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CHAPTER - II

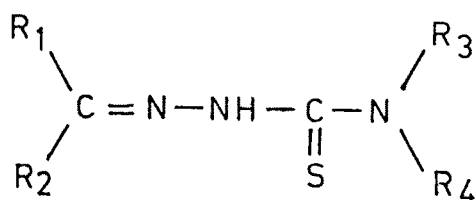
INTRODUCTION, SYNTHESIS AND CHARACTERIZATION  
OF 2 CHLOROQUINOLINE 3 - CARBALDEHYDE  
THIOSE ICARBAZANE

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INTRODUCTION

Thiosemicarbazones (TSC) are a class of compounds obtained by condensing thiosemicarbazide with suitable aldehyde or ketones. These compounds have long been commonly used for identification of individual aldehyde or ketones. However, the first report on analytical use of this class of compounds was made by Scott et al.<sup>1</sup> Since then the volumetric 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 paper dealing with their applications in analytical problems. The review of the work on transition metal complexes of thiosemicarbazides and thiosemicarbazones was written by Campbell,<sup>2</sup> Singh et al.<sup>3</sup> recently gave a critical review on analytical application of thiosemicarbazones and semicarbazones.

Thiosemicarbazones (TSC) contains active grouping for chelation as shown below in structure (I)



which involves bonding through sulphur atom with possible further coordination by the hydrazino nitrogen atom (marked with an asterisk in (I) to give a five membered 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 occurs only through the sulphur atom. The coloured complexes are used in selective and sensitive determination of metal ions.

Domagk et al.<sup>4</sup> 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, metal-thiosemicarbazone complexes have been found to be active against influenza<sup>5</sup>, protozoa<sup>6</sup>, smallpox<sup>7</sup>, tumours<sup>8</sup> and possess very good pesticidal<sup>9</sup> and fungicidal<sup>10</sup> activity. It is a well established fact that drugs increase the activity when administered in the form of metal complexes<sup>11,12</sup> and a number of metal chelates have been used as antitumour agents.<sup>13</sup> In the cancer treatment, it has been shown that the active species is not the thiosemicarbazone itself but a metal chelate of thiosemicarbazone<sup>14,15</sup>. The antituber

activity of p-acetamido benzaldehyde thiosemicarbazone is found to be enhanced by the presence of a small amounts of copper ions.<sup>16</sup>

Thiosemicarbazones, in general, are prepared by condensing thiosemicarbazide with an aldehyde or ketone in the presence of a few drops of glacial acetic acid. Preparation of the monoderivatives is simple but the derivatives of thiosemicarbazones are a little difficult and required special treatment. Dipyridylglyoxal dithiosemicarbazone<sup>17</sup> was prepared by cyclizing the monoderivative with 6 M hydrochloric acid.

The most important single factor affecting the behaviour of this ligand is the nature of the sulphur donor atom. Significantly there has been no report to date of such a complex in which the sulphur atom is not coordinated to the metal. EPR, electronic and far IR spectra have also provided evidence for the existence of strong metal sulphur bonds in these compounds. As well as being very polarizable the sulphur donor atom is also much larger than first row donor atoms. The size of the sulphur donor atom will exert a considerable influence on the stereochemistry of complexes formed by N<sup>3</sup> substitution

TSC's since in these ligands the hydrazinic nitrogen is sterically hindered.

The great deal of work on pharmacology of thiosemicarbazones and it has frequently been suggested that their activity is related to their ability to chelate trace metals. Most of the chemical research has concentrated on structure and bonding in these complexes in solid state. Very little is known of their properties in solution.

#### Chemical Properties of Reagent :

Just as hydrozones are weaker bases than hydrazides, thiosemicarbazones are weaker bases than thiosemicarbazides. Hydrolysis of these compounds yields first the hydrazones, hence these compounds resemble hydrazones in many of their reactions.

Mild reductions of thiosemicarbazones yield l-substitute of thiosemicarbazide. Catalytic reduction of these compounds yield hydrazides which are further hydrolysed to hydrazines. Reaction with alkoxide such as sodium ethoxide converts semicarbazones into hydrazones and with a strong base, hydrocarbons are obtained. This reaction may be applied for replacement of the carboxyl group by  $\text{CH}_2$  group.

The reagents can be readily hydrolysed to give the original carboxyl 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 hydrochloric acid and titrate with standard iodate solutions.<sup>39</sup>

Analytical aspect of thiosemicarbazones :

Thiosemicarbazones form coloured metal complexes in conditions ranging from moderately acidic to moderately alkaline. However only a few are reported for the spectrophotometric determination of metal ions in highly acidic medium.<sup>18-20</sup> 3-Hydroxypicolinaldehyde thiosemicarbazone is used to determine Co(II) in highly acidic medium.<sup>18</sup> Similarly glyoxal dithiosemicarbazone reacts with Ag(I) and Hg(II) at pH 1.1.<sup>19</sup> Salicylaldehyde thiosemicarbazone has been used to determine Mo(VI) in presence of iron in highly acidic medium.<sup>20</sup>

Metal complexes are also extractable in various organic solvents resulting in an enhanced sensitivity thereby enabling extraction and simultaneous determination of metal ions. Dipyrldylglyoxal dithiosemicarbazone<sup>21</sup> reacts with Ni(II) and Co(II) at pH 5.2, but only the Ni(II) complex is extractable into the chloroform and hence allows the determination of both metals when present together. Biacetyl monoxime thiosemicarbazone<sup>22</sup> has been used to determine Bi(III) in presence of Cu(II), by extraction of the complex into isobutyl methyl ketone.

The reagent 2-Acetylpyridine-4-phenyl-3-thiosemicarbazone (APPT)<sup>23</sup> react with Fe(II) to form a green colour

complex ( $\lambda$  max = 610 nm) at certain pH values (4.9-11.0) with a high absorptivity. However, this complex can be extracted into benzene, in which the absorptivity remains constant for at least 3 hours while Fe(III) - APPT complex is not extractable. The complexes of APPT with Fe(II) and Fe(III) contained in the metal and ligand in 1:2 ratio.

3-Hydroxypicolinaldehyde thiosemicarbazone<sup>18</sup> (HAPT) forms a yellow orange colour complex with trace amounts of Cobalt (II). The spectrophotometric determination may be done in weakly alkaline medium or in very acidic medium. In the first case, the sensitivity is high but the selectivity low while in other, although the sensitivity is smaller, interferences are rare. The reagent form octahedral complex with Co(II) and act as terdentate chelating agents.

The ligand 1,3-cyclohexanedione bithiosemicarbazone monohydrochloride<sup>25</sup> has been used for the photometric determination of copper (II) and zinc(II), Cu(II) forms a yellow coloured 1:2 complex in slightly acidic medium while Zn(II) forms orange red coloured 1:1 complex in fairly alkaline medium. The ligand has been used for the determination if trace amount of metal ions in milk, vegetable oils and sheep liver samples.



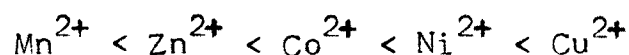
A new reagent 5,5-dimethyl-1, 2,3-cyclohexanetrione 1,2-dioxime-3-thiosemicarbazone<sup>26</sup> was synthesised and a simple, rapid, selective and sensitive method for spectrophotometric determination of iron in wines, minerals and foods was developed, based upon the formation of reagent - Fe(II) complexes. A violet colour is formed in strongly acid medium and the molar absorptivity of the complex is  $8.9 \times 10^3$  at 550 nm.

Recently Bingham, Alistair et al<sup>27</sup> studied the complex of 2-formylpyridine thiosemicarbazone with copper(II). The complexes were characterised by a variety of spectroscopic techniques and crystal and molecular structures were determined.

2,6-diacetylpyridine-bis thiosemicarbazone was prepared and its complex with Dioxouranium (VI) were characterised on the basis of elemental analysis, electrical conductance and IR and electronic spectral data by Yadav et al.<sup>28</sup>

Foye et al<sup>29</sup> reported synthesis and antimicrobial activities of N<sup>4</sup> - (2-acetoxyethoxymethyl) thiosemicarbazones. Significant growth inhibitory activity vs. gram positive and gram negative organisms, a yeast and a mold was found.

Physico-chemical studies on chelation behaviour of acenaphthenequinone monothiosemicarbazone (AQTS) with some bivalent metal ions was reported by Singh et al.<sup>30</sup> The stability constants of the chelates formed with divalent Mg, Mn, Co, Ni, Cu, Zn or Cd were determined pH metrically. The order of free energies and enthalpies of chelate formation for AQTS are :



Besides the application in spectrophotometry, thiosemicarbazones have been reported as gravimetric reagents for many metal ions,<sup>31-34</sup> as indicators in direct titrations of metal with EDTA<sup>35,36</sup> in titration in non-aqueous solvents.<sup>37</sup>

The literature survey has revealed that 2-chloroquinoline-3-carbaldehyde thiosemicarbazone has not been used for spectrophotometric determination of cobalt, manganese and chromium. Hence, the present work centers around the synthesis and application of this reagent in spectrophotometric determination of Co(II), Mn(II) and Cr(III).

Synthesis of 2-chloroquinoline-3-carbaldehyde  
thiosemicarbazone :

Preparation of 2-chloroquinoline-3-carbaldehyde :

2-Chloroquinoline-3-carbaldehyde was prepared by standard method<sup>38</sup> using vilsmier reagents (VR) as follows.

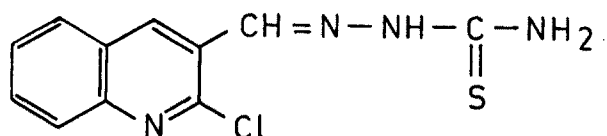
Dimethyl formamide (9.6 ml, 0.125 mol.) was cooled to 0°C in a flask equipped with a drying tube and phosphoryl chloride (32.2 ml, 0.35 mol.) was added drop wise with stirring. To this solution was added the acetanilide (0.05 mol.) and after 5 min. the solution was heated to 75°C under reflux for 16.5 hours. Then the reaction mixture was worked up as below.

The reaction mixture was poured into ice water (300 ml) and stirred for 30 min. at 0-10°C. The product was filtered off and washed well with water (100 ml), dried (68 %, 6.5 gm). Then the product was recrystallized from ethyl acetate m.p. 147 °C (reported m.p. 148° - 9°C). Due to the lack of reactivity of 2-chlorogroup,<sup>39</sup> it does not interfere with the derivative formed.

Synthesis of 2-chloroquinoline-3-carbaldehyde  
thiosemicarbazone :

The 2-chloroquinoline-3-carbaldehyde thiosemicarbazone (QAT) was synthesised by refluxing equimolar quantity of 2-chloroquinoline-3-carbaldehyde and thiosemicarbazide in minimum amount of ethanol for one hour. The crystalline product was obtained, washed with distilled water, ether and finally with ethanol. It was recrystallised from ethanol m.p. 225-226°C.

Structure of QAT :



Other Reagents :

Reagent grade chemicals were used for preparing the solutions required for the study of various diverse ions.

### Absorption Spectra of the Reagent :

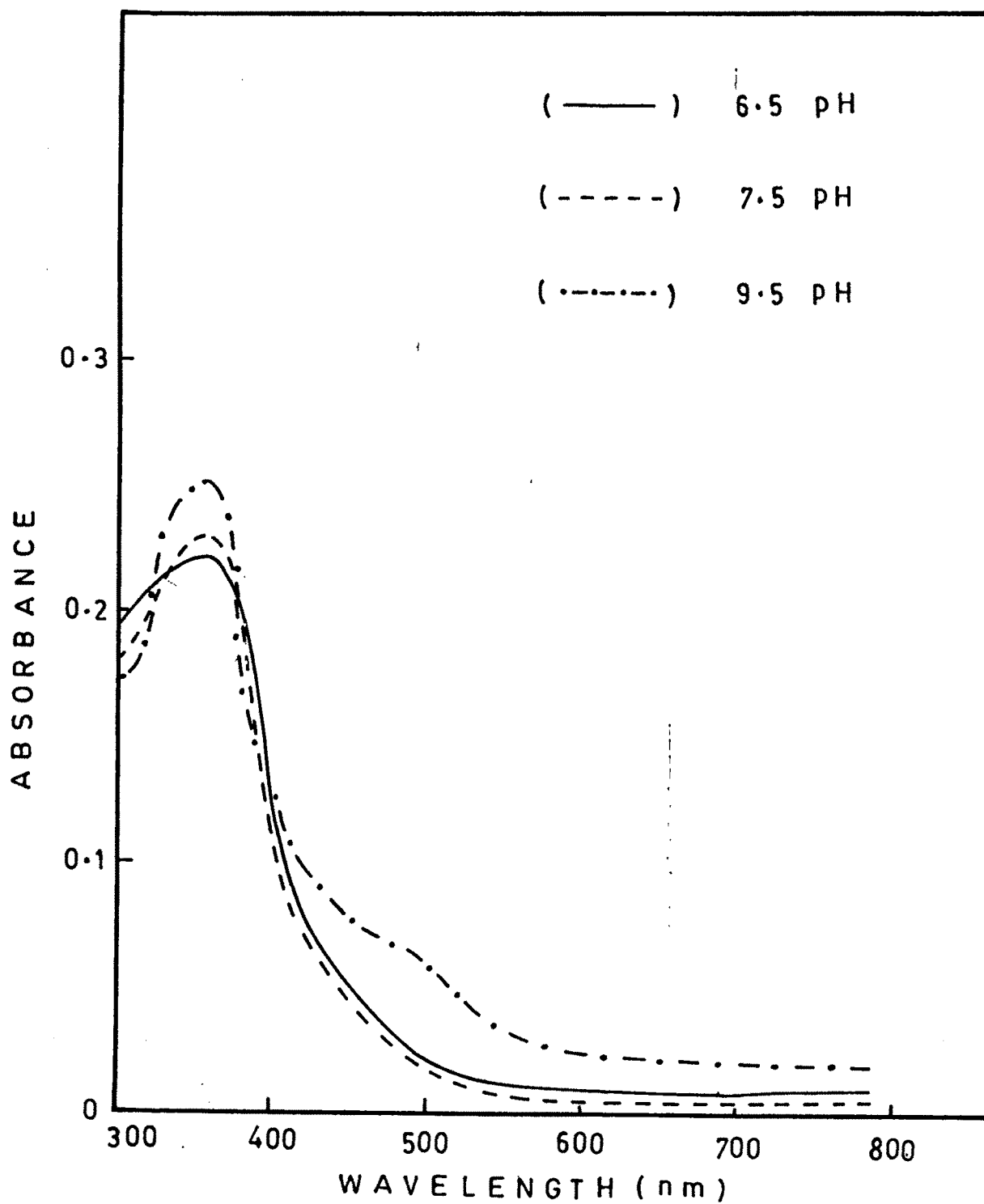
The absorption spectra of 2-chloroquinoline-3-carbaldehyde thiosemicarbazone in DMF + Water (3:2) solution at pH 6.5, 7.5 and 9.5 are shown in the Figure 2.1. The absorption curves exhibit strong absorption band at 350 nm with molar extinction coefficients of  $.1075 \times 10^4$ ,  $.1173 \times 10^4$ ,  $.127 \times 10^4$  L mole<sup>-1</sup> cm<sup>-1</sup> at pH 6.5, 7.5, 9.5 respectively. The UV spectrum of the reagent in DMF + Water (3:2) medium shows that reagent has maximum absorption in the UV region and not in visible region. The UV spectrum of the reagent in alkaline medium shows a shoulder at 480 nm.

### Infrared Spectra :

Infrared absorption spectra in the range 200 to 4000 cm<sup>-1</sup> were run on a Perkin Elmer IR Spectrophotometer using KBr pallet technique. The characteristic absorption bands were observed as follows :

3125 cm<sup>-1</sup>, NH stretch, 3280 cm<sup>-1</sup>, NH<sub>2</sub> stretch, 1650 cm<sup>-1</sup>, C = C; 1600 cm<sup>-1</sup> = C - N =; 1540 cm<sup>-1</sup>, pyridine ring; 750 cm<sup>-1</sup> = C = S.

FIG. 2.1 — ABSORPTION SPECTRA OF QAT  
IN DMF+H<sub>2</sub>O (3:2) AT pH  
(—) 6.5 , (---) 7.5 , (-·-·-) 9.5 .



Preparation of buffer solutions :

The following solutions of pH 1 to 11 were prepared by the following procedure :

pH	Composition of the mixture.
1	47.5 ml of $\frac{N}{5}$ HCl + 25 ml $\frac{N}{5}$ KCl and dilute to 100 ml.
2	5.3 ml $\frac{N}{5}$ HCl + 25 ml $\frac{N}{5}$ KCl and dilute to 100 ml.
3	20.55 ml of $\text{Na}_2\text{HPO}_4$ ( $\frac{N}{5}$ ) + 79.45 ml of ( $\frac{N}{10}$ ) citric acid.
4	41.0 ml of 0.2 M $\text{CH}_3\text{COOH}$ + 9 ml of 0.2 M $\text{CH}_3\text{COONa}$ .
5	14.75 ml 0.2 M $\text{CH}_3\text{COOH}$ + 35.26 ml $\text{CH}_3\text{COONa}$ .
6	9 ml of 0.2 M $\text{CH}_3\text{COOH}$ + 191.0 ml 0.2 M $\text{CH}_3\text{COONa}$ .
7	12 ml 0.05 M borax + 188 ml solution containing 12.40 g boric acid and 2.93 g of NaCl in 1 litre.
8	19.071 gm $\text{Na}_2\text{B}_4\text{O}_7$ dissolved in 500 ml distilled water.
9	19 gm $\text{Na}_3\text{PO}_4 \cdot 12 \text{H}_2\text{O}$ dissolved in 500 ml distilled water.
10	250 ml 0.1 M Boric acid + 219.5 ml 0.1 N NaOH- diluted to 500 ml.

- 11      60 ml 0.1 M NaOH + 200 ml 0.15 M  $\text{Na}_2\text{HPO}_4$ ,  
dilute to 500 ml.

In addition to these buffer solutions standard buffer of pH 4 was prepared by dissolving 10.21 g of potassium hydrogen phthalate in 1 litre.

Apparatus :

All the spectral measurements over the spectral region were done on a Carl Zeiss grating spectrophotometer and Hitachi 330. spekol by using 10 mm matched pair of glass cuvettes. For measurement of pH values Elico Digital pH meter was used. A standard Phthalate buffer (0.05 M) was used for the standardization of the pH meter.



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