PART II

SYNTHESIS

of

3-ARYL-2-MERCAPTO-QUINAZOL-4-ONES
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INTRODUCTION

Although a considerable amount of work in the synthesis of various quinazolone derivatives has been published, the sulphur containing quinazolone derivatives are comparatively less described. In this part 3-aryl-quinazol-4-ones described contain mercapto group in 2 position. Before the actual description of work, a brief resume of the sulphur containing quinazolone derivatives is given below. Most of such compounds are synthesized by the methods which are analogous to those employed for the other quinazolone derivatives.

(I): 4-MERCAPTO-QUINAZOLINES

Bogert and Hand (J. Am. Chem. Soc., 1903, 25, 372) have prepared 4-mercapto-quinazolines by condensing o-amino-thiobenzamides or acids
with acid anhydrides or amides respectively. The starting material for o-amino-thiobenzamide is anthranilic nitrile (see also Bogert and Chen, ibid., 1922, 44, 2352).

![Chemical reaction diagram]

Harry (J. Am. Chem. Soc., 1953, 75, 677) used thio-lactic acid with o-amino-benzonitrile and obtained 4-mercapto-2-methyl-quinazoline.

A method of more general character is one, that was developed by Leonard and Curtin (J. Org. Chem., 1946, 11, 349) in which quinazol-4-ones are treated with phosphorus pentasulphide in boiling xylene solution. It is an innovation of the original Kendall's method (Chem. Abstr., 1935, 29, 5670). The method has been adopted by Tomisek and Christensen (J. Am. Chem. Soc., 1948, 70, 2423); Russell et al. (ibid., 1949, 71, 2279); Jackman, Petrow and Stephens (J. Pharm. and Pharmacol., 1960, 12, 529) and Bhaduri, Khanna and Dhar (J. Sci. Industr. Res. India, 1962, 21B, 380).

The methods of preparation of 2-mercapto-quinazol-4-ones consist of the cyclisation of an o-carboxyl- or o-carbalkoxy-phenylthiourea derivatives.

(A) : Methods of preparation

McCoy (Ber., 1897, 30, 1688) heated mono-phenylthiourea and anthranilic acid in dilute aqueous alkali and obtained the simple 3-phenyl-2-mercapto-quinazol-4-one (II). Pawlewski (Ber., 1905, 38, 131) got the same product (II) without using alkali; while Duglass and Dains (J. Am. Chem. Soc., 1934, 56, 719) prepared similar products causing cyclisation by sulphuric acid.

This method has been employed recently by Amin et al. (Jour. Indian Chem. Soc., 1960, 37, 595) and has been subsequently used by others (Trivedi, ibid., 1960, 37, 801; Joshi and Giri, ibid., 1962, 39, 189). This method has also been used in the present work.

In another method by Rupe (Ber., 1897, 30, 1097), ethyl-anthranilate hydrochloride when heated for long time with concentrated potassium
thiocyanate solution formed 2-mercaptopo-quinazol-4-one, which was also obtained by Sachdev and Ralhan (J. Sci. Industr. Res., India, 1960, 19B, 215) by simply heating together anthranilic acid with ammonium thiocyanate for about half an hour (see also Sharma et al., ibid., 1956, 15B, 687). Very recently, Howard and Klein (J. Org. Chem., 1962, 27, 3701) got the same compound simply by heating methyl-anthranilate thiocyanate salt in xylene.

\[
\begin{align*}
\text{CONR} & + \text{SH} \\
\text{NH} & \\
\text{R} & : \text{H or CH}_3 \text{ or } \text{C}_2\text{H}_5, \quad \text{R} : \text{NH}_4 \text{ or K.}
\end{align*}
\]

Instead of alkali thiocyanate, aryl or alkyl isothiocyanates have been heated together with anthranilic acid and its derivatives and 3aryl-2-mercaptopo-quinazol-4-ones were obtained (Stewart, J. prakt. Chem., 1891, 44(ii), 415; Fortman, ibid., 1897, 55(ii), 132; McCoy, loc.cit.; Freundler, Bull. soc. chim., France, 1904, 31(iii), 882).


Ghosh (J. Indian Chem. Soc., 1930, 7, 981) studied the interaction of phenyl isothiocyanate with anthranilic acid and obtained 3-phenyl-2-thioquinazol-4-one (II) directly at higher temperatures. At lower temperature, he isolated the intermediate thio-ureido acid (I) which was also cyclised to (II) by heating, thus confirming the intermediate product (I).
This elegant method has been adopted by Amin et al. (loc. cit.) and has also been employed by Sachdev and co-workers (references cited above, and also J. Sci. Industr. Res., India, 1961, 20C, 178; et seq.); Butler and Partridge (J. Chem. Soc., 1959, 1512) and McCarty and co-workers (J. Am. Chem. Soc., 1960, 82, 964 and a personal communication to Dr. G. C. Amin) in preparing several 3-alkyl substituted 2-mercapto-quinazol-4-ones. This method is also followed in the present part to which the reference will be made later.

(B) : Reactions

2-Mercapto-quinazol-4-one derivatives are reactive and could undergo a variety of reactions of which some are briefly described below:

(1) Oxidation : 2-Mercapto-quinazol-4-ones could be oxidised by a number of reagents. For example, Busch has used mercuric oxide (Ber., 1892, 25, 285), alkaline potassium permanganate (Chem. centr., 1893, (ii), 578; Brit. Abstr., 1894, 66(i), 146) and alkaline hydrogen peroxide (J. prakt. Chem., 1895, 51(ii), 275). Other workers have also oxidised by similar methods (McCoy, Ber., 1897, 30, 1688; Kunckell, ibid., 1905, 38, 1213 and Pawlewski, ibid., 1906, 39, 1734). In all cases, the 2-mercapto group was converted into the ketonic group forming ultimately quinazol-2:4-dione derivatives.
(2) **Action of Alkyl halides and Benzyl chloride**: McCoy (Ber., 1897, 30, 1682) has reported the S-alkylation of 2-mercapto-quinazol-4-ones with alkyl halides in alcoholic alkali:

\[
\text{C-SH} + \text{C}_2\text{H}_5\text{I} \rightarrow \text{C-S-C}_2\text{H}_5
\]

Ghosh (J. Indian Chem. Soc., 1930, 7, 981) and McCarty, Haines and VanderWerf (J. Am. Chem. Soc., 1960, 82, 964) have adopted this method for alkylation of mercapto group. McCarty et al. (loc. cit.) have also adopted a similar method for preparation of S-benzyl derivatives by using benzyl chloride.


(4) **Chlorination**: Chlorination of 2-mercapto-quinazol-4-one in chloroform resulted into 2-chloro-quinazol-4-one (McCoy, loc. cit.). Other examples seem to be unknown.
(5) **Action of Primary Amines**: McCoy (loc.cit.) has shown that when 3-phenyl-2-mercapto-quinazol-4-one is heated at $300^\circ$ with aniline, it gave 3-phenyl-2-phenylimino-quinazol-4-one (I), while the same reaction when carried out in a sealed tube at the same temperature, the product obtained was 3-phenyl-2:4-diphenylimino-tetrahydroquinazoline (II).

(6) **Action of Iodine solution**: A solution of 2-mercapto-3-phenyl-quinazol-4-one in acetic acid on treatment with iodine solution in potassium iodide gives a disulphide derivative (Ghosh, *J.Indian Chem. Soc.*, 1930, 7, 981). Other examples of this type of reaction seem to be unknown.

(7) **Action of Mineral Acids**: Ghosh (loc.cit.) heated 3-substituted 2-mercapto-quinazol-4-one (I) with concentrated sulphuric acid at $125^\circ$ and obtained a product to which he assigned structure (II):

(I) $R$: Phenyl; (IV) $R$: Allyl. (II) $R$: Phenyl; (V) $R$: Allyl.
McCarty (J.Org.Chem., 1962, 27, 2672) has proved it to be benzo-(d)-thiazolo-(2,3-b)-quinazol-11-one (III), which has been previously synthesized by Bose and Pathak (J.Indian Chem.Soc., 1934, 11, 463).

Ghosh (loc.cit.) also obtained a product with structure (V) on heating 3-allyl-2-mercapto-quinazol-4-one (IV) with 12 N hydrochloric acid. This structure too was found to be erroneous and McCarty et al. (personal communication to Dr. G.C. Amin) has proved it to be 2-methyl-2;3-dihydro-thiazolo-(2,3-b)-quinazol-5-one (VI).


Kendall and Duffin (U.S.Pat. 2527265-66 / 1950; Chem.Abstr., 1950, 44, 9287) treated quinazol-4-one-thio-acetic acid (I) (Kendall, loc.cit.) with acetic anhydride in pyridine and obtained for the first time a quinazolo-thiazole derivative having structure either (II) or (III):
Quite recently, Howard and Klein (J.Org.Chem., 1962, 27, 3701) confirmed structure (II) by an unambiguous synthesis. Narang and co-workers (J.Sci.Industr.Res., India, 1953, 12B, 467; 1956, 15B, 687, 690; 1960, 19C, 12; 19B, 217; Tetrahedron, 1961, 15, 53) have carried out extensive work on this ring-system and have proposed the nomenclature, in which the structure (II) is called '10:11-thiopegan' and structure (III), '9:10-thiopegan', respectively.


![Chemical Structure](image)

(III) : 2-THIO-3:4-DIHYDRO-QUINAZOLINES

2-Thio-3:4-dihydro-quinazolines are easily prepared from o-amino-benzylamines and carbon disulphide in presence of alcoholic alkali (Busch, Ber., 1892, 25, 2853; Busch and Brunner, J.prakt.Chem., 1895, 52(ii), 373).
Paal and Laudenheimer (Ber., 1892, 22, 2978) obtained these compounds from benzothiazone and primary aromatic amines, the former being obtained from o-amino-benzyl alcohol and carbon disulphide:

\[
\begin{align*}
\text{Ph.} \quad \text{NH}_2 \quad + \quad \text{CS}_2 \quad \xrightarrow{\text{EtOH}} \quad \text{Ph.} \quad \text{NH}_2 \quad + \quad \text{H}_2\text{O}
\end{align*} \]

Kippenberg's method consists in treating o-amino-benzyl alcohol derivatives with thiocyanic acid (Ber., 1897, 30, 1130).

That 3-aryl-4-hydroxy-2-thio-3:4-dihydro-quinazolines or their oxygen ethers which are colourless give brilliant red to purple colours in strong acid solutions has given much impetus to the study of these compounds. They can be prepared by the action of aryl isothiocyanates on o-amino-benzaldehydes, phenyl ketones or their derivatives (Gheorghiu, Compt. rend., 1933, 197, 622; Monolescu, Bull. soc. chim., France, 1937, 4(v), 1126; Monolescu and Pavelescu, Ann. sci. univ. Jassy, 1939, 25(i), 223; Chem. Abstr., 1939, 33, 4994; Sandovaenu, ibid., 1940, 26(i), 531; Chem. Abstr., 1941, 35, 3260).

\[
\begin{align*}
\text{Ph.} \quad \text{NH}_2 \quad + \quad \text{Ph.N:C:S} \quad \xrightarrow{\text{EtOH, Heat}} \quad \text{Ph.} \quad \text{NH}_2 \quad + \quad \text{H}_2\text{O}
\end{align*} \]

They are colourless solids but in sulphuric acid or perchloric acid solution, they give brilliant shades varying from red to purple. Such salts also result from their heavy metal salt complexes in halogen acids (Monolescu, loc. cit.).
Busch (loc.cit.) oxidised 3-phenyl-2-thio-3:4-dihydro-quinazoline (I) by heating it with mercuric oxide in alcohol and obtained 3-phenyl-3:4-dihydro-quinazol-2-one (II):

These quinazoline derivatives undergo ring cleavage on heating with aromatic amines (Sadoveanu, loc.cit.).

Mănolescu and Pavelescu (loc.cit.) have shown that 3-aryl-2-thio-quinazoline derivatives which are colourless at room temperature are transformed into coloured substances at elevated temperatures. The colour is supposedly due to the ionic dissociation produced by opening the hetero-ring.

(IV) : QUINAZOL-2:4-DITHIONES

Quinazol-2:4-dithiones or 2:4-dimercapto-quinazolines or more simply benzoylenethioureas are not much common like their oxygen analogues.

Kötz (J.prakt.Chem., 1893, 47(ii), 303) has prepared simple quinazol-2:4-dithione by the action of alcoholic potassium hydrosulphide on 2:4-dichloro-quinazoline:
Harry (J. Am. Chem. Soc., 1953, 75, 675) has synthesized it for possible application as hypoglycemic agent.

Bogert and Scatchard (J. Am. Chem. Soc., 1919, 41, 2052) obtained these compounds by the action of phosphorus pentasulphide on 2:4-diketoquinazolines:

The nitro group in the above compound undergoes reduction during the pentasulphide reaction (see also, Elion and Hutchings, J. Am. Chem. Soc., 1947, 69, 2138; Russell et al., ibid., 1949, 71, 2279). Bogert and Scatchard (loc. cit.) have also shown that quinazol-2:4-dithione reacts with ammonia and a wide variety of amines with replacement in 4 position only. Similarly, on treatment with hydrochloric acid, the 4-mercapto-group is converted into the hydroxyl group resulting into the formation of 4-hydroxy-2-mercapto-quinazoline derivative, tautomeric with 2-mercapto-quinazol-4-one.

Murofushi and Ashikawa (J. Chem. Soc., Japan, 1949, 52, 12; Chem. Abstr., 1951, 45, 1444) have reported the use of 2:4-dimercaptoquinazoline as desensitising agent in photographic emulsions.
It will be seen from the above short review of the literature on the subject that the preparation of 2-mercapto-quinazol-4-ones requires condensation between anthranilic acids or their derivatives and (a) mono-arylthioureas or (b) aryl isothiocyanates. The present work comprises of the synthesis of 3-aryl-2-mercapto-quinazol-4-ones substituted in both benzene nuclei. This is achieved by the condensation of substituted anthranilic acids with (a) mono-arylthioureas as well as (b) aryl isothiocyanates, the preparations of which are briefly touched below.

(a) : Mono-arylthioureas :

(i) The mono-arylthioureas were prepared by the addition of ammonia to aryl isothiocyanates in ethanol though other solvents could be used (Kaye and Parris, J.Org.Chem., 1951,16,1862; Buu-Hoi, J.Chem. Soc., 1955,1573).

\[ R.N:C:S + NH_3 \rightarrow RHN.CS.NH_2 \]

(ii) In another method, ammonium thiocyanate and solution of the amine in requisite quantity of hydrochloric acid were evaporated together (Lange and Reed, J.Am.Chem.Soc., 1926,48,1069; Saijo, J.Pharm. Soc. Japan, 1952,72,1009).

\[ R.NH_2 . HCl + NH_4.CNS \rightarrow RNH_2 . HSCN + NH_4.Cl \]

\[ RNH_2 . HSCN \rightarrow RNH.CS.NH_2 \]

(b) : Aryl isothiocyanates :

(i) The aryl isothiocyanates were prepared by first synthesizing sym-diarylethythioureas from carbon disulphide and an aryl-amine in
presence of some catalyst. Here potassium hydroxide was used as
catalyst (Raiford and McNulty, J. Am. Chem. Soc., 1934, 56, 680; Bernstein,
et al., ibid., 1951, 73, 906). These diarylthioureas were then decomposed
in presence of acid or acetic anhydride when aryl isothiocyanates were
formed:

\[
\begin{align*}
2 \text{R.NH}_2 + \text{CS}_2 & \rightarrow \text{RNH.CS.NHR} + \text{H}_2\text{S} \\
\text{RNH.CS.NHR} & \rightarrow \text{R.N.C.S} + \text{R.NH}_2
\end{align*}
\]

The product is separated by steam distillation and is sufficiently pure
for further work (Werner, J. Chem. Soc., 1891, 59, 396; Skita and Rolfses,
Buu-Hoi, loc. cit.).

(ii) In another method, the decomposition of ammonium dithio-
carbamate (formed from amine, carbon disulphide and ammonia) by lead
nitrate was used:

\[
\begin{align*}
\text{R.NH}_2 + \text{CS}_2 + \text{NH}_3 & \rightarrow \text{RHN.CS.S.NH}_4 \\
\text{RHN.CS.S.NH}_4 + \text{Pb(NO}_3)_2 & \rightarrow \text{R.N:C.S} + \text{NH}_4\text{NO}_3 + \text{PbS} + \text{HNO}_3
\end{align*}
\]

Instead of lead nitrate, many other salts could also be used (Hodgkins

When 2-mercapto-quinazol-4-ones were oxidised by alkaline hydrogen
peroxide, quinazol-2:4-diones were formed. To prepare these diones,
mono-arylureas were required. These were prepared by the action of
potassium cyanate on amine hydrochloride (Weith, Ber., 1876, 21, 820):

\[
\begin{align*}
\text{RNH}_2\cdot\text{HCl} + \text{KCNO} & \rightarrow \text{RNH}_2\cdot\text{HCNO} + \text{HCl} \\
\text{RNH}_2\cdot\text{HCNO} & \rightarrow \text{RNH.CO.NH}_2
\end{align*}
\]

The reaction can also be brought about in acetic acid. A method in
which nitro-urea is used is not much convenient.
Thus, all the mono-arylthioureas, aryl isothiocyanates and mono-arylureas required during the present work were prepared by the typical methods described in experimental and are tabulated below:

<table>
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<th>S. No.</th>
<th>Aryl Group</th>
<th>Mono-arylthiourea RHN.CS.NH₂</th>
<th>Aryl isothiocyanate R.N.C:S †</th>
<th>Mono-arylurea RHN.CO.NH₂</th>
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<tr>
<td></td>
<td></td>
<td>m.p. °C</td>
<td>Ref. nos.</td>
<td>b.p. or (m.p.) °C</td>
</tr>
<tr>
<td>1</td>
<td>Phenyl</td>
<td>153-54</td>
<td>1 to 7</td>
<td>221-22</td>
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<td></td>
<td></td>
<td>153+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>o-Tolyl</td>
<td>155</td>
<td>8</td>
<td>238-40</td>
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<td></td>
<td>160-61</td>
<td>9,10,23</td>
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<td>p-Tolyl</td>
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<td>237</td>
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<td>14</td>
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<td>(26)</td>
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<td>188+</td>
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</tr>
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<td>5</td>
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<td>15</td>
<td>266-67</td>
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<td></td>
<td>148+</td>
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† The products are separated by steam distillation and are sufficiently pure for further reactions.
+ These melting points were observed of the products prepared during the work.
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<td>175+</td>
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<td>(45)</td>
<td>8</td>
<td>212</td>
<td>44</td>
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Ref. no.: publication:

2. Rathke, Ber., 1885, 18, 3102.
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Cosack, Ber., 1880,13,1089.
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38 Steiner, Ber., 1875,8,519.
39 Muhlhauser, Annalen, 1881,207,244.
40 Sah and Chang, Ber., 1936,69B,2764.
43 Doht, Monatsh, 1906,27,213.
Diagramatic Representation: Section (I)

Synthesis of 6-Chloro-3-aryl-2-mercapto-quinazol-4-ones and their derivatives

\[ \text{Cl} \quad \text{CH}_3 \quad \text{Ac}_2\text{O} \quad \text{O} \quad \text{Cl} \quad \text{COOH} \]

\[ \text{Cl} \quad \text{NH}_2 \quad \text{Cl} \quad \text{H}_2\text{N} \quad \text{NH}_2 \quad \text{N-Ar} \]

\[ \text{Cl} \quad \text{NH}_2 \quad \text{Cl} \quad \text{H}_2\text{N} \quad \text{NH}_2 \quad \text{N-Ar} \]

(a) \[ 180-90^\circ \text{ Refluxing in EtOH} \]

(b) \[ \text{Cl} \quad \text{COOH} \quad \text{Dil. HCl} \]

\[ \text{H-N-Ar} \quad \text{C-S} \]

\[ \text{H}_2\text{N} \quad \text{C-S} \]

\[ \text{Ar} = \text{Phenyl}, \quad \text{o-, m-, p-Tolyl}, \]
\[ \text{o-, p-Anisyl}, \quad \text{o-, m-, p-Chloro-phenyl} \]
5-Chloroanthranilic acid required for this purpose was prepared by the oxidation of 5-chloro-2-acetamino-toluene by means of neutral potassium permanganate and the subsequent hydrolysis of the N-acetyl-anthranilic acid thus produced (Höchster, Farbwerke, Ger. Pat. 152484 / 1904; Chem. Zentr., 1904, II, 168). The other method of direct chlorination leads to the impure product (Eller and Klemm, Ber., 1922, 55, 221; Endicott, Alden and Sherrill, J. Am. Chem. Soc., 1946, 68, 1303).

Anthranilic acid itself has been condensed with mono-phenylthiourea by McCoy (Ber., 1897, 30, 1688) and 3-phenyl-2-mercapto-quinazol-4-one structure was assigned to it, the formula of thioureido acid (I) as the intermediate being assumed.

In the present work, 5-chloroanthranilic acid was condensed with mono-phenylthiourea and this should, by above analogy, give 6-chloro-3-phenyl-2-mercapto-quinazol-4-one. Here the condensation was carried out by heating the two reactants together at high temperature.
Further, the same product was obtained by the action of phenyl isothiocyanate on 5-chloroanthranilic acid in ethanolic solution. This method has been utilised by McCoy (loc.cit.) for 3-phenyl compound and Pawlewski (Ber., 1906, 39, 1734) for 3-allyl-2-mercapto-quinazol-4-one.

Ghosh (J. Indian Chem. Soc., 1930, 7, 981) carried out the reaction in cold and obtained a mixture of o-phenyl-thiocarbamido-benzoic acid (I) and the expected 3-phenyl-2-mercapto-quinazol-4-one (II) from phenyl isothiocyanate and anthranilic acid, thus confirming the contention of McCoy (loc.cit.).

That the latter method gives 2-mercapto-quinazol-4-ones, has been amply supported by the work of McCarty (personal communication to Dr. G.C. Amin), Sachdev, Dhami and Atwal (Tetrahedron, 1961, 14, 304) and Sharma and Singh (J. Sci. Industr. Res., India, 1961, 20C, 178) et seq.

6-Chloro-3-phenyl-2-mercapto-quinazol-4-one was treated with dry bromobenzene in presence of anhydrous potassium carbonate and finely divided copper powder (Ullmann Reaction). The product was isolated after removing excess of bromobenzene by steam distillation. This product was assigned the constitution 6-chloro-3-phenyl-2-thiophenyl-quinazol-4-one (IV) in which the new phenyl nucleus has substituted the hydrogen atom attached to the sulphur atom of the mercapto group.

Further, benzoyl chloride under the conditions of Schotten-Baumann reaction was added to the same 6-chloro compound and 6-chloro-3-phenyl-2-thiobenzoyl-quinazol-4-one (IV) was obtained in a similar way.
In both these cases the phenyl and the benzoyl groups are assumed to replace the hydrogen atom attached to the sulphur atom:

\[ \text{N-Ph} \quad \text{C-S-Ph} \quad \overset{\text{XR}}{\rightarrow} \quad \text{N-Ph} \quad \text{C-S-R} \]

(VIII) can have alternate structure (IX) in which the position of the hydrogen atom is with nitrogen and consequent change in the position of the double bond. In the present work the compounds formed by the action of bromobenzene and benzoyl chloride were assumed to be in 'thiol' state as indicated in (III), which is the most logical.

The 'thiol' form predominated or formed at the demand of the reagent (in this case bromobenzene or benzoyl chloride) is supported by the observation of McCarty, Haines and VanderWerf (J. Am. Chem. Soc., 1960, 82, 964). These authors carried out the alkylation of 3-phenyl-2-mercapto-quinazol-4-one (II) by a number of the alkylating agents and found that the alkylation occurs at the sulphur atom rather than the nitrogen atom. This was proved by acid hydrolysis of 3-phenyl-2-thioethyl-quinazol-4-one (VI) to 3-phenyl-quinazol-2:4-dione (VII) and confirming the simultaneous formation of ethyl-thiol by preparing a derivative.
They (loc.cit.) have also reported the formation of isomeric N-methyl derivative, from N-methylanthranilic acid, which has different properties from S-methyl compound:

In this connection, Hine ("Physical Organic Chemistry", McGraw-Hill Book Co. Inc., New York, 1956, p. 121) has suggested that in an irreversible attack on an unsymmetrical immonium or sulphonium ion, the product resulting from attack at the primary position may perhaps be favoured, whereas in a reversible reaction, the predominant product is simply the more stable of the two isomers.

The work of Sharma, Sachdev and Narang (J.Sci.Industr.Res., India, 1956,15B,687) and Sharma and Singh (ibid., 1961,20C,178) supports the 'thiol' form of 2-mercapto-quinazol-4-one derivatives. They have prepared thiopegan derivatives, which are possible, only if hydrogen atom is united to sulphur atom (see Introduction of this part : p.83).


It may be pointed out that when 2-mercapto-quinazol-4-ones are prepared by means of aryl isothiocyanate method, the first form may be 'thione' immediately passing into more stable 'thiol' form. The spectroscopic data on this subject are lacking, though some work on quinazoline derivatives has been reported (Weissberger, "Technique of Organic Chemistry", Vol.IX, 1956, p.535; Mason, J.Chem.Soc., 1955, 2336.
It is reported that quinazoline derivatives themselves are weak bases and are soluble in alkali rather than acid (Albert, Brown and Wood, J.Chem.Soc., 1954, 3852). Their basicity is similar to other diaza-naphthalene compounds as observed by ultra-violet spectra of neutral molecule. But in absence of more data, nothing can be predicted.

By comparison with the known work on 2-mercapto derivatives and the formation of benzoyl derivative and condensation of the compounds prepared in this work with bromobenzene, it appears that 2-mercapto-quinazol-4-ones exist in the thiol form predominantly.

Hence, the structure assigned to the first compound of this series obtained by the action of (a) mono-phenylthiourea and (b) phenyl isothiocyanate on 5-chloroanthranilic acid was 6-chloro-3-phenyl-2-mercapto-quinazol-4-one and other compounds prepared in similar manner from the other thiourea derivatives were also considered to possess the similar structure.

In order to confirm the structures assigned, the 3-aryl-2-mercapto-quinazol-4-one derivatives were oxidised by alkaline hydrogen peroxide (Busch, J.prakt.Chem., 1895, 55(ii), 275; Kunckell, Ber., 1905, 38, 1213; Pawlewski, ibid., 1906, 39, 1734). It was found that some fine white particles which proved to be sulphur, separated during the reaction. The compound thus isolated was without sulphur and proved to be 6-chloro-3-phenyl-2-hydroxy-quinazol-4-one (Ia) or the corresponding keto tautomer, 6-chloro-3-phenyl-quinazol-2:4-dione (Ib):
The enol form in this case appears to be unstable and normally the dione form predominates. However, the spectroscopic data in this case are lacking. It gives chloro derivative easily with phosphorus pentachloride and hence there may be enol form during this reaction operating. But no unambiguous evidence is available for this supposition.

The other methods of oxidation of 2-mercapto-quinazol-4-ones which have been reported in literature are: (i) mercuric oxide suspension in ethanol (Busch, Ber., 1892, 25, 285) and (ii) alkaline potassium permanganate (Busch, loc.cit.; McCoy, Ber., 1897, 30, 1688). Dave, Mewada and Amin (work under publication) have used sodium hypochlorite to oxidise 3-aryl-2-mercapto-quinazol-4-ones prepared by them (J. Indian Chem. Soc., 1960, 37, 595). No chlorination was observed. In all cases, normally, the 2-mercapto group is disengaged and quinazol-2:4-dione derivatives are formed.

That the compound formed in this case is 6-chloro-3-phenyl-quinazol-2:4-dione (Ib) was proved by preparing an authentic specimen by fusion of 5-chloroanthranilic acid with mono-phenylurea at 180°. The resulting mass was extracted with sodium hydroxide and the filtrate on acidification gave the desired product. The alkali solution showed blue-violet fluorescence. This method of preparation of quinazol-2:4-dione is one which has been used very early by Griess (J. prakt. Chem.,
Diagramatic Representation: Section (II)

Synthesis of 7-Chloro-3-aryl-2-mercapto-quinazol-4-ones
and their derivatives

\[
\begin{array}{c}
\text{Ar} = \text{Phenyl, } \\
o-, m-, p-\text{Tolyl,} \\
o-, p-\text{Anisyl,} \\
o-, m-, p-\text{Chlorophenyl}
\end{array}
\]
In a similar manner, the other 6-chloro-3-aryl-2-mercapto-quinazol-4-ones were prepared. The reactions in all cases were smooth. All were converted into the corresponding 6-chloro-3-aryl-quinazol-2:4-diones by oxidation. The thiophenyl and thiobenzoyl derivatives for confirming the presence of 'thiol' group in each compound were also prepared.

All reactions and formulae are included in the diagram facing page 94.

SECTION II

SYNTHESIS OF 7-CHLORO-3-ARYL-2-MERCAPTO-QUINAZOL-4-ONES

In the preceding section, 6-chloro-3-aryl-2-mercapto-quinazol-4-ones were described. In this section, the isomeric 7-chloro compounds are described.

For this work 4-chloroanthranilic acid was prepared from 4-chloro-2-acetamino-toluene by oxidation and that followed by hydrolysis, a method similar to that employed for 5-chloro isomer (Cohn, Monatsh., 1901, 22, 485; see however, Hunn, J. Am. Chem. Soc., 1923, 45, 1027).

4-Chloroanthranilic acid was condensed with mono-phenylthiourea as well as phenyl isothiocyanate as before and 7-chloro-3-phenyl-2-mercapto-quinazol-4-one was obtained.
In this case also the 2-mercapto derivative was condensed with bromobenzene in presence of potassium carbonate and copper powder at 165-70° and 7-chloro-3-phenyl-2-thiophenyl-quinazol-4-one was obtained. Similarly, with benzoyl chloride the corresponding 2-thiobenzoyl derivative was prepared. The condensation was smooth and the compounds formed readily.

The 'thiol' structure was indicated in this case also. Thus, the position of the chlorine atom in benzene nucleus of quinazol-4-one derivative does not contribute any adverse effect on the reactivity of 2-mercapto group in 6-chloro- or 7-chloro-3-phenyl-2-mercapto-quinazol-4-one.

Again, the 7-chloro-3-phenyl-2-mercapto-quinazol-4-one on oxidation by alkaline hydrogen peroxide gave the dione: viz., 7-chloro-3-phenyl-quinazol-2:4-dione, whose structure was confirmed by preparing its authentic sample from the parent 4-chloroanthranilic acid and mono-phenylurea fusion method and subsequent extraction by alkali and acidification.

As in the preceding section, all the other eight mono-arylthioureas and aryl isothiocyanates were condensed with 4-chloroanthranilic acid and the corresponding 7-chloro-3-aryl-2-mercapto-quinazol-4-ones were obtained. These were oxidised to the corresponding diones in a similar way. The thiophenyl and thiobenzoyl derivatives were also prepared in each case.

Thus, the change of chlorine atom from 6 to 7 position does not hinder any reaction which is normally possible with the 6-chloro isomers of 3-aryl-2-mercapto-quinazol-4-ones. The reactions are indicated in the chart facing page 100.
Synthesis of 6-Methyl-3-aryl-2-mercapto-quinazol-4-ones and their derivatives

\[ \text{Hg}_2\text{N-C-NH.Ar} \]

\[ \text{At} = \text{Phenyl, o-, a-, p-tolyl, o-, p-Anisyl, o-, m-, p-Chloro-phenyl} \]

[Diagram of the synthesis process]

\[ \text{Ar} = \text{Phenyl, o-, m-, p-Tolyl, o-, p-Anisyl, o-, m-, p-Chloro-phenyl} \]

\[ \text{H}_2\text{N-C-NH.Ar} \]
SYNTHESIS OF 6-METHYL-3-ARYL-2-MERCAPTO-QUINAZOL-4-ONES

The compounds synthesized in this section are similar to those obtained in section first. In the present section methyl group is in 6 position in place of chloro group in the former section. The compounds were prepared on the same line.

In this case 5-methylanthranilic acid was used, the preparation of which is already considered in the previous part.

5-Methylanthranilic acid was condensed with mono-phenylthiourea as well as phenyl isothiocyanate. In both cases, the same compound - 6-methyl-3-aryl-2-mercapto-quinazol-4-one was obtained. The constitution was assigned on analogy and general properties. (See also Sengupta, Bami and Sharma (J.Sci.Industr.Res., India, 1959, 18 C, 28), who have reported the preparation of 6-methyl-3-allyl-2-mercapto-quinazol-4-one by the condensation of 5-methylanthranilic acid with allyl isothiocyanate.). It was condensed with bromobenzene under the conditions of Ullmann's reaction and also with benzoyl chloride under the conditions of the Schotten - Baumann reaction. Both compounds were smoothly obtained.

The sulphur atom was eliminated by the oxidation by means of hydrogen peroxide in sodium hydroxide solution, and 6-methyl-3-arylnquinazol-2:4-dione was produced, the constitution of which was confirmed by preparing it independently by the fusion of 5-methylanthranilic acid with mono-phenylurea, followed by alkali extraction and acidification.
Synthesis of 8-Methyl-3-aryl-2-mercapto-quinazol-4-ones and their derivatives

\[ \text{H-N-} \text{Ar} \quad \text{C-S} \quad \text{H}_2\text{N} \]

- Reactions:
  - (a) 170-80°C
  - Refluxing in EtOH

- Reagents:
  - \( \text{C}_6\text{H}_5\text{Br} \)
  - \( \text{C}_6\text{H}_5\text{CO.Cl} \)

- Products:
  - [Ar = Phenyl, o-, m-, p-Tolyl, o-, p-Anisyl, o-, m-, p-Chlorophenyl]
Similarly, other mono-arylthioureas and aryl isothiocyanates were condensed with 5-methylanthranilic acid and 6-methyl-3-aryl-2-mercaptoquinazol-4-ones were prepared. These were also oxidised to the corresponding diones and also condensed with bromobenzene and benzoyl chloride as well. The corresponding diones were also prepared by condensing 5-methylanthranilic acid with mono-arylureas. These are shown diagrammatically in the chart facing page 102.

SECTION IV

SYNTHESIS OF 8-METHYL-3-ARYL-2-MERCAPTO-QUINAZOL-4-ONES

These compounds are isomeric with those described in the previous section. 3-Methylanthranilic acid required for the preparation of these quinazol-4-one derivatives was prepared according to the method already described in the first part of this thesis.

3-Methylanthranilic acid was condensed with mono-phenylthiourea and 8-methyl-3-phenyl-2-mercapto-quinazol-4-one was obtained. The same compound was again prepared by using phenyl isothiocyanate in place of mono-phenylthiourea. As before, the condensation with bromobenzene gave 8-methyl-3-aryl-2-thiophenyl-quinazol-4-one and with benzoyl chloride the corresponding 2-thiobenzoyl derivative was obtained.

The oxidation by means of alkaline hydrogen peroxide gave 8-methyl-3-phenyl-quinazol-2:4-dione as would be expected by analogy. It was directly compared with an authentic specimen prepared by fusion together of 3-methylanthranilic acid and mono-phenylurea.
In a similar manner, the same series of mono-aryl thioureas and aryl isothiocyanates were condensed with 3-methylantranilic acid. These compounds were also converted into the corresponding (i) quinazol-2:4-diones by the alkaline peroxide oxidation, (ii) 2-thiophenyl derivatives by bromobenzene and (iii) 2-thiobenzoyl derivatives by means of benzoyl chloride reaction. These are shown diagrammatically in the chart facing page 103.

From the above outline of the work described in this part, it will be seen that a potentially large amount of work can be carried out in this fertile field of 2-mercapto-quinazol-4-one derivatives. In the present work, only four series - two of chloro and two of methyl substituted compounds - have been described. It is also intended to try other substituents like bromo, iodo, nitro, ethyl, methoxy, ethoxy, etc., in place of chloro and methyl groups in the same as well as other positions of the benzene ring.

As a class, these compounds in particular give precipitates and characteristic colours with many metallic salt solutions. Hence, they may find use as analytical reagents on micro or macro scale. As a matter of fact, 3-phenyl-2-mercapto-quinazol-4-one appears to be a promising reagent for colorimetric estimation of divalent copper (Dave, personal communication). It was recently observed that some amino-quinazol-4-ones could be used as Fast Bases in azoic dyes giving orange shades with 2-hydroxy-naphthylides (Dr. G.C. Amin, personal communication).

In view of the pharmacological potentiality of chloro and methyl substituted quinazol-4-ones, it would yield interesting results on such
testing. It is intended to get tested the compounds described in this work.

Thus, the study of quinazol-4-ones may be useful in more than one way and some of these problems will be taken up at a suitable opportunity.