CHEMISTRY OF BENZOXAZOLONE

2-Benzoxazolone (I) is also a cyclic isoster of coumarin (II) whose antibacterial activities have been extensively investigated and performed.\textsuperscript{1,2}

![Chemical structures](image)

(I) \hspace{1cm} (II)

2(3H)-Benzoxazolone (1) heterocycle (abbreviated BOA) is a bicyclic ring system composed of a phenyl ring fused to carbamate.\textsuperscript{3,4,5} This particular structural feature has several important consequences for the medicinal chemist:

(i) One edge is lipophilic, while the other one is hydrophilic with two hydrogen bonding accepting sites and a single hydrogen bonding donating site.

(ii) BOA is a weak acid in aqueous solution (pKa = 8.7), somewhat comparable to pyrocatechol (2) (pKa = 9.2), reason for which BOA is often referred to as a pyrocatechol bioisoster.

(iii) BOA constitutes a scaffold of high versatility in organic synthesis, allowing for a wide variety of chemical modifications implying a good directionality in the implementation of the side chains on a rigid platform.

(iv) BOA shares structural resemblance with phenylurethane (3) and coumarin (4) so it to endowed with hypnotic, analgesic and antipyretic properties of the former and bactericide properties of the latter.\textsuperscript{6,7}
BOA (1) in many design also serves as a phenol substitute. To some extent, the sulfur bioisoster, i.e. 2(3H)-benzothiazolone (5), the methylene bioisoster, i.e. 2-oxindole (6) and the nitrogen bioisoster, i.e. benzimidazol-2-one (7) have been employed with great success in situations where either a phenol or catechol had to be replaced by a more adequate residue. The methylene ring expansion of BOA, i.e. benzoxazolinone (8), follows the same strategy of bioisosterism.

CHEMICAL REACTIVITY:
The reactivity of BOA permits to define three major types of reactions:

(i) N-substitution (either alkylation or acylation)
(ii) Aromatic ring electrophilic substitution
(iii) Ring opening or expansion reactions
(i) N-substitution:

N-alkylation of 1 proceeds under base-catalyzed conditions to give derivatives of type (9), while N-acylation is submitted to generalized acid-base catalysis to give derivatives of type (10).

\[ \text{N-alkylation of 1} \]

\[ \text{N-acylation of 1} \]

(ii) Aromatic ring electrophilic substitution:

Aromatic electrophilic substitution is governed by the overwhelming preference for the 6-position which is observed not only for the straightforward halogenation, nitration, sulfonation and chlorosulfonation reactions, but also for the more troublesome friedel-craft acylation. Indeed, in the particular case of the friedel-craft reaction, due to the electron-rich character of BOA, the heterocycle is extensively complexed by the Lewis acid present in the reaction medium, acts as electrophilic attack of acylium ions. To overcome this problem, the reaction can be run using either a less reactive electrophilic species (polyphosphoric acid) or preferably the \( \text{AlCl}_3 \)-DMF complex to give 6-acyl derivatives of type (11). As a most fruitful alternative, N-acyl derivatives of type (10) can be rearranged at high temperature in a fries like reaction promoted by \( \text{AlCl}_3 \) to 6-acyl derivatives of type (12).
The precise position of acylation was unequivocally assessed in the case of 6-benzoyl-2(3H)-benzoxazolone by X-ray single-crystal diffraction and by $^1$H-NMR studies. The 6-acyl derivative was the only product which could be isolated from the reaction medium, no evidence (HPLC, $^1$H-NMR study) could be found for the concomitant formation of 5-acyl derivative. The 5-acyl derivatives were synthesized by an alternative route.

(iii) Ring opening or expansion reaction:
BOA derivatives are fairly stable in acid medium, they are quickly hydrolyzed in basic medium, leading to ring opening products such as 2-aminophenols (13). These 2-aminophenols can be acylated in position 4 (14). Subsequent ring closure leads to the otherwise inaccessible 5-acyl-BOA derivatives (15). Ring expansion of BOA derivatives to benzoxazinones (16) can be effected via the same 2-aminophenols.

(a) aq. NaOH, Δ; (b) RCOCl, AlCl₃,DMF; (c) CICOCOME, TEA; (d) BrCH₂COOME, TEA.

**GENERAL METHODS FOR THE PREPARATION OF BENZOXAZOLONE**

(1) 2-Benzoxazolinones, substituted at position-5, were prepared from corresponding 4-substituted 2-aminophenol either by fusion with urea or reaction with phosgene. Where R' = Br, I etc.

The sandmeyer reaction with 5-amino-2-benzoxazolinone provided an alternate route and preferred to higher yield.
Perumal et al. synthesized 2(3H)-benzoxazolone derivatives by the reaction between salicylic acid, ammonium azide and vilsmeier complex.

\[ \text{NH}_4\text{N}_3, \text{DMF/POCl}_3 \]

Where \( R_1, R_2, R_3 = H \)

References:
4. Sandmeyer, G. Ber. 1886, 19, 2656.
5. Graebe, J.; Rostovzef, S. Ber. 1902, 35, 2751.
CHEMISTRY OF SEMICARBAZIDE

Closely related to carbamide $\text{H}_2\text{N-CO-NH}_2$ is semicarbazide or semihydrocarbazide $\text{H}_2\text{N-CO-NH-NH}_2$, which is the half of amide and half of hydrazide of carbonic acid.

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

It is an important reagent for detection of aldehyde and ketone and may be regarded as hydrazide of carbamic acid.

GENERAL METHODS FOR THE PREPARATION OF SEMICARBAZIDE DERIVATIVES

1. Phenylsemicarbazide can be prepared by the action of hydrazine hydrate on phenylurea.$^1$

\[
\text{Ph-NH}_2 + \text{NH}_2\text{NH}_2 \cdot \text{H}_2\text{O} \rightarrow \text{Ph-NH} \quad \text{NH} \quad \text{NH}_2 \\
\]

2. It can be also prepared from potassium cyanate and hydrazine hydrochloride. Hydrazine cyanate is first formed which isomerise to semicarbazide.$^2$

\[
\begin{align*}
\text{KCN} + \text{H}_2\text{N-NH}_3^+ \text{Cl}^- & \rightarrow \text{H}_2\text{N-NH}_3^+ \text{NCO}^- + \text{KCl} \\
\text{H}_2\text{N-NH}_3^+ \text{NCO}^- & \rightarrow \text{H}_2\text{N} \quad \text{NH} \quad \text{NH}_2
\end{align*}
\]

This reaction takes place at room temperature.
3. Alkyl or aryl isocyanate react with hydrazine to give 4-substituted semicarbazide.

\[
\text{Phenyl isocyanate} \quad \text{Phenyl semicarbazide}
\]

4. Aromatic amine form symmetrical diaryl urea. A 4-substituted semicarbazide is formed as an intermediate.\(^{3,4}\)

In the present synthetic work, semicarbazide derivatives have been synthesized as per method – 3.

References:

CHEMISTRY OF THIOSEMICARBAZIDE

Thiosemicarbazide derivatives have been used in the synthesis of various heterocycles like 1,2,4-triazole etc. 1-Acetyl/aroyl-4-substituted-thiosemicarbazides have been found to possess a wide spectrum of medicinal activities. The common structure of thiosemicarbazide is given in figure (1).

\[
\begin{align*}
R^1\text{-NH-NH-} & \equiv \text{NH-}R^2 \\
\text{S} & \\
(1)
\end{align*}
\]

Where, \( R^1 = \text{Ar-CO, H, Ar, CH}_3\text{CO, Alkyl etc.} \)

\( R^2 = \text{Ar, Ar-CO, H, Alkyl etc.} \)

GENERAL METHODS FOR THE PREPARATION OF THIOSEMICARBAZIDE

1. 1-Acyl-4-alkyl, aryl or substituted aryl thiosemicarbazides were synthesized by the reaction of respective acid hydrazide and different alkyl isothiocyanates, in either dioxane or methyl cellosolve, according to the method of Yale et al.\(^1\)

\[
\begin{align*}
R^1\text{-NH-NH}_2 + & \text{SCN-R}^2 \rightarrow \text{Dioxane or Cellosolve} \\
R^1\text{-NH-NH-C} & \equiv \text{NH-R}^2 \\
\text{S} & \\
\end{align*}
\]

Where \( R^1 = \text{Ar-CO, H, Ar, CH}_3\text{CO, Alkyl etc.} \)

\( R^2 = \text{Ar, Ar-CO, H, Alkyl etc.} \)

2. Thiosemicarbazides unsubstituted in 4-position were synthesized by the condensation of the respective acid hydrazides with potassium thiocyanate under acidic condition.\(^2,3\)

\[
\begin{align*}
R^1\text{-NH-NH}_2 + & \text{KSCN} \rightarrow \text{Conc. HCl Methanol} \\
R^1\text{-NH-NH-C} & \equiv \text{NH_2} \\
\text{S} & \\
\end{align*}
\]

Where, \( R^1 = \text{Ar-CO, H, Ar, CH}_3\text{CO, Alkyl etc.} \)
3. The interaction of chloroarylation product of aryl isothiocyanate with some monoacylhydrazine was investigated. It was shown that the result of this reaction was the formation of 1,4-disubstituted thiosemicarbazides.4

\[ \text{R}_1\text{C}_8\text{H}_4\text{C}_\text{Cl} \text{N} = \text{C} = \text{S} + \text{R}_2\text{C} = \text{O} \text{NHNH}_2 \rightarrow \text{R}_1\text{C}_8\text{H}_4\text{C}_\text{Cl} \text{S} = \text{N} = \text{N} = \text{NH}_2\text{R}_2 \]

In the present synthesis work, thiosemicarbazide derivatives have been synthesized as per method-1 & 3.

References:
4. Volodymyr, V.; Ganushchak, I. Molecules 2003, 8, 263.
CHEMISTRY OF SCHIFF BASE

Schiff bases and semicarbazones share very similar chemistry, the reason being that, both these classes of compounds are formed by the condensation of amino and carbonyl function of aldehydes or ketone.

The presence of azomethine linkage in compounds has been shown to decrease their toxicity considerably.\textsuperscript{1,2} Schiff base of various aldehydes have shown encouraging antituberculosis activity \textit{in vitro} in laboratory.

Schiff\textsuperscript{3} for the first time reported the condensation of primary amine with carbonyl compounds. Hence the condensation products are referred to as ‘Schiff bases’.

\[
\text{R-CHO} + \text{H}_2\text{N-R} \rightarrow \text{R-CH=N-R}
\]

GENERAL METHODS FOR THE PREPARATION OF SCHIFF BASES

1. The simplest method appears to be the one in which condensation of equimolar quantities of an amine and an aldehyde is affected in boiling methanol.

2. In 1964, Tipson and Clapp\textsuperscript{4} obtained Schiff base by refluxing the amine and aldehyde in toluene with few drops of piperidine. The water formed during the course of reaction was removed by employing a Dean-Stark trap.

3. In 1953, Giovambettista and Rabassa\textsuperscript{5} Suggested acetic acid as a catalyst for the synthesis of Schiff bases in good yield. As the first method was found to give schiff bases in good yield, it was followed initially during the course of this investigation. Later on, it was found that the use of a few drops of acetic acid improve the yield.

4. Arenesulfonylhydrazones have been prepared by condensation of aren sulfonfonylhydrazine and ketone or aldehyde.\textsuperscript{6}
In the present synthetic work, Schiff bases have been synthesized as per the method-4.

References:

1. Popp F.D. J. Med. Chem. 1964, 7, 210
Quinazoline (1) is benz-1,3-diazine containing 4-hydroxy substituent serves as nucleus to most of compounds which are associated with wide spectrum of pharmacological activities.\textsuperscript{1} They are reported to exhibit properties of both the keto and enol forms (2).

\begin{center}
\begin{tikzpicture}
  \node[anchor=center] at (0,0) {\includegraphics[width=0.5\textwidth]{quinox.png}};
\end{tikzpicture}
\end{center}

(1)

(2)

The quinazoline nucleus is embedded in a large number of alkaloids, drugs, antibiotics, agrochemicals and antimicrobial agents. Many simple fused quinazolines are biologically active\textsuperscript{2} themselves or are essential component of very important naturally occurring substances (i.e. nucleic acid).

The ortho-fusion of benzene nucleus with pyrimidone ring (4) gives rise to a class of heterocyclic compounds containing 1:3 benzodiazine ring system (3). As early as 1869 Griess\textsuperscript{3} built up this ring system for first time in his compound (5) which he has named as ‘cyanoamido benzoyl’.

\begin{center}
\begin{tikzpicture}
  \node[anchor=center] at (0,0) {\includegraphics[width=0.5\textwidth]{quinox.png}};
\end{tikzpicture}
\end{center}

(3)

(4)

(5)
Later on the name 'Quinazoline' was proposed by Weddige.\(^4\) The numbering followed in this thesis is according to Poal and Busch\(^5\) (6). According to this nomenclature, the compound (5) of Griess is 2-cyano quinazoline-4-one or 2-cyano-4-keto quinazoline or more simply 2-cyano-4-quinazolone.

The quinazol-4-one are regarded as the derivatives of the parent compound quinazoline (7), which is isomeric with cinnadie (8), quinazoline (9) or p-phthalazine (10) differing in the position of the two N-atoms in the hetero ring.

![Chemical Structures]

**GENERAL METHODS FOR THE PREPARATION OF QUINAZOLINE**

1. 6-Nitro-4-oxoquinazoline (11) has been prepared by the condensation of 5-nitroanthranilonitrile with formic acid containing con. H\(_2\)SO\(_4\).\(^6\)

![Chemical Reaction]
2. 5-Nitroanthranilonitrile was condensed with DMF/acetal gives intermediate\(^7\) (12) which on further condensation with 3-bromoaniline in acetic acid yields quinazoline derivative of type (13).

\[
\begin{align*}
\text{O}_2\text{N} & \quad \text{CN} \\
\text{NH}_2 & \quad \text{CN} \\
\text{DMF/acetal} & \\
\rightarrow & \\
\text{O}_2\text{N} & \quad \text{N} \\
\text{NMe}_2 & \quad \text{CN}
\end{align*}
\]

(12)

\[
\begin{align*}
\text{Br} & \quad \text{N} \\
& \quad \text{NH} \\
\text{AcOH} & \\
\rightarrow & \\
\text{O}_2\text{N} & \quad \text{C} \\
\text{N} & \quad \text{N}
\end{align*}
\]

(13)

3. Szczepankiewicz, W. et al.\(^8\)\(^,\)^\(^9\) showed that the cyano function can be converted to 2-amino-N-aryl benzimidates (14) by reaction with an aniline and aluminium chloride, which on further reaction with formic acid yield 4-aryl aminoquinazoline (15).

\[
\begin{align*}
\text{CN} & \quad \text{NH}_2 \\
\text{NH}_2 & \quad \text{H}_2\text{N} \quad \text{Ar} \\
\text{AlCl}_3 & \\
\rightarrow & \\
\text{NH}_2 & \quad \text{N} \\
\text{H} & \quad \text{R} \\
\text{HCOOH} & \\
\rightarrow & \\
\text{NH} & \quad \text{R}
\end{align*}
\]

(14)

(15)
4. The Niementowski's synthesis:

In 1895, Niementowski\textsuperscript{10} described the synthesis of quinazolines 4(3H)-one (16) by fusion of anthranilic acid with formamide.

\[
\begin{align*}
\text{COOH} & \xrightarrow{120-130\,^\circ\text{C}} \text{COOH} \\
\text{NH}_2 & \quad \text{RCONH}_2, 3\text{ hours} \\
\end{align*}
\]

5. 4-Nitroanthranilic acid when condensed with formamide yield 7-nitro-4-hydroxyquinazoline (17).\textsuperscript{11}

\[
\begin{align*}
\text{COOH} & \xrightarrow{\text{HCONH}_2} \text{NH}_2 \\
\end{align*}
\]

6. J. B. Jiang et al.\textsuperscript{12} synthesized quinazoline-4(3H)-one (18) from substituted anthranilic acid derivatives followingly.
In the present synthetic work, quinazolines have been synthesized as per the methods - 1 & 5.

References:

Urea is the chief final product of the metabolism of nitrogen containing compounds in animals, it is eliminated in urine and an adult human excretes an average of 30g. urea in a day. Urea is used for the synthesis of barbiturates, phenobarbital or secobarbital. The barbiturates produce a depressant effect on the central nervous system and because of this effect they are useful as sedatives and sleep inducers.

Urea is one of the most important compound and used in fertilizer. Among other urea derivatives, phenyl urea derivatives are widely used in pharmaceutical chemistry.

The ureas are generally represented by the structure (1)

\[
\begin{align*}
&\text{R}_1 & \text{R}_2 & \text{R}_3 & \text{R}_4 \\
\text{N} & \text{C} & \text{N} & \text{O} \\
\end{align*}
\]

(1) Where \( R_a = \text{H, alkyl, aryl etc.} \)

The chemistry of urea deals with reactions promoted by the nucleophilic reactivity of these compounds, the center of the reaction being isolated either at O-atom or at N-atom.

**GENERAL METHODS FOR THE PREPARATION OF UREA**

1. Hydrochloride of amine and appropriate quantity of urea dissolved in water is refluxed. The crude product contains small quantity of di-substituted compounds which is removed by crystallization (2)

\[
\text{C}_6\text{H}_5\text{NH}_3\text{Cl}^- + \text{H}_2\text{N} = \text{C} = \text{NH}_2 \rightarrow \text{H}_2\text{N} = \text{C} = \text{NH}_2 + \text{NH}_4\text{Cl}
\]

(2)
2. Hydrochloride of amine when react with sodium cyanide and sodium hypochlorite or sodium peroxide yields corresponding phenyl urea derivative (3).¹

\[
\text{R} \quad \text{NH}_2\text{HCl} \quad + \quad \text{NaCN} \quad \xrightarrow{\text{Na}_2\text{O}_2} \quad \text{R} \quad \text{NH} \quad - \quad \text{C} \quad - \quad \text{NH}_2
\]

(3)

3. Phenyl isocyanate react with ammonia gives corresponding phenyl urea (4).¹

\[
\text{R} \quad \text{NaC} = \text{O} \quad + \quad \text{NH}_3 \quad \xrightarrow{\text{H}} \quad \text{R} \quad \text{NH} \quad - \quad \text{C} \quad - \quad \text{NH}_2
\]

(4)

4. A mixture of amine in hot water and glacial acetic acid was added with stirring to a warm aqueous solution of potassium or sodium cyanate yields corresponding phenyl urea (5).¹

\[
\text{R} \quad \text{NH}_2 \quad + \quad \text{KCNO/NaCNO} \quad \xrightarrow{\text{H}} \quad \text{R} \quad \text{NH} \quad - \quad \text{C} \quad - \quad \text{NH}_2
\]

(5)

5. A reaction of phenyl urethane with ammonia at 160-180 °C yields phenyl urea derivatives. (6).¹

\[
\text{R} \quad \text{NH} \quad - \quad \text{C} \quad - \quad \text{OR'} \quad + \quad \text{NH}_3 \quad \xrightarrow{-\text{R'} \text{OH}} \quad \text{R} \quad \text{NH} \quad - \quad \text{C} \quad - \quad \text{NH}_2
\]

(6)

6. Urea derivatives have been synthesized by condensation of primary amine and isocyanate.²
In the present synthetic work, urea derivatives have been synthesized as per the method -6.

References:

Since the first synthesis of thiourea and its derivatives were made in about 1870, a vast literature on these compounds has been accumulated. In fact an extensive knowledge of the properties and principles of synthesis and reactivity of thioureas were available at a relatively early stage in the history of thiocarbonyl chemistry. The main reason for this situation is that thioureas in general are well defined, crystalline compounds of high stability and being furthermore easily accessible by relatively simple synthetic procedures.

Thioureas have found wide application as pharmaceuticals, insecticides, preservatives, rodenticides and otherwise are of commercial use in dyes, photographic film plastics, textiles etc.

The thioureas are generally represented by the structure (1)

\[
\begin{align*}
\text{N} & \text{C} & \text{N} \\
\text{R}_1 & \text{S} & \text{R}_3 \\
\text{R}_2 & \text{S} & \text{R}_4 \\
\end{align*}
\]

Where, \(R_n = \text{H, alkyl, aryl etc.}\)

Thioureas are valuable synthon in organic synthesis especially within the field of heterocyclic chemistry.

The chemistry of thioureas deals with reactions promoted by the nucleophilic reactivity of these compounds, the centre of reaction being isolated either at S-atom or at N-atom.

**GENERAL METHODS FOR THE PREPARATION OF THIOUREA**

1. **Primary amine reacts with carbon disulfide:**

   However, several other well-established methods are available for the synthesis of thioureas. One of the cheapest method of preparing symmetrical thioureas is based on the reaction of primary amines (2) with carbon disulfide."
The mechanism of this is not quiet clear, but apparently an intermediate ammonium dithiocarbamate (3) is involved in the reaction, when carried out in the presence of ammonia or another amine, afforded by-products derived from later.

\[
\begin{align*}
R{-}NH_2 & \quad + \quad CS_2 \quad \rightarrow \quad \left[ R_1{-}NH{-}C{-}S{-}R_4 \right] \\
\end{align*}
\]

Where, \( R_n \) = alkyl, aryl etc.

The reaction is influenced by catalyst such as elemental sulfur, hydrogen peroxide, hydroxide ions, iodine & pyridine and is applicable also to the synthesis of cyclic thioureas as exemplified by the preparation of (5) from (4).\(^4\)

\[
\begin{align*}
R & \quad NH_2 & \quad + \quad CS_2 & \quad \rightarrow \quad \left[ R_1{-}NH{-}C{-}N{-}R_3 \right] \\
\end{align*}
\]

Where, \( R = H, \text{CH}_3 \)

Perhaps the most important standard method of synthesizing thiourea is based on the reaction of alkyl and aryl isothiocyanates with ammonia or amines.\(^2\) By this reaction mono substituted, 1,3-disubstituted and 1,1,3-trisubstituted thiourea can be obtained.

\[
\begin{align*}
R_1{-}N=C=S & \quad + \quad HN & \quad \rightarrow \quad R_1{-}NH{-}C{-}N{-}R_3 \\
\end{align*}
\]

Where, \( R_1, R_2, R_3 = H, \text{alkyl, aryl etc.} \)
2. (A) **Action of alkali thiocyanate on amine hydrochlorides**:

It has long been known that heating ammonium thiocyanate (6) at 160°C for several hours causes it to rearrange to thiourea.

\[
\begin{align*}
\text{NH}_4\text{SCN} & \xrightarrow{160^\circ\text{C}} \text{H}_2\text{N} \equiv \text{C} \equiv \text{NH}_2 \\
\end{align*}
\]

(6)

A mixture of a primary amine (7) and ammonium thiocyanate (6) is simply heated in the presence of hydrochloric acid in an inert solvent or aqueous medium generates substituted thiourea.

\[
\begin{align*}
\text{R—NH}_2 + \text{NH}_4\text{SCN} + \text{HCl} \rightarrow \text{R—NH}_3\text{SCN} + \text{NH}_4\text{Cl} \\
\end{align*}
\]

(7) (6)

(B) **Thiohydrolysis of cyanamides and carbodiimides**:

This method is based on the ability of carbodiimides (8) and cyanamides (9) to add \( \text{H}_2\text{S} \).

\[
\begin{align*}
\text{R—N=C=NH} + \text{H}_2\text{S} \rightarrow \text{R—NH—C—NH}_2 \\
\end{align*}
\]

(8)

\[
\begin{align*}
\text{R—NH—CN} + \text{H}_2\text{S} \rightarrow \text{R—NH—C—NH}_2 \\
\end{align*}
\]

(9)

(C) **Action of isothiocyanate on ammonia or primary amine**:
(I) Substituted isothiocyanate (10) react with primary amine (7) to give unsymmetrical 1,3-disubstituted thiourea (11).^6

\[
X—N=C=S + R—NH_2 \rightarrow X—NH—C—NH—R
\]

\((10) \hspace{2cm} (7) \hspace{2cm} (11)\)

(II) The application of benzoyl / carbethoxy isothiocyanate was investigated.\(^7\) Both these react easily with amine, forming the related 1-substituted-3-benzoyl / carbethoxy thiourea, which on alkali hydrolysis afforded the expected 1-substituted thiourea, after removing the benzoyl / carbethoxy group easily. This hydrolysis is readily accomplished in the cases of these thioureas, which are derived from primary amines. Since the benzoyl isothiocyanate and acyl thioureas are easily made, the procedure affords a method of identification of amines and also for the easy preparation of mono substituted thioureas.

\[
R—C—Cl + NH_4SCN \xrightarrow{Acetone} R—C—SCN + NH_4Cl
\]

\[
R—C—N=C=S \xrightarrow{R—NH_2} R—C—NH—C—NH—R'
\]

\[
R—COOH + H_2N—C—NH—R'
\]

Where R = Benzoyl, acetyl, carbethoxy etc.
Rasmussen et al.\textsuperscript{8} have reported improved procedures for the preparation of cycloalkyl, alkaryl, alkyl and aryl thioureas by the reaction of benzoyl isothiocyanate with aniline in acetone and by benzoylation of the resultant N-aryl-N'-benzoyl thioureas with 5\% aqueous NaOH.

\[
\begin{align*}
\text{R—NH}_2 + \text{C—N=S} & \xrightarrow{\text{Acetone}} \text{R—NH—C—NH—R} \\
\text{O} & \quad \text{C—N=S} & \quad \text{5 \% NaOH} & \quad \text{H}_2\text{N—C—NH—R}
\end{align*}
\]

The broad scope of the reaction is most clearly demonstrated by the large variety of thioureas that have been synthesized on the basis of active participation of aliphatic, aromatic, open chain and cyclic amines as well as amine derivatives such as ketimines, hydroxylamine, imino ester and amidines.\textsuperscript{1,2,3}

In the present synthetic work, thiourea derivatives were generated as per the method C – I.

References:

The three classes of simple triazines are theoretically possible. These are the 1:2:3 – triazine (vicinal or vic – triazine) (1), the 1:2:4 – triazine (asymmetrical or As – triazine, sometimes called “isotriazine”) (2) and the 1:3:5 – triazine (symmetrical or s – triazine, sometimes called “cyanidine”) (3).

Compounds, which can be referred to the monocyclic system (2) and (3), are known but 1,2,3 – triazines are known only in condensed system such as 1,2,3 – benzotriazines.

The six membered heterocycle consisting of three nitrogen atoms and three carbon atoms alternately located in the ring is known as symmetrical triazine (s-triazine) ring system (4). This heterocycle is ordinarily abbreviated as s-triazine (or syn-triazine), although the designation 1,3,5 – triazine is common.

Cyanuric chloride is a weak base because of low basicity as well as the ring nitrogen atom, which is α- to chlorine atoms. The replacement of a chlorine atom in cyanuric chloride by basic group is greatly facilitated by the ring nitrogen atom of the symmetrically built s – triazine nucleus.
At 0 °C cyanuric chloride is therefore already susceptible to alcoholysis and aminolysis as well as hydrolysis.

As discovered by Banks, these substitution reactions can be catalyzed by acid and in fact, the more electrophilic triazonium ion is more reactive will be cyanuric chloride itself. An acid catalysis can also take place in aqueous medium, provided that nucleophilic reactant does not prevent protonation of the triazine ring. For this reason, the reaction of cyanuric chloride with alcohols and aromatic amines in particular can be catalyzed by acids.

Zollinger investigated the reaction of cyanuric chloride with aniline in benzene and showed that it is catalyzed by acid and base or both.

To prevent a possible acid catalysis in the substitution of a chlorine atom in cyanuric chloride by -OH, -OCH₃ or -OC₂H₅ to give hydroxy and alkoxy dis chloro - s - triazine, the reaction is best carried out in the presence of an acid binding medium preferably sodium bicarbonate.

The reaction of cyanuric chloride with ammonia or amine depends on the temperature of the reaction, may replace one, two or all of the chlorine atoms.

2,4,6 - Trisubstituted triazines can be prepared by controlling the temperature and depending on the nucleophilicity of the group. One chlorine atom is replaced at 0-5 °C, second at 25-50 °C and third at 80-100 °C.

Order of addition of substituents onto the triazine core can occur in several ways. Due to the relatively poor nucleophilicity of aniline compared to aliphatic amines, coupling of the desired aniline to cyanuric chloride was selected first followed by aliphatic amines.

**GENERAL METHODS FOR THE PREPARATION OF s-TRIAZINE**

1,3,5 – Triazine and many of its derivatives are known and a number of preparative methods are known.
1. By trimerizing compounds of the general formula XCN. This is a very general reaction, in which X may be H, Halogen, alkyl, aryl, amino, hydroxyl etc.

\[
\begin{align*}
3 \text{X-CN} & \rightarrow \text{XCN} \\
X & \begin{array}{c}
\text{N} \\
\text{X}
\end{array} \begin{array}{c}
\text{N} \\
\text{X}
\end{array}
\end{align*}
\]

2. By cyclisation of biguanidines and related compounds.

\[
\begin{align*}
\text{H}_2\text{N-}\begin{array}{c}
\text{NH} \\
\text{C-} \\
\text{NH}_2
\end{array} & + \text{RCOX} \rightarrow \text{X} \\
\text{NH} & \begin{array}{c}
\text{N} \\
\text{X}
\end{array} \begin{array}{c}
\text{N} \\
\text{X}
\end{array}
\end{align*}
\]

3. By reaction of amidines or nitriles with acid anhydride and acid chlorides.

\[
\begin{align*}
2 \text{R-C-NH}_2 & + (\text{OCR})_2 \rightarrow \text{X} \\
\text{NH} & \begin{array}{c}
\text{N} \\
\text{X}
\end{array} \begin{array}{c}
\text{N} \\
\text{X}
\end{array}
\end{align*}
\]

4. Various methods for the synthesis of s-triazine derivatives have been reviewed by Smolin & Rappeport, Modest, and Hoggarth.

5. Cyanuric chloride or 2,4,6-trichloro-s-triazine was prepared in 1828 by serullas, who obtained it through the action of chloride on anhydrous hydrocyanic acid in direct sunlight.

\[
\begin{align*}
3 \text{Cl}_2 & + 3 \text{HCN} \rightarrow \text{X} \\
\text{Cl} & \begin{array}{c}
\text{N} \\
\text{Cl}
\end{array} \begin{array}{c}
\text{N} \\
\text{Cl}
\end{array}
\end{align*}
\]
6. 2,4,6-trisubstituted-s-triazine have been prepared by acid catalyzed trimerization of alkyl imidates.\textsuperscript{13}

\[
\begin{array}{c}
\text{NH} \\
3 \text{RC} \text{–OR}'
\end{array} \rightarrow
\begin{array}{c}
\text{R} - \text{N} - \text{N} - \text{R} \\
\text{R}
\end{array} + 3 \text{R'} \text{OH}
\]

1,3,5-Triazines are stable crystalline substances. The ring can be broken by prolong heating with acid or by heating with alcohol and ammonium chloride.\textsuperscript{14}

References:
The structure of coumarin and its derivatives are shown below. Coumarin and 4-hydroxy coumarin do not possess anticoagulant activity.

![Coumarin and 4-Hydroxy Coumarin](image)

Link, who pioneered the isolation and characterization of bishydroxycoumarin (dicoumarol) from sweet clover and concluded that the minimal requirements for anticoagulant activity are 4-hydroxy group, a 3-substituent, and a bis molecule.

![Warfarin and 3-Substituted 4-Hydroxycoumarin](image)

Coumarin is water insoluble; however 4-hydroxy substitution confers weakly acidic properties to the molecule that makes it water soluble under slightly alkaline conditions.
GENERAL METHODS FOR THE PREPARATION OF 4-HYDROXY COUMARIN

1. Simple process for the synthesis of 4-hydroxycoumarins\textsuperscript{1} in which phenol is treated with an equimolecular proportion of a malonic acid in the presence of 2-3 moles anhydrous zinc chloride and POCI\textsubscript{3} mixture as the condensing agent at temperature preferably between 60-70 °C. The success of this reaction is dependent upon the specific condensing action of the mixture of anhydrous zinc chloride and POCI\textsubscript{3}\textsuperscript{2} which are individually almost ineffective.

\[
\begin{array}{c}
\text{R} \quad \text{OH} \quad + \quad \text{COOH} \quad \text{COOH} \\
\text{Anhyd. ZnCl}_2/\text{POCl}_3 \quad \text{60 - 70 °C} \\
\end{array}
\]

2. 3-(2-Hydroxyphenyl)-3-oxopropionic acid is converted into 4-hydroxycoumarin in the presence of acid catalyst\textsuperscript{3}.

\[
\begin{array}{c}
\text{Cyclization of acetyl methyl salicylates in the presence of an alkali metal.}^4
\end{array}
\]
4. Condensation of o-hydroxy acetophenones with diethyl carbonate in the presence of an alkali metal.\textsuperscript{5}

\[
\text{HCO}_{\text{OEt}} + \text{OEt} \xrightarrow{\text{Alkali metal}} \text{OH}
\]

5. 4,7-Dihydroxycoumarin has been synthesized by condensation of resorcinol with cyanoacetic acid in the presence of ZnCl\textsubscript{2}/HCl to afford 4-amino-7-hydroxy coumarin, followed by hydrolysis with 50\% H\textsubscript{2}SO\textsubscript{4}.\textsuperscript{6}

\[
\text{OH} \xrightarrow{\text{CNCH}_2\text{COOH, ZnCl}_2/\text{HCl}} \text{NH}_2 \xrightarrow{\text{H}_2\text{SO}_4/\text{H}_2\text{O}} \text{OH}
\]

6. The cyclization reaction of benzoate into 4-hydroxycoumarin is described in the literature via 2-aminochromen-4-ones and subsequent acidic hydrolysis.\textsuperscript{7}
In the present synthesis work, 4-hydroxy coumarin has been synthesized as per the method 1.

References: