CHAPTER - I

SYNTHESIS OF REAGENTS AND THEIR CHARACTERISATION

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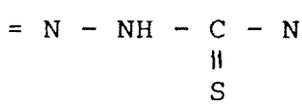
PART A : 3,5-DICHLORO SALICYLALDEHYDE THIOSEMICARBAZONE.

INTRODUCTION

Thiosemicarbazones are a class of compounds obtained by condensing thiosemicarbazide(TSC) with suitable aldehydes or ketones. These compounds are easily crystallisable and possess sharp melting points. Hence, they have long been commonly used for identification of individual aldehydes or ketones. However, the first report on analytical use of this class of compounds was made by Scott et al as late as 1945[1] . Since then voluminous work on their analytical applications has appeared in the literature. 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[3] et al recently gave a critical review on analytical applications of thiosemicarbazones and semicarbazones. Thiosemicarbazones contain active grouping for chelation as shown below -



which involves bonding through sulphur atom with possible further coordination by the hydrazino nitrogen atom to give a five membered chelate ring. Depending upon the type of aldehyde or ketone 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 occures only through the sulphur atom. The coloured complexes are used in selective and sensitive determination of metal ions. Domagk[4] et al. pioneered pharmaceutical applications of metal thiosemicarbazone for the treatment of tuberculosis. 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[5], protozoa[6], smallpox[7] and certain kinds of tumours[8] and possess very good pesticidal[9] and fungicidal[10] 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-acetamido-benzaldehyde thiosemicarbazone is found to be enhanced by the presence of a small amounts of copper ions[11]. These findings have led recently to an increased interest in the chemistry of transition metal chelates of thiosemicarbazones.

A large number of thiosemicarbazones are used as spectrophotometric reagents in analytical chemistry. They are used for trace determination of metal ions in various materials. Metal - thiosemicarbazone complexes are formed in conditions ranging from moderately acidic to moderately alkaline. However, there are relatively few reports on spectrophotometric determination of metal ions in highly acidic medium[12-14]. Metal complexes are also extractable in various organic solvents resulting in an enhanced sensitivity thereby enabling extraction and simultaneous photometric determination of metal ions[15-16]. It was generally observed that thiosemicarbazones containing hydroxy groups ortho to the aldehyde group gave good colour reactions. Besides the applications in spectrophotometry, thiosemicarbazones have been reported as gravimetric reagents for many metal ions[17-20], as indicators in the direct titration of metal with EDTA[21-22], in titration in non-aqueous solvents[23]. Recently reports have appeared on separation of metal ions using thiosemicarbazones by thin layer chromatography on alumina with ethyl acetate as a solvent[24].

In this chapter, the synthesis and characterisation of 3,5-dichloro salicylaldehyde thiosemicarbazone is described.

Synthesis of 3,5-dichloro salicylaldehyde thiosemicarbazone (3,5-dichloro SAT) :-

The starting material 3,5-dichloro salicylaldehyde was first prepared in the laboratory according to method of Duff[25] and this was used for condensation with thiosemicarbazide to obtain thiosemicarbazone.

I) Synthesis of 3,5-dichloro salicylaldehyde :-

3,5-dichloro salicylaldehyde was prepared according to the method of Duff[25]. A mixture of 300g glycerol and 70g boric acid was heated with stirring in a 2L beaker until the temperature was reached to 165° C. About 20 min were required for heating since a considerable amount of water had to be expelled.

An intimate mixture of 50g of 2,4-dichloro phenol and 50g of hexamine 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 min during which the temperature was maintained between 150-165° C by heating or cooling as necessary. Finally, the reaction mixture was allowed to cool to 115° C and was then acidified with a mixture of 50ml conc. H_2SO_4 in 150ml water. The method frequently employed for the isolation of o-hydroxyaldehyde 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 to about 110-120° C, while the steam was being passed through it. This was a distinct advantage in the case of difficulty volatile aldehydes.

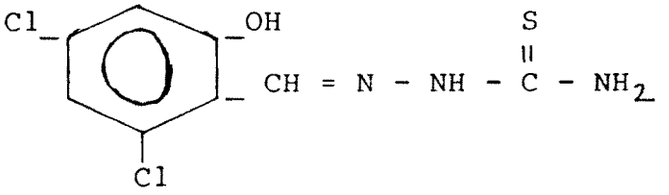
Yeeld 29% ; M.P. = 96° C

II) Synthesis of 3, 5-dichloro salicylaldehyde thiosemicarbazone :-

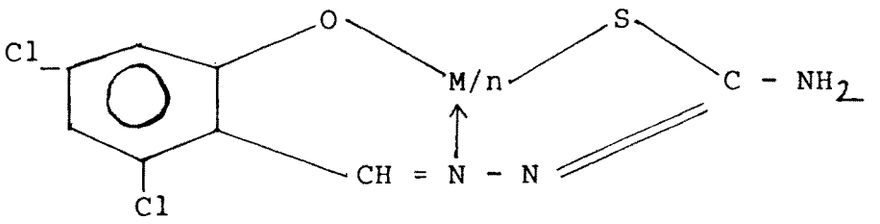
3,5-dichloro salicylaldehyde (2.3g;10nM) was dissolved in 20ml ethanol. Thiosemicarbazide (1g;10nM) was dissolved separately in 20ml of hot distilled water. The solutions were mixed, 2-3 drops of glacialacetic acid were added and the mixture was refluxed for 2 hrs. The mixture was then cooled in ice bath, 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 product has high melting point (above 330° C).

The crystal obtained were colourless and needle shaped which were analysed for carbon, hydrogen, nitrogen, sulphur and chlorine. Formula of the reagent is $C_8H_7Cl_2N_3OS$. Molecular Weight = 264

Structural Formula



The probable structure of the metal complex is as follows -



where n = 3

Elemental Analysis

	C	H	Cl	N	O	S
Found	36.25	2.60	26.59	15.91	6.15	12.10
Calculated %	36.36	2.65	26.52	15.91	6.06	12.12

For $C_8H_7Cl_2N_3OS$

Properties of the Reagent :-

3,5-dichloro SAT occurs as white needle shaped and light shining crystals with high melting point. The compound is sparingly soluble in cold water but soluble in hot ethanol. The solution of the compound in ethanol is stable for more than a week. The compound is stable towards light and heat. Its ethanolic solution is

colourless.

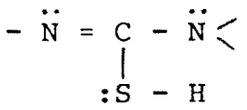
UV Spectrum of 3,5-dichloro SAT :-

The ultraviolet spectrum of 3,5,-dicholoro SAT in methanol is shown in Fig. 1. The spectrum shows three peaks at 238, 315 and 341nm.

PART B : SYNTHESIS AND CHARACTERISATION OF 4'-BROMO-PTPT.

INTRODUCTION

2-Mercaptopyrimidines is a class of compounds known to be cyclicthioureas. These are obtained by condensation of isothiocyanates with amines as a fine crystalline compounds. The active grouping for chelation as shown



is analogous to the grouping in thiourea in thiol[26] form such as

The Mercaptopyrimidines act as a chelating agent for metal ions by bonding through S atom sometimes N atom or possibly both jointly[27]. In most of the cases they behave as unidentate ligand by complexation through S atom of thiol group[28].

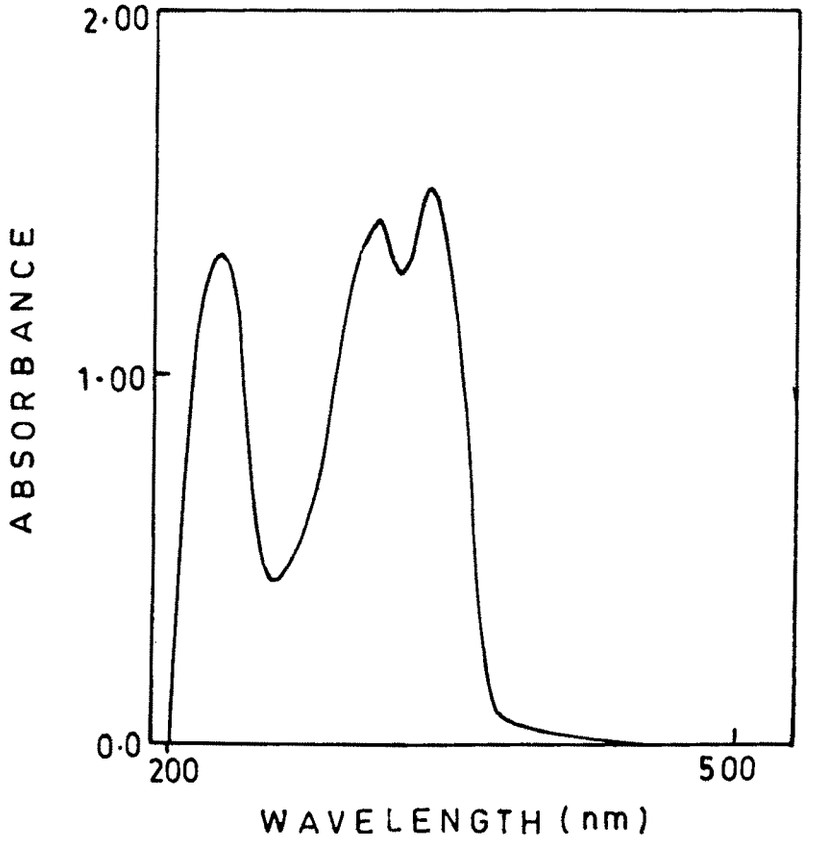


FIG. 1 — ABSORPTION SPECTRUM OF 3,5 — DICHLORO SAT IN METHANOL .

The first analytical application of this class of compounds was made by Singh et al as selective spectrophotometric reagents for the determination of some platinum group metals[28-31]. The analytical aspects of chemistry of substituted mercaptopyrimidines was also reviewed by Singh[32] et al. However, the use of such compounds as extractants for Platinum group metals and Gold has been reported for the first time in this laboratory[33-35]. The literature as well as our investigations on the use of mercaptopyrimidines in the extraction, separation and determination of Noble metals in particular revealed that the thioligands possess a fascinating analytical potentialities. This prompted us to undertake the studies on synthesis of thioligands with bromo-phenyl substituents at position 1 of mercaptopyrimidine moeity. With improved method for synthesis of mercaptopyrimidines by Mathes, a large number of compounds, their derivatives and the analytical utilities in the extractive photometric determination have been recently reported.

Like heterocyclicthiols, mercaptopyrimidines have been shown to be useful as vulcanization accelerators[36]. The compounds are biologically important as they have been reported to have antibacterial activity[37-38]. A number of papers have appeared on pharmacology of these compounds. Derivatives of pyrimidinethiols have been reported as antiwear additives for lubricating oils,

photographic adjucants[39-40]. There is a report in the use of these compounds as an intermediate in the preparation of fungicidal compounds[41].

Synthesis of 1-substituted pyrimidinethiol :-

1-(4'-bromophenyl)-4,4,6-trimethyl-(1H,4H)-pyrimidinethiol was prepared by the method of Mathes[42-45]. The synthesis was carried out in two steps. In the first step, 2-methyl-2-isothiocyanato-4-pentanone was prepared according to Bruson[46], while in the second step the product was condensed with p-bromoaniline to obtain 4'-bromo-PTPT.

A) Synthesis of 2-methyl-2-isothiocyanato-4-pentanone -

49.0g(0.5mole) of sulphuric acid dissolved in 50ml of water was added over a period of 15min to 98g(1 mole) of mesityl oxide at 15 . 76g (1 mole) of ammonium thiocyanate dissolved in 100ml of water was added quite rapidly to this mixture at room temperature. After stirring for 15 min the upper red, oily layer was separated and was washed with water until free from acid. The compound was dried by keeping it over night with anhydrous sodium sulphate.

Yield = 80%

Anal. calculated for $C_{17}H_{11}NOS$.

$C_{17}H_{11}N$ OS : C, 53.51; H, 7.0; N, 8.91;
O, 10.2; S, 20.38.

Found : C, 53.48; H, 7.06; N, 8.9
O, 10.18; S, 20.38.

B) Synthesis of 1-substituted mercaptopyrimidines (4'-bromo-PTPT) from, 2-methyl-2-isothiocyanato-4-pentanone and p-bromoaniline -

To synthesise 4'-bromo-PTPT, 2-methyl-2-isothiocyanato-4-pentanone (3.14g, 0.02 mole) was mixed with 4-bromoaniline(3.44g, 0.02mole) dissolved in 50ml ethanol. 15-25 drops of conc. H_2SO_4were added to the reaction mixture. The mixture was refluxed for 20-25 min and cooled. The crystalline product precipitated. The product was recrystallised from glacial acetic acid, washed with water and air dried. The compound is colourless with sharp M.P. 188°C and practical yield obtained was 68%.

Molecular Formula of compound is - $C_{13}H_{15}N_2SBr$.

Mol. Wt. 311.

Anal. Calculated for $C_{13}H_{15}N_2SBr$

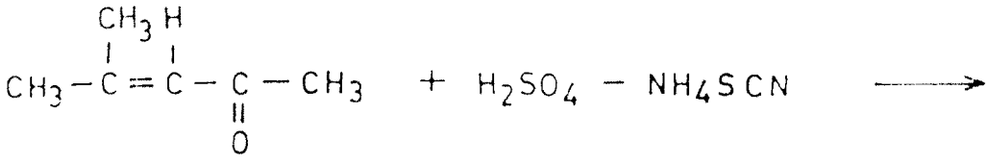
$C_{13}H_{15}N_2SBr$: C, 50.17; H, 4.82; N, 9.0;
S, 10.29; Br, 25.72.

Found : C, 50.20; H, 4.86; N, 8.9;
S, 10.30; Br, 25.74.

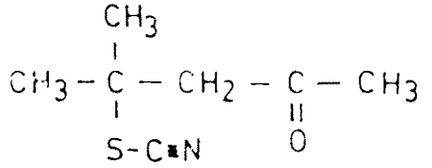
Properties of 4'-bromo-PTPT :-

The pyrimidinethiol is colourless fine crystalline, shining solid with a sharp M.P. 188°C. The compound is soluble in chloroform, DMF, DMSO and dioxan.

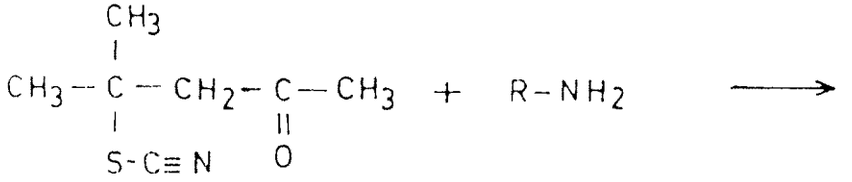
Reactions :—

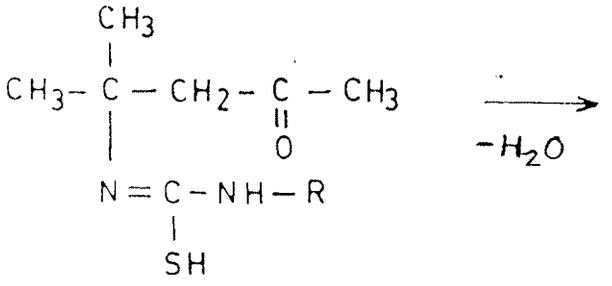


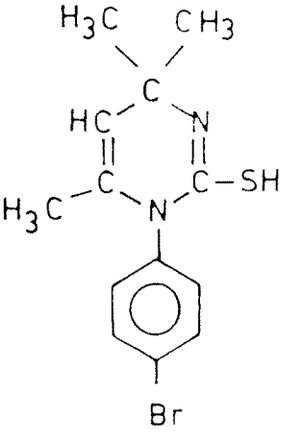
Mesityl Oxide



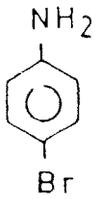
2- Methyl – 2 – isothiocyanato – 4 – pentanone







1 – (4′ – Bromophenyl) – 4,4,6 – trimethyl (1H, 4H) – 2 – pyrimidinethiol .

$R-NH_2 \equiv$ 

It is insoluble in water and sparingly soluble in ethanol, acetone and MIBK. Its solution in DMF chloroform, ethanol and DMSO is stable at room temperature for about 48 hours.

Determination of purity of 4'-bromo-PTPT :-

Aromatic thiols are much more acidic than corresponding phenols, hence, the thiol group as an acid has long been determined titrimetrically by several authors[47-48]. The purity of pyrimidinethiol was determined by non-aqueous titration of the thiol group using Azo-Violet (p-nitrophenyl-azoresorcinol) indicator, according to the method of Verma[49].

EXPERIMENTAL

REAGENTS

Sodium Methoxide Solution -

0.05 M Sodium methoxide in benzene-methanol (dry) was prepared as described by Fritz and Lisicki[47] and standardised against benzoic acid in acetone using Victoria Blue as an indicator.

INDICATOR

0.1% of solution of Azo-Violet in acetone was used.

PROCEDURE

A solution of 4'-bromo-PTPT containing 20-25mg in 25ml of DMF was prepared. The appropriate aliquots were taken for titration with 0.05M sodium methoxide by using 3-4 drops of the indicator solution. The colour change was red to blue.

The results of the purity carried out in the triplicate analysis indicate that the compound is 95.5% pure. The overall standard deviation calculated from the pooled data for 20mg of the compound used was 0.02mg.

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