compounds. Moreover, these compounds have been shown to be active against influenza(6), protozoa(7), smallpox(8) and certain kinds of tumours (9) and possess very good pesticidal (10), and fungicidal (11), activity. The biological activity of thiosemicarbazones may be attributed to the ability of the reagent to form chelates with traces of metal ions present in biological systems. The

antituber activity of p-acetamidobenzaldehyde thiosemicarbazone is found to be enhanced by the presence of a small amount of copper ions (12). Petering showed that the antituber activity of 3-ethoxy-2-oxobutyraldehyde his (TSC) is due to chelate formation with copper(13). These findings have led recently to an increased interest in the chemistry of transition metal chelates of thiosemicarbazones.

Because of the application of thiosemicarbazone to pharmacology there has been almost a unidirectional growth in the field of physiological activity of the ligands and their ability to form chelates with trace metals. Most of the chemical research is directed towards the structure and bonding in complexes in the solid state. No significant investigation is made about the properties of complexes in solutions, and virtually nothing is known of the reactions of the ligands and complexes. The major part of the work in solution chemistry deals with analytical applications though there is still much that remains to be investigated. As far as the ligands containing heterocyclic rings are concerned, it is probable that the metal chelates of ligands containing heterocyclic ring are of a great pharmacological interest ; and hence, all the phases of chemistry of thiosemicarbazones of metals interest both the chemists and the pharmacologists.

Preparation of the Reagents :

Semicarbazones are obtained by condensing semicarbazide hydrochloride with suitable aldehydes or ketones in the presence of sodium acetate. Sometimes hydrochloric acid must be present in the preparations of semicarbazones (14).

Thiosemicarbazones are prepared by condensing thiosemicarbazide with an aldehyde or ketone in presence of a few drops of glacial acetic acid. Preparation of the monoderivatives is simple but the di-derivatives are a little difficult and require special treatment. Dipyridylglyoxal dithiosemicarbazone was prepared by cyclizing the monoderivative with 6M-HCl.

Chemical Properties :

Just as hydrazones are weaker bases than hydrazines, semicarbazones and thiosemicarbazones are weaker bases than semicarbazides and thiosemicarbazides respectively. Hydrolysis of these compounds yield first the hydrazones, hence these compounds resemble hydrazones in many of their reactions.

Mild reductions of semi-carbazones and thiosemicarbazones yield -1-substituted semicarbazide and thiosemicarbazide, respectively. Catalytic reduction of these compounds yield hydrazides which are further hydrolysed to hydrazines. Reactions with alkoxides such as sodium ethoxide converts semicarbazones into hydrazones and with a strong base, hydrocarbones are obtained. This reaction may be applied for replacement of the carbonyl group by CH_2 group (Wolf-Kishner-Reaction).

The reagents can be readily hydrolysed to give the original carbonyl compound and hence are often useful for identification and isolation of carbonyl compounds. A method of obtaining the equivalent weight of the parent carbonyl compound is to hydrolyse the semicarbazone with aqueous HCl and titrate with standard iodate solution.

Applications in Spectrophotometry :

A large number of thiosemicarbazones are used as spectrophotometric reagents in analytical chemistry. Metal thiosemicarbazone complexes are formed in conditions ranging from moderately acidic to moderately alkaline conditions. Only a few are used to determine metal ions in highly acidic medium (15-17). 3-Hydroxy picolinaldehyde thiosemicarbazone is used to determine Co(II) in highly acidic medium(18). Similarly glyoxal dithiosemicarbazone reacts with Ag(I) and Hg(II) at pH 1:1(19). Salicyldehyde thiosemicarbazones have been used to determine Mo(VI) in presence of iron in highly acidic medium (20).

Extraction of the complexes not only increases the sensitivity but is also helpful in simultaneous determination of metal ions (21-22). Dipyridyl glyoxal-dithiosemicarbazone reacts with Ni(II) and Co(II), at pH 5.2, but only the Ni(II) complex is extractable into chloroform and hence allows the determination of both metals when present together (23). Biacetylmonoxime thiosemicarbazone has been used to determine Bi(III) in the presence of Cu(II), byextraction of the complex

into isobutyl methyl ketone (24). Presence of EDTA is sometimes necessary for complexation (25-27). Cyclo-hexane-1,2-dione dithiosemicarbazones has been used to determine the Cu(II) in alkaline medium (28). It was generally observed that semicarbazones containing hydroxy groups ortho to the aldehyde group give good colour reactions. Thiosemicarbazones are rather selective and sensitive for copper.

Besides the application in spectrophotometry thiosemicarbazones have been reported as gravimetric reagents for many metal ions (29-32); as indicators in the direct titration of metals with EDTA (33-34); in titration in non-aqueous solvents(35). Recently reports have appeared on separation of metal ions using thiosemicarbazones by thin layer chromatography on alumina with ethyl acetate as a solvent (36).

In this chapter, the synthesis and characterisation of 5-Methylsalicylaldehyde thiosemicarbazone is described.

I) Synthesis of 5-methyl Salicylaldehyde :

5-Methylsalicylaldehyde was prepared according to the method of Duff(37). A mixture of 240 ml glycerol and 70 gms of boric acid was heated with stirring in 2L beaker until the temperature was reached to 165^{o}C. About 20 minutes were required for heating since a considerable amount of water had to be

expelled. An intimate mixture of 50 gm of m-cresol and 50 gm of hexammine was prepared by grinding in a morter. The mixture was then added with vigorous stirring to the glycerol-glyceroboric acid solution previously cooled to 150°C. The reactants were stirred for 20 minutes during which the temperature was maintained between 150-165°C by heating or cooling to 115°C and was then acidified with a mixture of 50 ml conc H_2SO_4 in 150 ml water. The method frequently employed for the isolation of o-hydroxy-aldehyde from the above reaction consists of steam distillation of the acidified reaction mixture. Removal of the aldehyde by steam distillation was hastened by the fact that the various reaction mixture could be heated about 110-120°C, while the steam was being passed through it. This was a distinct advantage in the case of difficulty volatile aldehydes.

Yield = 30 % Melting point = 53°C.

II) Synthesis of 5-MethylSalicylaldehyde thiosemicarbazone :

5-Methyl salicylaldehyde (1 g) was dissolved in 20 ml of ethanol. Thiosemicarbazide (1g) was dissolved separately in 20 ml of hot distilled water. The solutions were mixed, 2-3 drops of glacial acetic acid were added, and the mixture was refluxed for 2 hrs. The mixture was then cooled in icebath, the pale yellow crystals separated out. The product was filtered through suction pump, dried in air. It was further crystallised twice from 1:1 water ethanol mixture (v/v) to give white crystals.

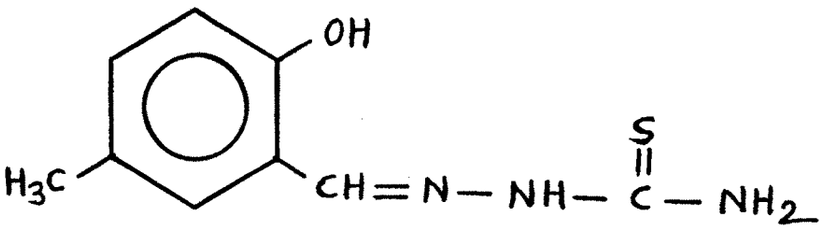
The crystals obtained were colourless and needle shaped which were analysed for carbon,hydrogen,nitrogen,sulphur.

Yield = 70-80 % Melting point = 222°C.

Formula of reagent is ⟶ $C_9H_{11}N_3OS$

Molecular weight = 209

Structural formula ⟶



Anal. Calculated for $C_9H_{11}N_3OS$

C, 51.67; H, 5.26; N, 20.10; S, 15.31.

Mol Wt. = 209

Found C, 51.65; H,5.30; N, 20.10; S,15.33.

Properties of the reagent :

5-Methyl salicylaldehyde thiosemicarbazone occurs as white needle shaped and light shining crystals with high melting point (M.P.222°). The compound is highly soluble in methanol and acetone. It is sparingly soluble in ethanol but soluble in hot. It is also soluble in dimethyl sulphoxide and dimethyl formamide. The solution of the compound is ethanol is stable for more than a week and is colourless. The compound is stable towards light and can be stored for several months.

PART-B:

1-(2,4-Dichlorophenyl)-4,4,6-Trimethyl (1H,4H)-2-Pyrimidinethiol

Thioligands offer an immense analytical potentialities. This has prompted the researchers in the field of analytical chemistry to synthesise and to examine the new thioligands with regard to their utility as analytical reagents.

Pyrimidinethiols also known as cyclicthioureas have been reported by Singh et al.(38-41) as selective spectrophotometric reagents for the determination of Pd(II) and Os(VIII). Recently Singh et al.(42) reviewed the analytical aspects of the chemistry of substituted mercaptopyrimidines. However, we have investigated for the first time the use of such compounds as extractnts for the platinum group metals and gold (43-45). The literature as well as our findings on the application of mercaptopyrimidines revealed that these possess fascinating analytical potentialities. Hence, this study has been undertaken with a view to investigating the effect on analytical characteristics of the structural changes in the reagent molecule.

Mathes reported the improved method for the synthesis of mercaptopyridine and since then synthesis of a large number of such compounds and their derivatives have been reported (46-49). These compounds are easily prepared by condensing 2-Methyl-2-isothiocyanato-4-pentanone with amines, aminoacids and hydrazines in presence of strong mineral acid. They are easily crystalised and possess sharp melting points. This method of preparation of

such class of compounds conforms to the well known reaction of isothiocynates with amines to give thioureas. Hence, these may be considered as cyclic thioureas. Like heterocyclicthiols, mercaptopyrimidines have been shown to be useful as vulcanization accelerators (50). The compounds are biologically important as they have been reported to have antibacterial activity(51,52). A number of papers have appeared on the pharmacology of these compounds. Derivatives of pyrimidinethiols have been reported as antiwear additives for lubricating oils, photographic adjucants (53,54). There is a report on the use of these compounds as an intermediate in the preparation of fungicidal compounds (55).

The active grouping for chelation as shown

$$-N=\underset{\underset{SH}{|}}{C}-N\!\!<$$ is analogous to the

grouping in thiourea in thiol form (56).

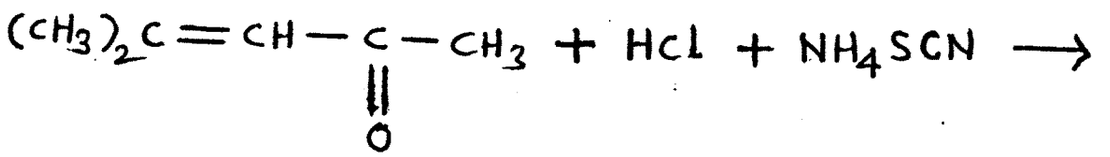
$$HN=\underset{\underset{SH}{|}}{C}-NH_2$$

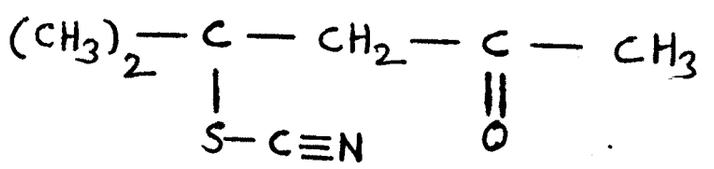
The mercaptopyrimidines act as chelating agents for metal ions by bonding through S atom, sometimes N, or possibly both jointly(57). In most of the cases they behave as unidentate ligand by complexation through S atom of the thiol group (58).

SYNTHESIS OF 1-SUBSTITUTED PYRIMIDINETHIOL

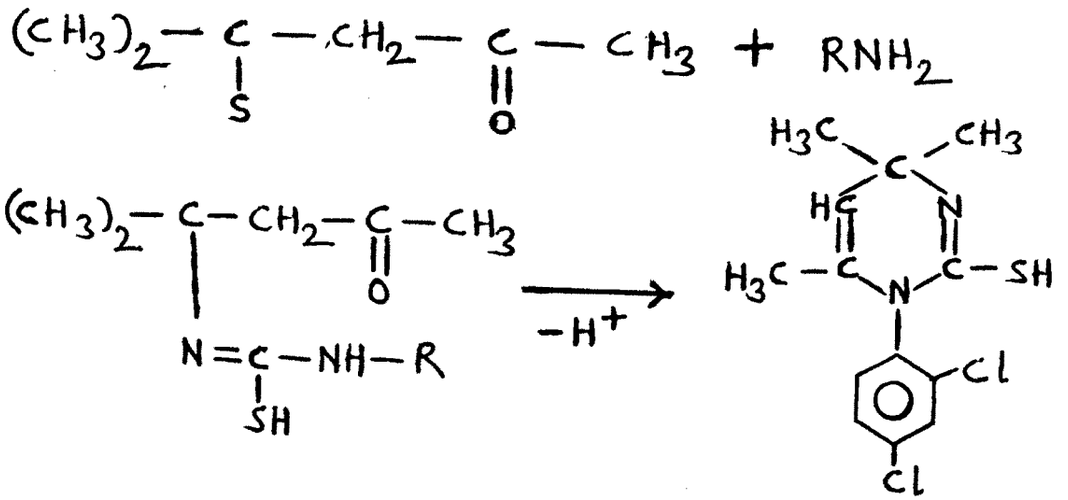
1-(2',4'-Dichlorophenyl)-4,4,6-Trimethyl -(1H,4H)-2-pyrimidinethiol was prepared by the method of Mathes(46-49) using 2,4-dichloroaniline. The synthesis was carried out in two steps. In the first step, 2-methyl-2-isothiocyanato-4-pentanone was prepared according to Bruson(59) while in the second step, the product was condensed with 2,4-dichloroaniline to obtain the desired compound.

Reactions :-





2- Methyl - 2 - thiocyano - 4 - pentanone



1-(2',4'-Dichlorophenyl)-4,4,6-trimethyl-
-(1H,4H)-2-pyrimidinethiol.

A) Synthesis of 2-Methyl-2-isothiocyanato-4-pentanone:

49.0 g (0.5 mole) of sulphuric acid dissolved in 50 ml of water was added over a period of 15 min to 98 g (1 mole) of mesityloxide at 15°. 76 g (1 mole) of ammonium thiocynate dissolved in 100 ml of water was added quite rapidly to this mixture at 20°. After stirring for 15 min, the upper red oily layer was separated and washed with water until free from acid. Compound was further purified by distillation at 100° (10 min).

Yield = 80 %

Anal. Calculated for $C_7H_{11}NOS$

C, 53.51; H, 7.00; N, 8.91; S, 20.38

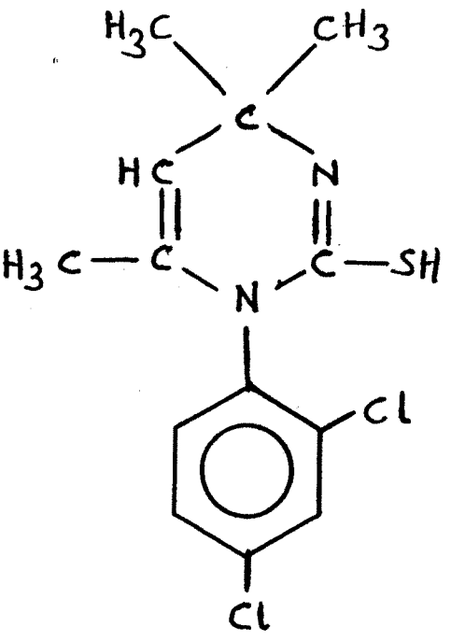
Found, C,53.48; H, 7.06; N, 8.90; S, 20.38.

B) Synthesis of 2,4-dichloro PT PT

To synthesise 1-(2,4-dichlorophenyl)-4,4,6-trimethyl(1H,4H)-2-pyrimidinethiol (2,4-dichloro PTPT),2-methyl-2-isothiocyanato-4-pentanone (3.14 g, 0.02 mole) was mixed with 2,4-dichloroaniline (3.24 g, 0.02 mole) dissolved in 50 ml ethanol. 15-25 drops of conc H_2SO_4 were added to the reaction mixture. The mixture was refluxed for 20-25 min and cooled. The crystalline product precipitated. The product was crystallised from glacial acetic acid, washed with water and air dried. The compound is colourless with a sharp M.P. 228°C. The practical yield on the basis of amine taken was 56%.

Molecular formula is $C_{13}H_{14}N_2SCl_2$

Structural formula is



Molecular weight is 301.00

Analysis calculated for $C_{13}H_{14}N_2SCl_2$

C, 51.82; H, 4.69; N, 9.38; S, 10.63; Cl, 23.59.

Found, C ,51.73; H, 4.68; N, 9.40; S,10.70; Cl,23.55.

Properties of 2,4-dichloro PTPT

The pyrimidinethiol is a colourless fine crystalline solid with a sharp M.P. 228°C. The compound is soluble in chloroform, DMF, DMSO and dioxan. It is insoluble in water and sparingly soluble in ethanol, acetone and methylisobutylketone. Its solution in DMF, dioxane, chloroform and DMSO is stable at room temperature for about two days and hence needs no protection from light.

Determination of Purity of 2,4-dichloro PTPT

Aromatic thiols are much acidic than corresponding phenols, hence the thiol group as an acid has long been determined titrimetrically by several authors (60-61). The purity of the pyrimidinethiol was determined by non-aqueous titration of the thiol group using Azoviolet (P-nitrophenyl-azoresorcinol) indicator according to the method of Verma (62).

EXPERIMENTAL :

Reagents :

Sodium Methoxide Solution:

0.05 M sodium methoxide in benzene methanol was prepared as described by Fritz and Lisicki (60) and standardized against benzoic acid in acetone using Victoria Blue as indicator.

Indicator : 0.1 % solution of Azo-violet in acetone was used.

Procedure :

A solution of 2,4-dichloro PTPT containing 15-20 mg in 25 ml of DMF was prepared. The appropriate aliquots were taken for titration with 0.05 M sodium monoxide by using 3-4 drops of the indicators solution. The colour change was from red to blue.

The results of the purity carried out in triplicate indicate the compound to be 99.80% pure. The overall standard deviation calculated from the pooled data for 16 mg of the compound used was 0.036 mg.

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