Studies in

3-ARYL-QUINAZOL-4-ONES

GENERAL

INTRODUCTION
The ortho fusion of a benzene nucleus with a pyrimidone ring (II) gives rise to a class of heterocyclic compounds containing 1:3-benzodiazione ring system (I). As early as 1869, Griess (Ber., 1869, 2, 415) built up this ring-system for the first time in his
compound (III) which he named as 'bicyanoamide benzoyl'. Later on the name 'Quinazoline' was proposed by Weddige (J. prakt. Chem., 1887, 36(ii), 141.). The numbering followed in this thesis is according to Paal and Busch (Ber., 1889, 22, 2683) (IV) and is now in current usage in Chemical Abstracts. According to this nomenclature, the compound (III) of Griess will be 2-cyano-quinazol-4-one or 2-cyano-4-keto-quinazoline or simply 2-cyano-4-quinazolone.

\[
\begin{align*}
\text{(III)} & \quad \begin{array}{c}
\text{(IV)} \\
\end{array}
\end{align*}
\]

The quinazol-4-ones are regarded as the derivatives of the parent compound quinazoline (V) which is isomeric with cinnoline (VI), quinoxaline (VII) or phthalazine (VIII) differing in the positions of the two nitrogen atoms in the hetero-ring:

\[\text{\textcopyright It has been found from the literature that many systems of numbering the quinazoline ring-systems were in use in the early years of the development of this branch of chemistry. Different authors have used different nomenclatures even in a single series of papers. The positions variously designated are as in (a), (b) and (c). This naming and numbering is useful while reading earlier literature.}\]

\[
\begin{align*}
\text{(a)} & \quad \begin{array}{c}
\text{(b)} \\
\text{(c)} \\
\end{array}
\end{align*}
\]
The compounds containing the quinazoline ring-system fall into three distinct types according to their physical and chemical properties and their ease of formation: (1) quinazolines, (2) hydrogenated quinazolines and (3) quinazolones. The first two types are briefly dealt with here while the third one is described in details as it forms the subject matter of this thesis.

The quinazolines unsubstituted in the heterocyclic ring form the simplest class. They may or may not carry substituents in the carbocyclic ring. This group of compounds is not much investigated probably due to the lack of convenient methods of preparation.

The parent substance, quinazoline, is best prepared by the reduction of 2-nitrobenzal-bis-formamide, the condensation product of 2-nitrobenzaldehyde and formamide (Riedel, Ger.Pat. 174,941 (1903); Bogert and McCollm, J.Am.Chem.Soc., 1927,49,2631).

\[
\text{CHO} \xrightarrow{\text{HCONH}_2} \text{CH(NHCHO)}_2 \xrightarrow{\text{Zn + AcOH}} \]

The homologues of quinazoline are best prepared by Bischler's method as modified by Schofield, Swain and Theobald (J.Chem.Soc., 1952,324) and also by the method of Albert and Hampton (ibid., 1952, 4985) and Rodda (ibid., 1956,3509).
The second type of the compounds comprises of hydrogenated quinazolines such as 1:2:3:4- and 5:6:7:8-tetrahydro-quinazolines, and 2-keto- and 4-keto-1:2:3:4-tetrahydro-quinazolines.

Among the partially hydrogenated 1:2-dihydro- and 3:4-dihydro-quinazolines, the latter are more common. They are prepared by the reduction of nitro group in an N-acyl derivative of o-nitrobenzylamine (Gabriel, and Jansen, Ber., 1890, 23, 2807; 1891, 24, 3091; Wolff, Ber., 1892, 25, 3030; Gabriel and Colman, Ber., 1904, 37, 3643; Paal, J.prakt.Chem., 1893, 48(ii), 547; see also Elderfield, Williamson, Gensler and Kremer, J.Org.Chem., 1947, 12, 403).

The simple 1:2-dihydroquinazoline was comparatively recently described by Carrington (J.Chem.Soc., 1955, 2527).

1:2:3:4-Tetrahydro-quinazolines are formed by the action of aldehydes on o-aminobenzylamines (Busch and Brunner, J.prakt.Chem., 1895, 52(ii), 373; Busch, ibid., 1896, 53(ii), 414).

5:6:7:8-Tetrahydro-quinazolines are less common.
2-Keto-1:2:3:4-tetrahydro-quinazolines are formed by the action of an alkyl or acyl isocyanate on o-aminobenzyl alcohol, which gives on warming in acetic acid solution 3-substituted 2-keto-1:2:3:4-tetrahydro-quinazolines (Soderbaum and Widman, Ber., 1889, 22, 1665). Other methods are due to Gabriel and Stelzner (Ber., 1896, 29, 1300) and Busch (Ber., 1892, 25, 2853).

4-Keto-1:2:3:4-tetrahydro-quinazolines are formed by the reaction of formaldehyde or methylenediamine on o-aminobenzanilides (Feldman and Wagner, J.Org.Chem., 1942, 7, 31).

The third distinct type of the compounds contains the hydroxyl group in 2 or 4 or both the positions of the quinazoline ring-system. The 2- or 4-hydroxy compounds are tautomeric with the corresponding keto-dihydro-quinazolines. The 4-hydroxy-quinazoline (Ia) tautomeric with 3:4-dihydro-4-ketoquinazoline is commonly called 4(3)-quinazoline or simply 4-keto-quinazoline or 4-quinazolone or quinazol-4-one (Ib). Similarly, 2-hydroxy-quinazoline (IIa) is called (2(1)-quinazoline or 2-keto-quinazoline or 2-quinazolone or quinazol-2-one (IIb). 2:4-Dihydro-quinazoline (IIIa) is tautomeric with 2:4-diketo-1:2:3:4-tetrahydro-quinazoline, is commonly known
as 2:4-diketoquinazoline or quinazol-2:4-dione or simply benzoyleneurea. (IIIb).

This type of compounds, because of their tautomeric nature, are high melting, insoluble solids and resistive to many general chemical reactions. Compounds with alkoxy, aryloxy, halogeno, amino, mercapto, mercaptoethers and seleno and other groups in place of hydroxyl group are also considered under this class.

The work described in this thesis deals with this class of compounds: Part I describes the preparation of quinazol-4-ones and Part II deals with 2-mercapto-quinazol-4-ones as well as quinazol-2:4-diones, and hence they have been comprehensively described here.

II: QUINAZOL-2-ONES

Quinazol-2-ones are less common and only few compounds belonging to this type are known. They are prepared by the condensation of o-aminophenylketone with urea (Bischler, Ber.,
1893, 26, 1891) or o-aminobenzaldehyde with urea (Gabriel and Posner, Ber., 1895, 28, 1029):

\[
\begin{align*}
\text{COCH}_3 + \text{H}_2\text{N} & \xrightarrow{190^\circ} \text{CH}_3 \\
\text{NH}_2 & \quad \text{C:0} \\
\text{H}_2\text{N} & \quad \text{H}_2\text{O} + \text{NH}_3
\end{align*}
\]

Paal and Weil (Ber., 1894, 27, 36) have used the action of carbonyl chloride on o-aminobenzylamines to obtain 3-phenyl-3:4-dihydroquinazol-2-ones.

III : QUINAZOL-4-ONES

Various methods for the synthesis of this class of compounds are available and numerous quinazol-4-one derivatives have been prepared so far. Majority of these methods consists in condensation of anthranilic acid or its derivative with compounds containing an amino or an amido grouping. Some of the important methods are briefed below:

(A) : METHODS OF PREPARATION:

(1) : From N-acyl anthranilamides : Simple or substituted N-acyl-anthranilamide on heating at its melting point or else, refluxing with dilute aqueous alkali gives the corresponding quinazol-4-one derivative. The method was first adopted by Weddige (J.prakt.Chem, 1885, 31(ii), 125; 1887, 36(ii), 141) and followed by Korner (ibid., 1887, 36(ii), 155), Knape (ibid., 1891, 43(ii), 215), Bogert et al., J.Am.Chem.Soc., 1906, 28, 1449), Hirwe and Kulkarni (Proc.Ind.Acad.

\[
\begin{align*}
\text{CONHR'} & \quad \text{\(-H_2O\)} & \quad \text{CONHR'} \\
\text{NHCOR} & \quad \quad & \quad \text{CONHR'}
\end{align*}
\]

\[R \text{ and } R' = H, \text{aryl or/and alkyl}\]

Formyl-anthranilamide yields simple quinazol-4-one with loss of water molecule:

\[
\begin{align*}
\text{CO.NH}_2 & \quad \quad \text{Heat} & \quad \quad \text{NH.CH}_2 + \text{H}_2O \\
\text{NHCOR} & \quad \quad \quad & \quad \quad \text{NH.CH}_2 + \text{H}_2O
\end{align*}
\]

Quinazol-4-ones with substituent in desired positions can be prepared by selecting appropriately substituted anthranilamides; e.g., 6-chloro-2-methyl-3-phenyl-quinazol-4-one can be prepared by heating 5-chloro-N-acetylanthranilanilide at its melting point:

\[
\begin{align*}
\text{Cl} & \quad \quad \text{Heat} & \quad \quad \text{Cl} \\
\text{CO.NHC}_6\text{H}_5 & \quad \quad & \quad \quad \text{CO.NHC}_6\text{H}_5
\end{align*}
\]

(2) From Anthranilic acid and Formic acid Derivatives: Niementowski (J. prakt. Chem., 1889, 40(ii), 1; 1895, 51(ii), 564) has reported that heating anthranilic acid with formamide or anthranilamide with formic acid or ammonium anthranilate with formamide gives quinazol-4-ones.
This 'Niementowski Reaction' has been carried out with substituted anthranilic acids to give benz-substituted quinazol-4-ones. Aliphatic amides give alkyl substituents in the 2 position of the quinazolone nucleus. Generally, the yield suffers with increase in the molecular weight of the amide and it fails in case of higher amides. However, Sherrill et al (J. Am. Chem. Soc., 1946, 68, 1301) have obtained almost fifty per cent yield of 2-phenyl-quinazol-4-one by using thiobenzamide instead of benzamide:
Meyer and Wagner (J.Org.Chem., 1943,8,239) from their studies on Niementowski Reaction have suggested several modifications, e.g., interaction of isatoic anhydride and a diarylamine, in cases where the yield is poor or the rate of reaction is slow. McKee, McKee and Bost (J.Am.Chem.Soc., 1947,69,184) have also modified Niementowski Reaction which involves condensation of anthranilamide with ethyl-orthoformate:

\[
\text{CONH,} \quad \text{c h} \quad (\text{oc}_{2} \text{H}_5)_{3} \quad \text{Cl} \quad \text{Cl} \quad ^{N} \text{H} \quad \text{j h} \quad \text{+ 3 C}_2\text{H}_5\text{OH}
\]

(3): From Anthranilic acid and Acetonitrile or o-Aminobenzonitrile and Acetic acid: Bogert and Gotthelf (J.Am.Chem.Soc., 1900,22,129, 524; 1901,23,611) prepared 2-alkyl substituted quinazol-4-ones by heating N-acetylanthranilic acid with acetonitrile in a sealed tube:

\[
\text{COOH} \quad + \quad \text{CH}_3\text{CN} \quad \rightarrow \quad \text{O} \quad \text{N} \quad \text{NH.COR} \quad + \quad \text{CH}_3\text{COOH}
\]

However, they have reported that the yield obtained by this method is poor. This method is a general one and any alkyl cyanide can be used.

Bogert and Hald (J.Am.Chem.Soc., 1902,24,1031) have also reported a method which consists in similar heating of N-acylanthranilic nitrile with glacial acetic acid in a sealed tube:
In both the methods Bogert et al have assumed the formation of a hypothetical intermediate product:

![Chemical reaction diagram](image)

It will be seen upon examining the structures of the intermediate product, the secondary amide, that the -CO-NH-CO- group being symmetrical should be formed equally well from R-CN + R'-COOH as from R'.CN + R.COOH; in other words, as the condensation takes place solely between the -CN and -COOH, it is immaterial which group carries the -CN and which one -COOH. At higher temperature, acetic acid would split off, as indicated, with production of quinazol-4-one derivative.

(4) : By condensation of (a) Aromatic Amines or (b) their acyl derivatives or (c) Imidochlorides with Urethane derivatives:

(a) In their attempts to condense aniline with urethane into unsubstituted quinazol-4-one, Bhattacharya, Bose and Ray (J. Indian Chem. Soc., 1929, 5, 279) observed that this condensation was not possible, but acylanilides could be easily condensed with urethanes in presence of phosphorus pentoxide in an inert medium to give
substituted quinazol-4-ones. The method is a general one for preparation of 2-substituted quinazol-4-ones:

\[
\begin{align*}
\text{Ph-NH-CH}_3 + \text{H}_5\text{C}_2\text{O-C-NH}_2 & \xrightarrow{\text{P}_2\text{O}_5 \text{ Xylene (130-40°)}} \text{Ph-C-CH}_3 + \text{C}_2\text{H}_5\text{OH} + \text{H}_2\text{O} \\
\end{align*}
\]

(b) Similar reaction between acyl urethane and aromatic amines also gives 2-substituted quinazol-4-ones (Aggarwal, Das and Ray, J. Indian Chem. Soc., 1929, 6, 717); but this reaction is less general than the previous one. Aniline and many other amines do not condense with urethane derivatives similarly:

\[
\begin{align*}
\text{H}_3\text{C-NNH}_2 + \text{H}_5\text{C}_2\text{O-C-NH} & \xrightarrow{\text{P}_2\text{O}_5 \text{ Xylene (reflux)}} \text{Ph-NH-C-CH}_3 + \text{C}_2\text{H}_5\text{OH} + \text{H}_2\text{O} \\
\end{align*}
\]

(c) Shah and Ichaporia (J. Chem. Soc., 1936, 431) have reported a new method of synthesizing 2- and 2:3-substituted quinazol-4-ones by condensation of aniline imidochlorides with urethanes. The intermediate product, (phenyl iminobenzyl)-urethane derivative obtained can be cyclised to quinazolone on heating.

By condensing benzanilide imidochloride with sodium urethane, they obtained phenyliminobenzyl urethane which was easily cyclised to 2-phenyl-quinazol-4-one (I) on heating. Benzanilide imidochloride was condensed easily with acetyl urethane giving acetyl-(phenyliminobenzyl)-urethane. It was then cyclised to 2-phenyl-3-acetyl-
quinazol-4-one (II), which could not be obtained by direct acetylation of (I).

\[
\text{Cl} \quad \text{Na} \quad \text{COOEt} \quad \text{H} \quad \text{COCH} \quad \text{Ph} \quad \text{Cl}
\]

Levy and Stephen (J.Chem.Soc., 1956,985) have reported that condensation of ethylanthranilate with aniline imidoehloride followed by cyclisation of the condensation product gives 2:3-diaryl-substituted quinazol-4-ones:

\[
\text{COOR} + \text{N-Ar} \quad \text{Cl-C-Ar} \quad \text{COOR} + \text{N-Ar} \quad \text{Cl-C-Ar}
\]

Stephen et al (J.Chem.Soc., 1956,4173) have extended this method for preparing quinazol-4-ones from anthranilic acid ester or its ammonium salt and compounds containing -N:C-Cl system:

\[
\text{COOR} + \text{Cl-C-Ar} \quad \text{COOR} + \text{Cl-C-Ar}
\]

2-Chlorolepidine
(5) : Aromatic amine and Isatoic anhydride : Clark and Wagner (J. Org. Chem., 1944, 9, 55) have reported a method in which 3-substituted-quinoxal-4-ones can be obtained on heating isatoic anhydride with a primary amine and ethyl-orthoformate :

\[
\text{[Diagram of reaction]} \quad \text{[Equation: } \text{O}^\text{N-C=O} + \text{R.NH}_2 + \text{H(OOC}_2\text{H}_5)_3 \rightarrow \text{O}^\text{N-C=O} + 3 \text{C}_2\text{H}_5\text{OH} + \text{CO}_2 \text{]} \]

(6) : Condensation of Acyl-anthranil or 3:1:4-Benzoxazone derivative with Amines : Acet-anthranils (3:1:4-benzoxazones) (I) can be easily prepared by heating anthranilic acid or its N-acyl derivative with acetic anhydride. The acet-anthranils, on heating with ammonia or a primary amine yield, in one step, or on cyclisation of the intermediate product (II), the corresponding quinoxal-4-one derivative (III)

The method is of general applicability in that a wide variety of amines — aliphatic, aromatic and heterocyclic — and semicarbazides, hydrazines, etc., can be used.

(7) : Conversion of Quinazolines into Quinazolones : Quinazoline derivatives have been converted into quinazolones by oxidation but these are, generally, not practical methods.

(a) Gabriel and Colman (Ber., 1904, 37, 3643) observed that quinazoline derivative on alkaline permanganate oxidation gives some quinazol-4-one along with large amount of 4:5-pyrimidine-dicarboxylic acid:

\[
\begin{align*}
\text{2} & \quad \xrightarrow{\text{(O)}} \quad \text{quinazol-4-one} + \text{4:5-pyrimidine-dicarboxylic acid}.
\end{align*}
\]

The yield of the quinazol-4-one can be increased by employing 2-substituted quinazoline derivatives and using chromic oxide in acetic acid as the oxidising agent (Bischler and Lang, Ber., 1895, 28, 279).

(b) A moderate yield of quinazol-4-one derivative is obtained if the quinazoline to be thus oxidised contains a 3-aryl substituent. Paal and Krecke (Ber., 1890, 23, 2634) isolated 2-methyl-3-phenyl-quinazol-4-one by the alkaline permanganate oxidation of 2-methyl-3-phenyl-3:4-dihydro-quinazoline. On further oxidation, methyl group in 2-position was converted into carboxylic group which underwent simultaneous
decarboxylation and 3-phenyl-quinazol-4-one was obtained (see also Paal and Busch, Ber., 1889, 22, 2683; Busch and Brunner, J. prakt. Chem., 1895, 52(ii), 373):

\[ \text{H}_2\text{C}_6\text{N-Ph} \xrightarrow{\text{KMnO}_4 \text{(OH)}^\text{-}} \text{O} \text{C}_6\text{N-Ph} \]

\[ \text{O} \text{C}_6\text{N-Ph} \xrightarrow{\text{KMnO}_4 \text{(OH)}^\text{-}} \text{C} \text{N-Ph} \]

\[ \text{C} \text{N-Ph} \xrightarrow{- \text{CO}_2} \text{N-Ph} \text{COOH} \]

(c) Marr and Bogert (J. Am. Chem. Soc., 1935, 57, 729) have observed that a methyl group in 4 position of the quinazoline nucleus is more reactive than the one in 2 position, e.g. when 2:4-dimethyl-quinazoline is treated with sodium hypobromite, the methyl group in the 4 position is attacked first in preference to that in the 2 position:

\[ \text{CH}_3 \text{C}_6\text{N-Ph} \xrightarrow{\text{NaOBr}} \text{CH}_3 \text{C}_6\text{N-Ph} \xrightarrow{\text{NaOBr}} \text{C} \text{N-Ph} \text{COOH} \]

(8) : Condensation of N-Acetylanthranilic acid with Aromatic Primary Amines in presence of Phosphorus trichloride : Grimmel, Guenther and Morgan (J. Am. Chem. Soc., 1946, 68, 539) have developed a new method to prepare quinazol-4-one derivatives from organic phosphazo compounds. They obtained 2-methyl-3-phenyl-quinazol-4-one by the interaction of
phenyl phosphazoanilide and N-acylanthranilic acid in boiling toluene. The reaction is illustrated as under:

\[
\begin{align*}
\text{Ph}$^\text{P}$-HN & + 2 \text{Ph}$^\text{N}$-$\text{CH}_3 \quad \xrightarrow{\text{H}_3\text{PO}_4} \quad \text{Ph}$^\text{N}$-$\text{C}_6\text{H}_5$-$\text{CH}_3 + \text{H}_3\text{PO}_4 + \text{H}_2\text{O}
\end{align*}
\]

They have evolved (ibid., 1946, 68, 542) a new method to prepare quinazol-4-ones in a single step at moderate temperature from the simple starting materials. The method consists in heating primary amines with N-acetylanthranilic acid or its derivative in toluene or any other suitable inert solvent in presence of phosphorus trichloride. The method is of fairly general application:

\[
\begin{align*}
\text{Ph}$^\text{N}$-$\text{C}_R \quad + \quad \text{Ph}$^\text{N}$-$\text{CH}_3 \quad \xrightarrow{\text{P}_\text{Cl}_3} \quad \text{Ph}$^\text{N}$-$\text{C}_R \quad \text{Ph}$^\text{N}$-$\text{C}_R
\end{align*}
\]

Bami and Dhatt (J. Sci. Indstr. Res., 1957, 16B, 558) have reported the preparation of quinazol-4-one derivatives by interaction between N-acetylanthranilic acid and suplanilamide in phenol.

(B) : REACTIONS :

Quinazol-4-ones as a class are colourless crystalline solids with very feeble basic character. They are insoluble in water or ether, fairly soluble in alcohol and acetone and highly soluble in aqueous alkali from which they can be precipitated on acidification. Some of their important reactions are briefly described below:
(1) **Oxidation**: Oxidation with potassium permanganate (Paal and Busch, Ber., 1889, 22, 2683; Busch, J. prakt. Chem., 1895, 51(ii), 113) or chromic acid (Soderbaum and Widman, Ber., 1889, 22, 2933) gives quinazol-2,4-dione or benzoylurea:

\[
\text{C}_6\text{H}_4\text{N} = \text{C} = \text{N} + \text{OH} \xrightarrow{\text{KMnO}_4 \text{ or CrO}_3} \text{C}_6\text{H}_4\text{N} = \text{C} = \text{N} + \text{CO}_2 + \text{H}_2\text{O}
\]

During this oxidation, any alkyl group attached to either ring is converted to a carboxylic group, which may get decarboxylated at elevated temperatures.

(2) **Reduction**: Ordinary methods of reduction are without effect on the quinazolone ring. However, it can be reduced by sodium amalgam to 1:2-dihydro derivative (Giovanni and Jacini, Gazz. chim. ital., 1944, 74, 3; Chem. Abstr., 1944, 38, 5825).

(3) **Nitration**: Behoff (J. prakt. Chem., 1890, 42(ii), 347) nitrated 2-methyl-quinazol-4-one and obtained 6-nitro product, the position of the nitro group being established by Thme's synthesis (ibid., 1891, 43(ii), 473) of the same substance from the ethyl ester of 5-nitro-2-acetamino-benzoic acid in alcoholic ammonia at 170° (see also Bogert and Cook, J. Am. Chem. Soc., 1906, 28, 1449; Tomisek and Christensen, ibid., 1948, 70, 2423). Further Bogert and Geiger (ibid., 1912, 34, 683) from their studies on nitration of quinazolones, have concluded that these are not readily nitrated. The satisfactory nitration requires a high temperature and the use of nitrating mixture of fuming nitric acid and
concentrated sulphuric acid. But only one nitro group can thus be introduced in the quinazolone molecule, which enters the 6 position. Aryl radicals attached to the quinazolone nucleus, at positions 2 and/or 3 for example, may also undergo nitration during the process. Quinazolones with nitro groups in different positions of the benzenoid part are prepared by synthetic methods (Bogert and co-workers, J. Am. Chem. Soc., 1905, 27, 649; 1908, 30, 809). Tomisek and Christensen (loc. cit.) have reported that 2:4-dimethyl-quinazoline on nitration gives 6-nitro-2-methyl-quinazol-4-one

and Curtin (J.Org.Chem., 1946, 11, 341) have prepared 4-amino-quinazoline from the 4-ketoquinazoline by methylation and the treatment of the 4-methylether with methanolic ammonia in a bomb. He further stated that even quinazol-4-one could directly react with ammonia in a bomb and gave 4-amino derivative.

Dewar (loc.cit.) as well as Macbeth and Rodda (Nature, 1945, 156, 207) have reported a direct synthesis of 2-amino-quinazoline from guanidine nitrate and o-aminobenzaldehyde:

\[
\text{CHO} + H_2N-C-NH_2 \xrightarrow{\text{NH}_2\text{HNO}_3} \text{C-NH}_2
\]

Grout and Partridge (J.Chem.Soc., 1959, 3540) have directly obtained 3-substituted 2-amino-quinazol-4-ones by cyclisation of the product obtained by the interaction of methyl-anthranilate with a cyanamide:

\[
\text{COOCH}_3 + R.NHCN \xrightarrow{} \text{COOCH}_3 \xrightarrow{} \text{N-R}
\]

(5) **Alkylation**: The quinazolones unsubstituted in 3 position exist in tautomeric form (I and II):

\[
\text{(I)} \xleftrightarrow{\text{OH}} \text{(II)}
\]
In alkaline solution, the ions of each compound exist as resonance hybrids, so the entering alkyl group may become attached to either nitrogen atom (III) or the oxygen atom (IV):

\[
\begin{align*}
(\mathrm{I}) & \quad \text{O} \quad \text{N} \quad \text{CH} \\
(\text{OH}) & \quad \text{O} \quad \text{N} \quad \text{CH} \\
+ \quad \text{RX} & \quad \rightarrow \\
(\mathrm{III}) & \quad \text{O} \quad \text{N} \quad \text{R} \\
(\text{OR}) & \quad \text{O} \quad \text{N} \quad \text{CH} \\
+ \quad \text{RX} & \quad \rightarrow \\
(\mathrm{IV}) & \quad \text{O} \quad \text{N} \quad \text{CH}
\end{align*}
\]

Such alkylation will therefore give product (III) or (IV) or a mixture of both. Bogert and Seil (J. Am. Chem. Soc., 1907, 29, 517) have observed that alkylation generally depends upon the nature of the alkylation agent and the condition of alkylation rather than the nature of the quinazolone to be alkylated.

Morley and Simpson (J. Chem. Soc., 1948, 360; 1949, 1354) have reported that when 6-nitro-quinazol-4-one was methylated with dimethyl sulphate in alkali, 3-methyl derivative was the sole product; while

\[
\begin{align*}
\text{O} \quad \text{N} \quad \text{CH} & \quad \text{O} \quad \text{N} \quad \text{CH} \\
\text{O} \quad \text{N} & \quad \text{CH} & \quad \text{(CH}_3\text{)}_2\text{SO}_4 & \quad \text{KOH} & \quad \text{O} \quad \text{N} \quad \text{CH}_3
\end{align*}
\]

alkylation of 4-acetamido- or 4-phenoxyl-6-nitro-quinazolone when methylated using methyl p-toluene sulphonate, 1-methyl derivative
was obtained with simultaneous hydrolysis of the group present in the 4 position:

\[
\begin{align*}
\text{R} & \quad \text{O} \quad \text{N} \quad \text{C} \quad \text{N} \quad \text{C} \quad \text{H} \\
\text{CH}_3 & \quad \text{O} \quad \text{N} \quad \text{C} \quad \text{N} \quad \text{C} \quad \text{H} \\
\text{SO}_3\text{CH}_3 & \quad \text{O} \quad \text{N} \quad \text{C} \quad \text{N} \quad \text{C} \quad \text{H} \\
(\text{R} : -\text{NH.COCH}_3 \quad \text{or} \quad -\text{OC}_2\text{H}_5)
\end{align*}
\]

Leonard and Curtin (loc.cit.) have studied alkylation of quinazolones and they have found diazomethane as a specific methylating agent.

The N-alkyl-quinazol-4-ones are high melting, colourless, odourless crystalline solids, non-volatile with steam and stable to concentrated mineral acids. The alkoxy-quinazolines, on the contrary, are oily liquids or low melting solids; the lower members have a pleasant odour, are volatile with steam and are easily hydrolysed by hot dilute acids.

(6) Reaction with Phosphorus pentachloride in Phosphorus oxychloride: Bogert and May (J.Am.Chem.Soc., 1909,31,507) have observed that when quinazol-4-one is heated with phosphorus pentachloride in phosphorus oxychloride, it is converted into 4-chloroquinazoline, which is also obtained from 3-methyl-quinazol-4-one on similar treatment, the methyl group being removed during the reaction:
A few exceptions to this general reaction have been found: e.g., 5-nitro-quinazol-4-one is not affected even with the excess of reagent under various conditions, while 8-nitro-quinazol-4-one gives the corresponding 4-chloro derivative (Elderfield, J. Org. Chem., 1947, 12, 405). The 4-chloro-quinazolines give, upon reaction with primary amines, the corresponding 4-N-substituted amino-quinazolines (Magidson et al., J. Gen. Chem., U.S.S.R., 1938, 8, 1799; Chem. Abstr., 1939, 23, 4993; Smith, Elisberg and Sherrill, J. Am. Chem. Soc., 1946, 68, 1301; McKee and Bost, ibid., 1947, 69, 940).

Tomisek and Christensen (J. Am. Chem. Soc., 1948, 70, 874) have condensed 4-chloro-quinazoline with sodium salt of 4-keto-quinazoline:

It is interesting to note that the compound formed is N-ether (I) rather than the O-ether (II):
Elderfield, Williamson Gensler and Kremer (J. Org. Chem., 1947, 12, 405) in their attempts to prepare 4-thiophenyl derivative of 8-nitro-6-methoxy-4-chloro-quinazoline by means of sodium thiophenate have reported that a striking replacement of nitro group by thiophenyl occurs in addition to the expected reaction in the 4 position (I):

![Chemical structure](attachment:image.png)

Compound (I) on hydrogen peroxide oxidation and subsequent hydrolysis gives a sulphone derivative (II).


![Chemical structure](attachment:image.png)

The same compounds can be alternately prepared by the action of hydrogen sulphide or sodium hydrosulphide on 4-chloro-quinazolines (Kendall, Brit. Pat. No. 425609 / 1935; Chem. Abstr., 1935, 29, 5670).
(8) : **Reaction with Aldehyde** : 2-Methyl-quinazol-4-ones give styryl derivatives when heated with aldehydes, e.g., 2-methyl-quinazol-4-one on heating with p-anisaldehyde gives the corresponding 2-styryl-quinazol-4-one due to the reactive methylene group in the 2 position (Bogert and co-workers, J.Am.Chem.Soc., 1912, 34, 516; 1936, 58, 1701; Heilbron et al., J.Chem.Soc., 1925, 2167; Monti and Simonetti, Gazz.chim.ital., 1941, 71, 651; Chem.Abstr., 1942, 36, 5476).

\[
\begin{align*}
\text{2-methyl-quinazol-4-one} & \quad + \quad \text{p-anisaldehyde} \\
\text{2-styryl-quinazol-4-one} &
\end{align*}
\]


(9) : **Reaction with Alkali** : Heller and co-workers (J.prakt.Chem., 1928, 120(ii), 49; 1930, 126(ii), 76; 1931, 131(ii), 82) heated 2-aryl-3-aryloyl-amino-quinazol-4-ones with dilute aqueous alkali and obtained 3:5-diphenyl-4-(o-carboxyphenyl)-triazoles. The course of this complex reaction is shown below:

\[
\begin{align*}
\text{2-aryl-3-aryloyl-amino-quinazol-4-one} & \quad \xrightarrow{\text{dil. alkali}} \quad \text{3:5-diphenyl-4-(o-carboxyphenyl)-triazole}
\end{align*}
\]
(10) : Reaction with Grignard Reagent : The action of Grignard Reagent on the quinazol-4-ones has varied effects depending upon the substitution in the hetero-ring of the quinazolone nucleus.

Koelsch (J. Am. Chem. Soc., 1945, 67, 1718; also see Hammer et al., J. Chem. Soc., 1931, 251) has observed that if a quinazolone nucleus carrying a substituent in 3 position is attacked by benzyl magnesium chloride, the heterocyclic ring opens:

\[
\begin{align*}
\text{O} & \\
\text{N-Ph} & \\
\text{CH} & \\
\text{N} & \\
\text{C-CH} & \\
\end{align*}
\]

but, if the 2 position also carries a substituent along with 3 position, the attack of the Grignard Reagent takes place in the 4 position (Koelsch, loc. cit.; Hammer et al., loc. cit.; Sen and Cepadhyaya, J. Indian Chem. Soc., 1948, 25, 437; 1950, 27, 40).

\[
\begin{align*}
\text{R : Phenyl or} & \\
\text{R': Aryl or Alkyl} & \\
\end{align*}
\]

However, Mustafa et al. (J. Am. Chem. Soc., 1955, 77, 1612) have observed that if both 2 and 3 positions in the quinazol-4-one carry a phenyl nucleus, a benzoxazine derivative is obtained with elimination of an aryl amine:

\[
\begin{align*}
\text{O} & \\
\text{N-Ph} & \\
\text{C-Ph} & \\
\text{N-Ph} & \\
\text{C-Ph} & \\
\end{align*}
\]
Zaheer and Kacker (J. Chem. Soc., 1956, 415) have reported that 2-alkyl-3-aryl-quinazol-4-ones also give benzoazines, the probable course of reaction being discussed (see also Zaheer, Sidhu and Kacker, J. Indian Chem. Soc., 1962, 38, 622).

(11) Bromination: The quinazolones are not easily brominated by the action of bromine in aqueous potassium bromide, in glacial acetic acid or in acetic anhydride solution. The Juvalta Process (Ger. Pat. 50177) which consists in brominating the substance in fuming sulphuric acid at high temperature followed by subsequent neutralisation with solid sodium carbonate in ice-cold solution was found satisfactory by Bogert and Geiger (J. Am. Chem. Soc., 1912, 34, 524). They prepared monobromo derivatives of quinazol-4-one and 2-methyl-quinazol-4-one by this method leaving the position of bromine in the quinazolone molecule undecided.

(IV) Quinazol-2:4-diones:

Quinazol-2:4-diones, also called benzoyleneureas, could be easily prepared. As these compounds contain two keto groups, a brief description is included in this thesis for the sake of completion of the discussion of keto-quinazoline derivatives.

(A) Methods of preparation: Some of the important methods of preparation of quinazol-2:4-diones are summarised below:

(1) In 1869, Griess (Ber., 1689, 2, 415) reported for the first time the synthesis of quinazol-2:4-dione by passing cyanogen gas through an ethanolic solution of anthranilic acid and hydrolysing the resulting 2-ethoxy-4-keto-dihydro-quinazoline. The fusion of a dry mixture
of urea and an anthranilic acid also gives the quinazol-2:4-dione (Griess, J.prakt.Chem., 1872, 5(ii), 371; Abt, ibid., 1889, 39(ii), 140; Bogert and Scatchard, J.Am.Chem.Soc., 1919, 41, 2056).

\[
\begin{align*}
\text{COOH} & \quad + \quad \text{H}_2\text{N} \quad \text{C}:\text{O} \\
\text{NH}_2 & \quad \text{H}_2\text{N} & \quad \text{H}_2\text{N} \\
\text{COOH} & \quad \text{H}_2\text{N} \quad \text{C}:\text{O} \\
\end{align*}
\]

This has become the conventional method for the preparation of quinazol-2:4-diones and has been followed in this thesis. Even the action of aqueous hydrocyanic acid on anthranilic acid (Griess, J.prakt.Chem., loc.cit.; Bogert and Scatchard, loc.cit.; Gabriel and Colman, Ber., 1905, 36, 3561; Scott and Cohen, J.Chem.Soc., 1921, 664) or the action of potassium cyanate on the hydrochloride of anthranilic acid also gives the same product (Bogert and Scatchard, J.Am. Chem.Soc., 1916, 38, 1611; ibid., loc.cit.; Huntress and Gladding, ibid., 1942, 64, 2644; Lange and Sheibley: Blatt (Ed.), "Organic Syntheses", Coll.Vol.II, 1943, p.79):

\[
\begin{align*}
\text{KOCN} & \quad \rightarrow \quad \text{NaOH} \\
\end{align*}
\]

(2) : The reaction of anthranilic acid with diaryl-carbodiimides gives 3-aryl-quinazol-2:4-diones (Busch, Blume and Pungs, J.prakt. Chem., 1909, 72(ii), 513; Zetzsche and Voigt, Ber., 1941, 74B, 183; also see Khorana, Chem.Reviews, 1953, 53, 156).
(3) If urea or urethan or ethylchlorocarbonate is heated for a long time with anthranilamide, the same compound is obtained (Abt, loc.cit.). Isatoic anhydride could be used instead of anthranilamide (Clark and Wagner, J.Org.Chem., 1944, 2, 55; Partridge, Vipond and Waite, J.Chem.Soc., 1962, 2550). Substituted anthranilic acids could be also used for preparation of Benz-substituted derivatives.

Another method reported by them consists in similar treatment with sym.-diphenylureas.

\[
\text{ benzene } \xrightarrow{\text{CO}_2} \text{ quinazol-2:4-dione }
\]

The yield of the quinazol-2:4-diones is however, very poor, not exceeding three per cent in any case, a large amount of the ortho- and para-aminobenzoic acids being recovered.


\[
\text{f } \xrightarrow{\text{AlCl}_3 - \text{NaCl}} \text{ fusion}
\]

(5) : Oxindoles and amyl nitrite in methanolic sodium carbonate solution form an insoluble product which on heating with acid gives 3-hydroxy-quinazol-2:4-diones (Jancini, Gazz. chim. ital., 1944, 74, 3; Chem. Abstr., 1944, 38, 5825; Baeyer, Ann., 1866, 140, 21).
The same compound could also be obtained by benzoylation of o-phthalohydroxamic acid and subsequent hydrolysis by alkali (Hurd, Buess and Bauer, J.Org.Chem., 1954, 19, 1142) or by heating o-carbethoxy phenylurethan in hydroxylamine solution:

\[
\begin{align*}
CONHONa + 2 \text{PhCOCl} & \rightarrow \text{CONHOCOPh} \\
\text{CONHONa} & \text{heat} \\
\text{COOEt} + \text{NaOEt} & \rightarrow \text{CONHOCOPh} \\
\text{NHOOCOEt} & \text{(Alkaline hydrolysis)}
\end{align*}
\]

The 3-hydroxy compounds obtained as above yield quinazol-2:4-diones by the action of ferric hydroxide (Jacini, loc.cit.).

The above general methods could be used with a variety of the benzene substituted derivatives. Further, the 3-hydroxy group in the above compound could be esterified afterwards or at the start by using aroylchloride in place of benzoylchloride as mentioned above.

Quinazol-2-ones or quinazol-4-ones could be further oxidised to these diketones by potassium permanganate (Busch, J.prakt.Chem., 1895, 51(ii), 113) or chromic acid (Soderbaum and Widman, Ber., 1889, 22, 2933).

(B) : REACTIONS

The amide linkage in quinazol-2:4-dione should be looked upon as keto - enol tautomeric showing reactions characteristic of both the forms:
The reactions associated with quinazol-2:4-diones unsubstituted or mono-substituted in the hetero-ring are complex and unpredictable because of their tautomeric nature referred to above. For example, the entering group may become attached to either the N-atom or the O-atom in hydroxyl group or the hydroxy group may be replaced, thus resulting into any of these products or more often their mixture.

(i) Alkylation: Alkylation of sodium or potassium salts of quinazol-2:4-diones with methyl iodide in methanol leads to the formation of 1:3-dimethyl-quinazol-2:4-dione (Bogert and Seil, J. Am. Chem. Soc., 1907, 29, 517).

the reaction of sodium alkoxide on the 2:4-dichloro-quinazolines and pure N-alkyl-quinazolones by the methylation of sodium salt of quinazol-2:4-diones.

(ii) : Action of phosphorus pentachloride in phosphorus oxychloride: When quinazol-2:4-dione is heated with an equivalent of phosphorus pentachloride in phosphorus oxychloride solution, the corresponding chloro or dichloro quinazoline is formed. This has become a general method for the preparation of 2-chloro- and 4-chloro-quinazolines. The 4 position is distinctly more reactive to the nucleophilic substitution than is the 2 position (Lange and co-workers, J.Am.Chem.Soc., 1930,52,3696; 1932,54,4305; 1935,57,1068; Tomisek and Christensen, J.Am.Chem.Soc., 1945,67,2112).

(iii) : Reduction : Quinazol-2:4-diones are not easily reduced. Niementowski (J.prakt.Chem., 1889,40(ii),1) has reported that 7-methylquinazol-2:4-dione on distillation with zinc dust gave only a trace of 7-methyl-quinazoline, while, the ring was completely destroyed when the same was heated with hydriodic acid and red phosphorus in acetic acid at 210° for two hours.
(iv) : Action of alkali : Kizber and Glagoleva (J.Gen.Chem. U.S.S.R., 1953,21,1028; Chem.Abstr., 1954,48,8790; also see Dokunikhin and Gaeva, ibid., 1953,23,606; Chem.Abstr., 1954,48,7018) have reported that quinazol-2:4-diones on heating with alkali decompose into corresponding anthranilic acid and an amine : e.g., 3-(p-tolyl)-quinazol-2:4-dione decomposed into anthranilic acid and p-toluidine.

![Chemical structure]

: (V) : POLYNUCLEAR QUINAZOLONE DERIVATIVES

Besides the quinazolones substituted either in the hetero or the carbocyclic or in both the rings referred to above, complex quinazolones wherein the quinazolone nucleus is fused with other heterocyclic rings like pyrrole, indole, isocinole, phthalazine, pyridazine, quinoline, isoquinoline, quinazoline, triazine, thiazole, etc., have been studied. It is interesting to note that majority of these ring-systems have been built up in the last decade. A brief survey of the compounds representing such fused-ring quinazolones is given here, which does not claim to be complete in all respects and is only indicative of the extensive study of the quinazolone derivatives. The methods in many cases are simple and elegant.

(i) : Pyrrolo quinazolones : Spath and Platzer (Ber., 1935,68, 2221) prepared pyrrolo(2,1-b)quinazol-4-one by the reaction of pyrrolidone on isatoic anhydride. The same product was also obtained by the cyclodehydrobromination of 2-n-propylbromido-quinazol-4-one (Morris, Hanford and Adams, J.Am.Chem.Soc., 1935,57,951).
(ii) : Indolo quinazolone : In 1892, O'Neil (Chem. News, 1892, 65, 124; Brit. Abstr., 1892, 62, 991) reported isolation of a yellow product (II) obtained by the permanganate oxidation indigo (I). Perkin (Proc. Chem. Soc., 1906, 22, 198) obtained the same product as a result of air-oxidation during vacuum sublimation of indigo. It was given the following structure (II), at last by Friedlander and Roschdestwensky (Ber., 1915, 48, 1841) :

\[\text{Indigo} \quad \rightarrow \quad \text{6-Oxo-indolo(2,1-b)quinazol-12-one} \]

Butler, Partridge and Waite (J. Chem. Soc., 1960, 4970) obtained indolo-quinazolone (II) in their attempts to prepare triazo-chrysene (III) :
(iii) Iso-indolo quinazolones: Asahina et al. (J. Chem. Soc., 1927, 1708) have reported the preparation of product (III) by the interaction of methylantranilate (I) with phthalimidine (II) in excess of phosphorus trichloride:

\[
\begin{array}{c}
\text{COOCH}_3 \quad \text{HNCH}_2 \quad \text{O:C} \\
\text{NH}_2 \quad \text{(I)} \quad \text{(II)} \\
\end{array}
\xrightarrow{\text{PCl}_3 \text{ Heat}}
\begin{array}{c}
\text{O} \quad \text{H} \quad \text{N} \\
\text{(III)} \\
\end{array}
\]

12H-Iso-indolo(1,2-b) quinazol-10-one

Grippa and Caracci (Gazz. chim. ital., 1938, 68, 109; Chem. Abstr., 1938, 32, 6249) have reported that the fusion of phthalic anhydride with anthranilamide gives a product (IV) which on dehydration gives compound (V):

\[
\begin{array}{c}
\text{CONH}_2 \\
\text{(IV)} \\
\end{array}
\xrightarrow{}
\begin{array}{c}
\text{O} \\
\text{(V)} \\
\end{array}
\]

11-Oxo-iso-indolo(2,1-a) quinazol-5-one

(iv) Phthalazino quinazolone: Honzl (Chem. Abstr., 1956, 50, 5623) refluxed compound (I) with hydrazine in ethanol and obtained a product thought to have the following structure (II). Recently, Beyer and Voelker (Z. Chem., 1961, 1, 224; Chem. Abstr., 1962, 56, 5955) have reported that the formation of 2:3-disubstituted derivative of (II) by the condensation of 3-substituted anthranilic acid with 1:4-dichloro- or hydroxy-phthalazines in presence of phosphorus
oxichloride, thus confirming the structure (II) proposed by Honzl (loc.cit.) by analogy.

\[
\begin{align*}
\text{CH}_3 & \quad C:O \\ \text{O} & \quad + \quad N_2H_4 \\
\text{Ethanol} & \\
\end{align*}
\]

\[
\text{CH}_3
\]

(v) **Pyridazino quinazolone**: Bogert and Beal (J. Am. Chem. Soc., 1912, 34, 516) obtained a product, thought possible to have structure (I) by heating 2-methyl-3-amino-quinazol-4-one with benzil.

\[
\begin{align*}
\text{N-NH}_2 & \quad + \quad C_6H_5 \\
\text{CH}_3 & \quad \rightarrow \\
\end{align*}
\]

Beyer and Voelker (loc.cit.) obtained 2:6-disubstituted derivative of (I) by the reaction between 3-substituted anthranilic acid and 3-chloro-6-substituted pyridazines in presence of phosphorus oxichloride, thus supporting the structure proposed by Bogert and Beal (loc.cit.).

(vi) **Quino-quinazolone (Benz-quinazocoline)**: In 1892, Ephraim (Ber., 1892, 25, 2710) condensed anthranilic acid with 2-chlorolipidine and the product was given anthranil structure (I); while Bose and Sen (J. Chem. Soc., 1931, 2840; Bose, Curr. Sci. (India), 1934, 2, 430) proposed structure (II) which has been supported by Siede and Tschelinzew (J. Gen. Chem. U.S.S.R., 1937, 7, 2318; Chem. Abstr., 1938, 32, 572).
Structure (II) has been further supported by Stephen et al. (J.Chem.Soc., 1956, 4173).

\[
\begin{align*}
\text{COOH} & \quad \text{Cl} \\
\text{NH}_2 & \quad \text{CH}_3
\end{align*}
\]

\(2\)-chloro-lepidine

\(5\)-Methyl-quinazo(2,1-b) quinazol-12-one

(vii) : Quinazo quinazolone : Aggarwal and Ray (Jour.Indian Chem. Soc., 1929, 6, 723) condensed anthranilic acid with 4-hydroxy quinazoline (I) and obtained product (II):

\[
\text{COOH} + \text{NH}_2 \xrightarrow{\text{PCl}_3} \text{(II)}
\]

6-Substituted-quinazo(4,3-b) quinazol-8-one

However, one of the products (II, R : C\(_6\)H\(_5\)) similarly synthesized by Stephen and Stephen (J.Chem.Soc., 1956, 4173; 4178) was shown to be a mixture of (I) with N-(2-phenyl-4-quinazolinyl)-anthranilic acid. This renders the authenticity of the other products reported by Aggarwal and Ray (loc.cit.) questionable.

(viii) : Benzo-quinazo-quinazolone : Indravati (J.Madras univ. (India), 1955, 25B, 125; Chem.Abstr., 1956, 50, 11350) obtained benzo-(g)-quinazo-(3,2-c) quinazol-4-one by heating anthranilic acid
with (I) in presence of phosphorus trichloride.

(ix) Triazole quinazolone: The reaction of acetylurethan with p-nitrophenyl hydrazine yielded product (I) which on condensation with anthranilic acid gave a compound with structure (II). (Ghosh and Betrabet, Jour. Indian Chem. Soc., 1930, 7, 899; Allen et al., J. Org. Chem., 1959, 24, 796).

(x) Thiazolo-quinazolones (Thiopegans): In 1950, Kendall and Duffin (U.S. Pat. 2527265-66; Chem. Abstr., 1950, 44, 9287) treated (I) with acetic anhydride and pyridine and obtained for the first time a product which could be either linear (II) or angular (III) quinazolino-thiazole derivative. Extensive contributions to these ring-systems have come from Narang and his associates (Sci. & Cult. (India), 1952, 18, 43; Research Bull. E.-Punjab univ. (India), 1953, No. 36, 139; J. Org. Chem., 1955, 20, 302; Jour. Indian Chem. Soc., 1954,
They have found that 2-carbethoxy phenylthiourea (IV) condensed with \( \alpha \)-haloketones (V) to yield products which were thought to have structure (VI) rather than structure (VII). Howard and Klein (J. Org. Chem., 1962, 27, 3701) have, quite recently, confirmed structure (VI) by an unambiguous synthesis. These compounds were named by Narang and co-workers as '10-11-Thiopegan' (VI) and '9:10-Thiopegan' (VII) respectively.

(xii): Benzothiazolo quinazolone: Bose and Pathak (Jour. Indian Chem. Soc., 1934, 11, 463) condensed anthranilic acid with 2-chloro-benzothiazoles and obtained a product (I), which has been also obtained by Katz (J. Am. Chem. Soc., 1953, 75, 712) as well as by McCarty (J. Org. Chem., 1962, 27, 2672) following alternate routes.
(xii) : **Naphtho-thiazolo-quinazolone** : Bose and Pathak (Jour. Indian Chem. Soc., 1934, 11, 463) obtained a product by condensation of a substance which they called '2-chloro-α-naphthothiazole' (m.p. 75°) with anthranilic acid. They assigned structure (I) to this product and named it α-naphthothiazolonyl quinazoline.

The inconsistency here is apparent, but a further difficulty arises in trying to identify the 2-chloronaphthothiazole employed initially. None melting at 75° has been reported, the closest being (II), which melts at 80°, and which, upon condensation with anthranilic acid would lead to (III). It therefore seems probable that Bose and Pathak's
product is (III) instead of (I), and there are consequently no examples as such of the first ring-system. The erroneous linear formula (I), however, has found its way into the 'Ring Index' as well as in many of the abstract journals.

(xiii) : **Benz-isothiazolo-quinazolone** : Stephen and Stephen (J.Chem.Soc., 1957,490) treated pseudo-saccharin chloride (I) with anthranilic acid (or its salts, esters or amides) and obtained product (II), which on dehydration gave product (III).

\[
\text{(I)} \quad \text{Cl} \quad \begin{array}{c}
\text{NH} \\
\text{COOH}
\end{array} + \begin{array}{c}
\text{Cl} \\
\text{S}_2
\end{array} \quad \rightarrow \quad \begin{array}{c}
\text{NH} \\
\text{COOH}
\end{array}
\]

\[
\text{(II)}
\]

\[
\text{(III)}
\]

\[
\text{5-Oxo-(1,2-d)benz-isothiazolo (3,2-b)quinazol-7-one}
\]

(VI) : **QUINAZOLONE VAT DYES**

There are a large number of patents claiming various quinasolone derivatives as dye intermediates. They are mostly obtained by the condensation of 2-chloro- and 4-chloro- or 2:4-dichloroquinazolines with variety of aromatic amino, hydroxyl and sulph-hydryl compounds containing chromophoric groups. For example, 6-nitro-2:4-dichloroquinazoline with 2-aminoanthraquinone gives a yellow vat dye (BASF, Brit.Pat. 771347 and 763328).
Baumann and Schwechaten (I.G. 1937, P.B. report No. 70339) obtained a yellow dye of probable structure (II) by the treatment of (I) with aluminium chloride in nitrobenzene. The dye is sensitive to alkali or pyridine solutions possibly because of the ring rupture (dotted line in (II)). Structure (III) remained unaffected by similar treatment.
A brown vat dye having structure (VI) was reported to result from the condensation of (V) with isatin chloride (IV) (Berthold, Rohland and Bottcher, I.G. 1938, P.B. report, No. 70342). It is an indolo-naphtho-quinazolone derivative.

\[
\begin{array}{c}
\text{(IV)} \\
\end{array} \quad \text{+} \quad \begin{array}{c}
\text{(V)} \\
\end{array} \quad \rightarrow \quad \begin{array}{c}
\text{Indolo-}(2,1-b)-naphtho-(2,3-b)-5:14:16-triketo-6-nitro-quinazol-8-one.
\end{array}
\]

The dyes containing dibenzo-quinazo-isoquinoline nucleus were prepared by Lesser and Gad (Ger. Pat. 536448; Frdl., 1933, 18, 1475) who obtained them as shown below:

\[
\begin{array}{c}
\text{COOH} \\
\text{NH}_{2} \\
\text{HN} \\
\text{O}:\text{C} \\
\text{H}_{3}\text{C} \\
\end{array} \quad \rightarrow \quad \begin{array}{c}
\text{(VII)} \\
\end{array}
\]

5-Keto-dibromo-(f,ij)-10-keto-quinazo-(3,2-b)-isoquinoline

Compound (VII) is an orange red solid; its dibromo derivative is orange yellow; the 13-chloro derivative of (VI) is orange red while its 13-acetylamino derivative is red.

Instead of anthranilic acid in above, 2-amino-naphthalene-3-carboxylic acid (Lesser and Gad, loc. cit.), 1-amino-anthraquinone-
2-carboxylic acid and 2-amino-anthraquinone-3-carboxylic acid (Lesser, Gad and Bruck, Ger.Pat. 561640; Frdl., 1934, 19, 2166) have been used and different shades of orange vat dyes were obtained. The substituents like chlorine or methyl did not improve fastness, only led to bronziness (Braunsdorf, I.G. 1938; P.B. report No. 70338).

Baumann and Schwechten (I.G. 1937; P.B. report No. 70339) reported product (X) by condensing (VIII) with (IX) under acidic dehydrating conditions. It dyed cotton orange, but showed only fair soda-fastness and poor light-fastness.

Thus, quinazolone vat dyes are not fast dyes and as such are not of much commercial importance even though their structures are sufficiently similar to other standard vat dyes having no nitrogen atom in their molecules.
Naturally occurring compounds containing quinazolone ring-system are relatively few. So far only few quinazolones have been isolated from plants. For example, Evodiamine (I) and Rutaecarpine (II) have been isolated from Evodia rutaecarpa (Asahina and Mayeda, J.Pharm.Soc. Japan, 1916, No.416; Brit.Abstr., 1916,(i),621; J.Pharm.Soc.Japan, 1921, No.863; Brit.Abstr., 1921,(i),48) and the following structures (I & II) have been assigned to them respectively (Asahina, Manske and Robinson, J.Chem.Soc., 1927,1708), the constitution of Rutaecarpine being confirmed by the actual synthesis in 1927 by Robinson et al. (loc.cit.).


The drug in its crude form has been employed in the treatment of asthma in India. Chopra (Indian Med.Gaz., 1925,10,354) has reported its bronchodilatory property and indicated its possible use as an expectorant. Amin and Mehta (Nature, 1959,184,1317) have suggested that the beneficial action of the leaves of this plant in respiratory disorders may be attributed to the small quantities of Vasicinone (IV) already present or formed by auto-oxidation of Vasicine in the plant. They have isolated it in the active form (leavo) from the crude total alkaloids by partition chromatography in a crystalline form. They have also reported it as a definite bronchodilator against histamine-induced broncho constriction (Bovet and Bovet-Nitti, Medicament du système Nerveux Vegetatiuf; Karger, Basle, 1948).

\[
\text{(III) Vasicine}
\]

\[
\text{(IV) Vasicinone}
\]

\[
\begin{align*}
\includegraphics{febrifugine.png}
\end{align*}
\]

(V) Febrifugine (dichroine)

Febrifugine is a powerful antimalarial, having about hundred times the activity of quinine against P.lophurae in ducks, but it is very toxic. It is also found in many Hydrangea species (Ablondi et al., J.Org.Chem., 1952,17,14,19). Clinical tests have shown Febrifugine to alleviate acute vivax malaria temporarily, but it also induces nausea in medium dosage (Hewitt, Wallace, Gill and Williams, Amar.J.Trop.Med. Hyg., 1952,1,768; Coatney, Cooper, Culwell, White and Imboden, J.Nat. Malar.Soc., 1950,2,183). Replacement of the pyridine group of the Febrifugine by thiophene (Baker, Joseph, Schaub, McEvoy and Williams, J.Org.Chem., 1953,18,178) led to the decrease in the antimalarial activity having a quinine equivalent of ten only.
Chakravarti, Chakravarti and Chakravarti (J. Chem. Soc., 1953, 3337; Sci. & Cult. (India), 1953, 18, 539, 553) have isolated Arborine (VI) from Glycosmis arborea, Correa, a plant used in Ayurvedic system of medicine as febrifuge and anthelmintic, and they have assigned to it the following structure confirming it by actual synthesis.

\[
\begin{align*}
\text{(VI)} \\
\text{Arborine}
\end{align*}
\]

Chatterjee and Ghosh Majmudar (Sci. & Cult. (India), 1952, 17, 306; 1953, 18, 505, 604; J. Am. Chem. Soc., 1953, 75, 4365) have obtained from Glycosmis pentaphylla, Correa, three alkaloids, one of which has been proved to be a quinazolone derivative, identical with Arborine (Chakravarti et al., Tetrahedron, 1961, 16, 228).

Pakrashi and Bhattacharya (J. Sci. Indstr. Res. India, 1962, 21B, 49) from their chemical investigation of Glycosmis arborea (Roxb.) DC. (Rutaceae) previously believed to be Glycosmis arborea Correa (Pakrashi and co-workers, ibid., 1961, 20B, 186; Chem. & Ind., 1961, 464; Ann. Biochem., 1960, 20, 103) have isolated three new alkaloids Glycosmine, Glycerine and Glycosminine. They are yet to report the structure of these alkaloids. One or more of them might turn out to be quinazoline derivative.

All the alkaloids referred to above are the quinazoline derivatives with substituents in different positions of the heteroring of the quinazoline nucleus.
continuous series of sixteen papers (J.Org.Chem., 1952,17,14-176) have described the isolation of antimalarial alkaloids from Dichroa febrifuga Lour. and Hydrangea species. Sengupta, Bami and Sharma (J.Sci.Indstr.Res.(India), 1959,18C,28) have reported 3-allyl-2-mercapto-quinazol-4-one and its 6-methyl derivative to possess antimalarial activity several times greater than the quinine dosage. On the other hand, of the twenty-nine 3-(p-substituted)-sulphonamide derivatives of quinazolone screened against Plasmodium gallinaceum in chicks, only 2-ethyl-3-p-(2'-pyrimidyl)-sulphanamido-phenyl-6-chloro-quinazol-4-one showed antimalarial activity at a dose four times the minimum effective dose of quinine (Basu, Dhatt, Prakash, Bami and Singh, J.Sci.Indstr.Res.(India), 1962,21C,245). As a class, therefore, sulpho-quinazolones have little potentiality as antimalarials. The therapeutic importance of natural quinazolone derivatives has been already mentioned earlier.

Gujral et al., (Indian J.Med.Res., 1955,43,637; Medicin, 1955, II(3),1) have tested some 2-alkyl-3-phenyl-quinazol-4-ones and found them as new hypnotic agents; 2-methyl-3-(o-tolyl)-quinazol-4-one possessing excellent hypnotic activity with much less toxicity as compared to that of diallyl barbituric acid, in comparable doses. The drug is now marketed under the name Melsedrin (Boots Pure Drug Co. Ltd.) and Tuazole (Strasenburgh Laboratories, U.S.A.).

Klosa (Ger.Pat. 1132332 / 1962; Chem.Abstr., 1962,57,3458) has synthesized 2-methyl-3-(2'-methyl-3'-chlorophenyl)-quinazol-4-one and he has reported it to possess strong sedative action with much less toxicity. Several 3-phenyl (and 3-allyl)-2-alkylthio (and 2-thio)-
quinazol-4-ones (McCarty et al., J.Am.Chem.Soc., 1960,82,964; Trivedi, Jour.Indian Chem.Soc., 1960,37,801) have been synthesized as possible ataractic agents; while Joshi and Giri (ibid., 1962,39,189) have reported them to be of use as positive organic pesticides.

Iyer and co-workers (J.Sci.Industr.Res. India, 1956,15C,1; 1957, 16C,157; 1958,17C,193; 1961,20C,175) have reported variously substituted 2-alkyl-3-substituted- and 2:3-dialkyl-8-hydroxy-quinazol-4-ones and their Mannich bases as potential amoebicides. Gupta et al.,(ibid.,1959, 18C,1) have been successful in screening of 8-hydroxy (and 8-methoxy)-quinazol-4-ones against experimental tuberculosis in guinea pigs. Agarwal and co-workers (ibid., 1962,21C,189,309), quite recently, have observed 8-hydroxy-quinazol-4-one derivatives to possess the ability to suppress vaccinal pock formation in chlorio-allantoic membrane of chick embryos thus reducing their mortality. 3-n-Propyl- and 3-benzoyl-8-hydroxy (and 8-methoxy)-quinazol-4-ones were observed to possess appreciable amoebicidal activity both in vitro and vivo against 'Entamoeba histolytica' and against intestinal amoebiasis in rats (Kaushiva, Paper read at the symposium on 'Amoebiasis and other Intestinal Infections' held at the Central Drug Research Institute, Lucknow (India), 1959).

Wellcome Foundation (Brit.Pat. 806772 / 1958; Chem.Abstr., 1959, 53,12316) have synthesized 6-methyl-2:4-diamino-quinazolines and observed them to be effective against Gram positive and Gram negative bacteria. Quinazoline and its several substituted products prevent fogging when added to photographic emulsion and developer (Komm, Tetanal - Photowerk, Ger.Pat. 724261 / 1942; Chem.Abstr., 1943,37,5670; Birr, E.-Ger.Pat. 11382 / 1956; Chem.Abstr., 1959,53,6854).
Bhaduri, Khanna and Dhar (J. Sci. Industr. Res. (India), 1962, 21B, 378) have synthesized 3β- (and 3γ-) dialkylaminoethyl (and propyl)-quinazol-4-ones and quinazol-4-thiones and reported some of them to possess pronounced spasmolytic activity. 2-substituted 6-sulphonamido-quinazol-4-ones have diuretic effect but cause a pronounced natriuresis and chloruresis in experimental animals (Cohen, Klarberg and Vaughan, J. Am. Chem. Soc., 1959, 81, 5508).


A number of quinazoline analogues of naturally occurring physiologically active quinazolines have been synthesized with a view to study their medicinal efficacy and compare its activity. 2-Phenylquinazoline-4-carboxylic acid (VII), an analogue of cinchophen, has been prepared from isatin through N-benzoyl isatoic acid (Bogert and Nabenhauer, J. Am. Chem. Soc., 1924, 46, 1702). In a similar way, an analogue of cusparine (VIII) belonging to the Angostura alkaloids has been synthesized from 2-methyl-quinazol-4-one by condensing it with 3:4-methylenedioxy benzaldehyde followed by reduction and
methylation (Marr and Bogert, J. Am. Chem. Soc., 1935, 57, 729; Papa and Bogert, ibid., 1936, 58, 1701). They (ibid., 1935, 57, 1329) have also reported a partial synthesis of quinazoiline analogue of papavarine (IX).

\[
\text{COOH} \\
\begin{array}{c}
\text{C} \\
\text{N} \\
\text{C} \\
\text{N}
\end{array}
\text{N} \\
\text{C} \\
\text{CH} \\
\text{2} \\
\text{CH} \\
\text{2} \\
\text{N}
\]

(VII)

\[
\begin{array}{c}
\text{MeO} \\
\text{N}
\end{array}
\text{MeO} \\
\text{CH}_2
\begin{array}{c}
\text{N} \\
\text{C} \\
\text{N} \\
\text{C}
\end{array}
\text{N} \\
\text{C} \\
\text{C} \\
\text{OMe}
\]

(IX)

\[
\text{OMe} \\
\text{OMe}
\]

(VIII)

PRESENT WORK

From the foregoing pages, it is evident that the 'Quinazolone Chemistry' is a living subject and a large number of compounds are synthesized having diverse potential value.

In Part I of the present thesis 2:8-dimethyl- and 2:6-dimethyl-3-aryl-quinazol-4-ones have been synthesized by the condensation of different primary aromatic amines with 3-methyl- and 5-methyl-anthranilic acids respectively.

Part II is divided into four sections. In first two sections, 6-chloro- and 7-chloro-3-aryl-2-mercapto-quinazol-4-ones derived from 5-chloro- and 4-chloro-anthranilic acids respectively, have
been described. These have been prepared by two methods: condensation of chloroanthranilic acids with (a) mono-arylthioureas and (b) aryl-isothiocyanates. The mercapto-quinazol-4-ones have been further oxidised by hydrogen peroxide to the corresponding chloro-3-aryl-quinazol-2:4-diones, structures of which have been confirmed by their direct synthesis from the chloro-anthranilic acids and aryl-ureas. Further, these 2-mercapto-quinazol-4-ones have been treated with bromobenzene as well as benzoyl chloride under suitable conditions when hydrogen atom of the mercapto group was replaced, proving the 'thiol' structure.

In the remaining two sections, similarly 6-methyl- and 8-methyl-3-aryl-2-mercapto-quinazol-4-ones have been synthesized by the two methods referred to above. These compounds were oxidised to the corresponding quinazol-2:4-diones, which were also obtained directly from the corresponding methyl-anthranilic acids and aryl-ureas. The mercapto-quinazolones also gave products with bromobenzene and benzoyl chloride.