CHAPTER I

OXIDATION OF THIOUREAS: A REVIEW

The work presented in this thesis deals mainly with the oxidation of binary mixtures of thioureas. Hence this review deals mainly with the literature available on the oxidation of thioureas. The discussion in the review is based on the nature of the products obtained from the oxidation of thioureas.

Depending on the substitution pattern, the oxidising agent, the polarity of the medium and the conditions used, thioureas on oxidation are converted to acyclic and cyclic products. Acyclic products include ureas, cyanamides, formamidine sulphonic acids, bis(formamidino) disulphides, bis(formamidino) sulphides, amidinothioureas and S-dioxides; whereas the important cyclic products obtained are 1,2,4-thiadiazoles and benzothiazoles.

Acyclic products from the oxidation of thioureas are discussed first followed by cyclic products. The oxidative cyclisation of thioamido and amidinothiono systems such as thioamides, amidinothioureas, dithiobiurets, dithiobiureas and amidinothiosemicarbazides has been dealt
with subsequently since these can be considered as formal analogs of thioureas and hence are of current interest.

ON THE NATURE OF THIOAMIDO GROUP

The concept of a thione-thiol tautomerism in thioamide derivatives is one of long-standing. During oxidation, thiourea behaves as a compound containing a thiol group.\(^1\)\(^-\)\(^5\) The thiol form of these compounds has often been invoked to explain S-alkylation and S-acylation of these compounds. Infrared studies,\(^6\)\(^-\)\(^9\) however, indicate the almost exclusive predominance of the thione form in thiourea, thiosemi-carbazones, thiohydrazides and thiourethanes. It has been pointed out that the chemical behaviour of thioureas suggestive of a thiol type structure \(\text{HN}=\text{C}-\text{NH}_2\) can be accounted for on the basis of a 20-30% contribution of canonical forms (1) and (2) to the resonance in thiourea.\(^10\)

\[
\begin{align*}
\text{H}_2\text{N}-\overset{\text{S}}{\text{C}}-\text{NH}_2 & \quad \leftrightarrow \quad \text{H}_2\overset{\text{N}}{\text{N}}=\overset{\text{C}}{\text{S}}-\text{NH}_2 \\
& \leftrightarrow \quad \text{NH}_2-\overset{\text{S}}{\text{C}}=\overset{+}{\text{NH}}_2
\end{align*}
\]

(1) \hspace{1cm} (2)

Infrared\(^11\) and Raman\(^12\) studies, determination of dipole moment\(^10\) and x-ray crystallographic studies\(^13\) support the above view.

Thiourea and substituted thioureas on oxidation in acidic media yield disulphide salts.\(^14\)\(^-\)\(^23\) This suggests that in the presence of acids, thiourea exists as the protonated
form (4) of the zwitterionic structure (3). The formation

\[ \begin{array}{c}
RNH-\overset{\text{S}}{\overset{\text{H}}{\overset{\text{NHR}}{\text{H}}}} \quad \overset{\text{H}^+}{\longrightarrow} \quad RNH-\overset{\text{SH}}{\overset{\text{NHR}}{\text{H}}} \\
(3) \quad \quad \quad \quad (4)
\end{array} \]

of stable salts of thiourea with acids also supports the above view.

I. ACYCLIC PRODUCTS FROM THE OXIDATION OF THIOUREAS

(A) Exhaustive oxidation of thioureas

The exhaustive oxidation of thioureas for estimation purposes leads to urea and sulphate or to sulphate, carbonate and nitrogen depending upon the conditions and the reagents used. Oxidation of thiourea with alkaline hydrogen peroxide\(^{24-26}\) yields cyanamide, urea and sulphate. Other

\[ \text{H}_2\text{N}-\overset{\text{S}}{\overset{\text{H}}{\overset{\text{NHR}}{\text{H}}}} \overset{(0)}{\longrightarrow} \quad \text{RNHCN} + \text{H}_2\text{N}-\overset{\text{O}}{\overset{\text{H}}{\overset{\text{NH}_2}{\text{H}}}} + \text{SO}_4^- + \text{H}_2\text{O} \]

\( R = \text{H or alkyl} \)

oxidising agents which are used for the exhaustive oxidation are bromine in acid medium,\(^{29}\) bromate-bromide mixture in acid medium\(^{30}\) and iodine in presence of sodium bicarbonate.\(^{29}\) Tiwari and Pande\(^{31}\) titrated thiourea and its allyl and phenyl derivatives with N-bromosuccinimide; the reaction products are urea and elemental sulphur. Recently a rapid
and precise procedure for the oxidative estimation of thiourea and its alkyl and aryl derivatives with iodine trichloride in presence of mercuric chloride has been reported; the end products are the corresponding urea and sulphate.

(B) S-dioxides and sulphonic acid

Thiourea dioxide (5) has been obtained by the oxidation of thiourea by hydrogen peroxide at 0°C in presence of secondary alcohols or aliphatic ketones as promoters. Similar preparation of dioxide is known from 1-methyl, 1-ethyl, 1-butyl, 1-phenyl and 1-benzyl-thioureas also. Oxidation of thiourea with peracetic acid has been reported to yield formamidine sulphonylic acid (6).

\[
\begin{align*}
\text{RNH-S-NHR} & \quad \longrightarrow \quad \text{RNH-C=NR} \\
\text{RNH-S-NHR} & \quad \underset{\text{CH}_3\text{COOH}}{\underset{2}{\longrightarrow}} \quad \text{H}_2\text{N-C=SO}_3\text{H} \\
\end{align*}
\]

(C) Disulphides

Oxidising agents such as bromine, iodine, hydrogen peroxide, iodine monochloride, ceric salts and chloramine-T easily convert thioureas to bis(formamidino) disulphide salts (8). During oxidation with halogen, the intermediate
formation of sulphenic acid derivative (7) has been suggested and the mechanism\textsuperscript{37} which has been proposed is depicted below:

\[
\begin{align*}
\text{H}_2\text{N}-\text{C}-\text{NH}_2 + \text{X}_2 & \longrightarrow \text{X}^- \cdot \text{S} - \text{C} \cdot \text{S} - \text{C} \cdot \text{NH}_2 + 2\text{X}^- \\
\text{NH}_2\text{CSNH}_2 & \xrightarrow{\text{H}_2\text{N}} \text{H}_2\text{N} - \text{C} - \text{S} - \text{C} - \text{NH}_2 + 2\text{X}^-
\end{align*}
\]

The intermediate sulphenyl halide (7) reacts with thiourea, to form the disulphide salt (8). These disulphide salts are relatively stable and thus represent the final oxidation products of substituted thioureas in non-polar solvents. In the case of disulphides obtained from alkyl and aryl thioureas also, the intermediate formation of sulphenyl halide has been suggested.\textsuperscript{38}

(D) Amidinothioureas

The oxidation of 1-aryltioureas using oxidant and thiourea in the ratio 1:2 has been reported to give 1-aryl-(1-arylamidino)thiourea salts (10).\textsuperscript{39} The reaction pathway suggested involves the initial formation of the bis(1-aryl- amidino) disulphide salt (9). This then decomposes into thiourea, cyanamide and sulphur. The thiourea and cyanamide
in situ recombine in presence of acid to give the amidinothiourea (10). The formation of amidinothiourea from 1-arylthiourea and aryl cyanamide in presence of acid has been observed earlier independently.\textsuperscript{40}

\[
\begin{align*}
\text{ArNH-C-NH}_2 + 2\text{HX} &\rightarrow \text{ArNH-C-S-S-C-NHAr}.2\text{HX} \\
\text{ArNH} &\rightarrow \text{ArNH-CN} + \text{ArNH-C-NH}_2.\text{HX} \\
\end{align*}
\]

Srivastava\textsuperscript{41} prepared a few amidinothioureas from 1-alkyl-3-aryl, 1-alkyl-1-aryl and 1-aryl-3,3-dialkylthioureas by their oxidation with bromine in ethanol. It was suggested that bis(formamidino) disulphide and bis(formamidino) sulphide salts were involved as the intermediates.

II. CYCLIC PRODUCTS

Depending on the nature of the substituent, the oxidant and the reaction conditions, substituted thioureas yield mainly 2-aminobenzothiazoles, benzothiazolylguanidines and thia diazoles as the cyclic products.

2-Aminobenzothiazole is formed by the oxidative cyclisation of one molecule of arylthiourea, whereas 1,2,4-thiadiazoles and benzothiazolylguanidines are built up from two molecules of thioureas used.
Since the oxidations of differently substituted thioureas yield different cyclic products, the following review on the oxidation of thioureas is classified on the basis of the nature of reaction medium and further subdivided according to the substitution pattern.

(A) Oxidation of thioureas in non-polar media

It is long known that on oxidation, thiourea and alkyl substituted thioureas yield bis(formamidino) disulphide salts\(^4,16,17,18,19,21,42\) as the final product in non-polar solvents. Aromatic thioureas yield the bis(formamidino) disulphides\(^43,44\) only when the oxidation is carried out carefully with equimolar quantity of the oxidant. With excess oxidant in non-polar medium, aromatic thioureas are converted to 2-aminobenzothiazole derivatives\(^45-53\). The various oxidising agents which bring about this conversion are halogens, sulphur monochloride, sulphuryl chloride, thionyl chloride etc.

The bis(N-arylamidino) disulphide salts (11) have been shown as intermediates in the oxidation of 1-aryl-thioureas to 2-aminobenzothiazoles by Barnikow and co-workers\(^38,54,55\). The disulphide salt reacts with halogen\(^38\) and give sulphenyl halide (12). Sulphenyl halide then cyclises to the aminobenzothiazole (13) by an intramolecular
electrophilic attack.

\[
\text{ArNH-C-NH}_2 + \text{Br}_2 \rightarrow \text{ArNH-C-S-S-C-NHAr}.\text{2HBr}
\]

(11)

Different 1-arylthioureas, additionally substituted as in 1,3-diaryl-,\(^{56-59}\) 1-alkyl-3-aryl-,\(^{60-63}\) 1,1-alkylaryl-,\(^{47,64-67}\) 1,3-dialkyl-3-arylthioureas\(^{68,69}\) have been similarly cyclised to the related 2-aminobenzothiazole derivatives.

The above reaction has been extended to several heterylthiourea such as (14) and many heteropolycyclics were thus prepared.\(^{70}\) A few examples are given below: 1,2,4-thiadiazolo[3,2-b]thiazole\(^{71}\) (15), 1,2,4-thiadizolo[2,3-a]pyridine\(^{71,72}\) (16) and 1,2,4-thiadiazolo[2,3-a]pyridine (17).\(^{71}\)
(B) Oxidation of thioureas in polar media

1. Oxidation of parent thiourea

Oxidation of thiourea in polar medium using various oxidising agents has not so far been reported to yield any heterocycles. However, the expected 3,5-diamino-1,2,4-thiadiazole (19) has been obtained by the oxidation of amidinothiourea (18). Amidinothiourea in turn has been obtained from bis(formamidino) sulphide hydrochloride by isomerisation and by the hydrosulphurisation of dicyandiamide.

\[
\begin{align*}
H_2N-C-NH_2 + NH_2CN + HCl &\rightarrow H_2N-C-S-C-NH_2\cdot 2HCl \\
\downarrow &
H_2S
\rightarrow H_2N-C-NH-C-NH_2\cdot HCl &\rightarrow \text{18 (19)}
\end{align*}
\]

2. Oxidation of alkylthioureas

The oxidation of alkylthioureas to bis(substituted-amidino) disulphide salts is well known. Srivastava studied in detail the oxidation of alkylthioureas (20, \( R^1 = \text{alkyl}, \ R^2 = \text{H or alkyl} \)). He prepared the N-alkyl derivative of the disulphide salts (21, \( R^1 = \text{alkyl}, \ R^2 = \text{H} \)). The disulphide salts were
found to extrude sulphur when warmed in ethanol and yielded bis(N-alkylamidino) sulphide salts (22; R^1 = alkyl, R^2 = H). The sulphide salts on refluxing in ethanol for 30-40 min. isomerised to the related amidinothiourea (23; R^1 = alkyl; R^2 = H), a reaction analogous to the isomerisation of S-acylthioureas to N-acylthioureas. Subsequent oxidation of these amidinothioureas afforded the related 1,2,4-thiadiazolidines (24; R^1 = alkyl; R^2 \neq H). Of these products, excepting the benzyl derivative all were isolated in the form of their picrates.

\[
\begin{align*}
2R^1NH-C-NHR^2 & \xrightarrow{\text{Br}_2\text{or SOCl}_2} RNH-C-S-S-C-NHR^1 .2HX \\
(20) & \quad (21)
\end{align*}
\]

\[
\begin{align*}
\xrightarrow{S} R^1NH-C-S-C-NHR^2 .2HX & \quad \xrightarrow{RX} \\
(22)
\end{align*}
\]

\[
\begin{align*}
R^1NH-C-NR^1-C-NHR^2 .HX & \xrightarrow{R^2N=C-S-NR^2} R^1N-C=NR^1 \\
(23) & \quad (24)
\end{align*}
\]

The structure of the benzyl derivative was assigned as 3-benzylimino-4-benzyl-5-imino-1,2,4-thiadiazolidine on the basis of following observations. The thiadiazole (24; R^1 = benzyl, R^2 = H) on reduction with hydrogen sulphide in acid medium yielded the amidinothiourea (23; R^1 = benzyl, R^2 = H).
On the other hand, reduction of the thiadiazole with ammoniacal hydrogen sulphide yielded N,N'-dibenzylguanidine and thiocyanic acid. These products were also formed when amidinothiourea was treated (23; \( R^1 = \text{benzyl}, R^2 = \text{H} \)) with ammoniacal hydrogen sulphide. This thiadiazole was also found to exhibit properties very similar to those observed for Hector's bases\(^{79}\) derived from 1-aryltioureas.

The bis(N,N'-dialkylamidino) disulphide salts (21; \( R^1 = \text{alkyl}, R^2 = \text{alkyl} \)) which were prepared by the oxidation of 1,3-dialkylthiourea with bromine or thdonyl chloride in chloroform, when warmed in ethanol extraded sulphur to form bis(N,N'-dialkylamidino) sulphide salts (22; \( R^1 = R^2 = \text{alkyl} \)). This also underwent isomerisation to the amidinothiourea (23; \( R^1 = R^2 = \text{alkyl} \)) which on oxidation afforded the thiadiazole (24; \( R^1 = R^2 = \text{ethyl, n-propyl, benzyl} \)).

Recently Kinoshita\(^80\) and co-workers who examined the oxidation of 1,3-dialkylthiourea with benzoyl peroxide in dichloromethane, obtained 2,4-dialkyl-3,5-bis(dialkylimino) 1,2,4-thiadiazolidines (25). They gave X-ray crystallographic and spectral data as evidence for the structure. These authors have put forth a radical mechanism for the oxidation reaction. The mechanism given is depicted below.
3. Oxidation of 1-arylthiourea

The first report on the formation of a thiadiazole by the oxidation of a thiourea derivative was made in 1889 by Hector.\textsuperscript{81-83} He obtained a base \( \text{C}_{14}\text{H}_{12}\text{N}_{4}\text{S} \) by the oxidation of 1-phenylthiourea and assigned a 1,3,4-thiadiazole structure for the product (26). He revised\textsuperscript{83} the structure assigned to this base to 3,5-diimino-2,4-diaryl-1,2,4-thiadiazolidine (27) on the basis of certain subsequent chemical evidences. These thiadiazoles are known, after their discoverer as "Hector's bases".

\[
\text{ArNH-C-NH}_2 \xrightarrow{[\text{O}]} \text{C}_{14}\text{H}_{12}\text{N}_{4}\text{S} + \text{S} + 2\text{H}_2\text{O}
\]

Dost\textsuperscript{47} observed that fuming hydrochloric acid converted Hector's base (phenyl analogue) into a non-basic keto compound, while alcoholic ammonia converted it into an isomeric base. This prompted Dost to suggest a 2-aryl-5-arylimino-3-imino-1,2,4-thiadiazolidine structure (28; \( \text{Ar} = \text{Ph} \)) for the compound. Lal and Krall,\textsuperscript{84} who made several...
unsuccessful attempts towards the synthesis of Hector's bases, favoured a 2-aryl-3-aryl imino-5-imino-1,2,4-thiadiazolidine structure for them (29; Ar = Ph). Kurzer, who synthesized a few 3,5-diarylamino-1,2,4-thiadiazoles showed that the isomeric base obtained by Dost from the oxidation product of 1-phenylthiourea was in fact 3,5-diphenylamino-1,2,4-thiadiazole (30; Ar = Ph).

\[
\begin{align*}
(26) & & (27) & & (28) \\
\text{HN} & \text{-NH} & \text{ArN-C=NH} & \text{HN-C=NH} & \text{HN-C=NH} \\
\text{PhN=C} & \text{-S} & \text{C=NPh} & \text{HN=C} - \text{S} & \text{NAr} \\
(29) & & (30) \\
\text{HN-C=NAr} & & \text{N-C-NHAr} \\
\end{align*}
\]

The reduction of Hector's base with ammoniacal hydrogen sulphide to 1,3-diphenylguanidine and thiocyanic acid was considered to support Hector's formulation (27), ruling out structure (28) put forward by Dost. More decisive evidence was obtained by the interconvertibility of 1-aryl-1-arylamidinothiourea (31) and Hector's base (27) by oxidation-reduction. This observation narrowed down the choice of the structure between the 4-aryl-3-aryl imino-5-imino-1,2,4-thiadiazolidine structure (32) and the Hector's structure (27).
The isomerisation of Hector's bases under basic conditions to 3,5-diarylamino-1,2,4-thiadiazole (30), proceeds probably by analogy to the isomerisation of 5-imino-4-methyl-1,2,4-thiadiazoline (33) to 5-methylamino-1,2,4-thiadiazole\(^89,90\) (34); by a ring opening at C3-N4 followed by exchange of =NH and -NPh groups by rotation about the $S-C_5$ bond. It is argued that the isomerisation can be represented more simply in terms of structure (32), than of (27) because the former requires the displacement of one aryl group while the latter requires two such changes. This isomerisation does not involve any fragmentation and that it is intramolecular has been shown by carrying out the isomerisation of a mixture of two differently substituted Hector's bases in refluxing aniline (C.P. Joshua; unpublished result). Only the respective 3,5-diarylamino-1,2,4-thia-
diazoles were formed. Hence, the structure of Hector's base has been reassigned as 4-aryl-3-arylimino-5-imino-1,2,4-thiadiazolidine (3A). The mass spectral study of the Hector's bases has shown that the spectral pattern is satisfactorily accounted by a 4-aryl-3-arylamino-5-imino-4,5-dihydro-1,2,4-thiadiazole structure. A recent X-ray crystallographic study on Hector's base also has now confirmed this structure.

Although a large amount of work has been carried out to elucidate the structure of Hector's bases, until the early nineteen sixties very little progress has been done to unravel the mechanism of the reaction. It was suggested that the initial product of oxidation in these cases also is the bis(arylamidino) disulphide salt. However earlier attempts to isolate these were unsuccessful. It was Kurzer and Sanderson who isolated first the bis(N-arylamidino) disulphide salt (35). They prepared these disulphides by the oxidation of arylthioureas with bromine in chloroform using thiourea and bromine in 2:1 molar ratio. In order to prevent the cyclisation of the thioureas to 2-aminobenzothiazoles, they chose disubstituted arylthioureas.

Later Kurzer and Sanderson were able to isolate the bis(N-arylamidino) disulphide salts from protic media also. These salts, on treatment with methanol, were found
to extrude sulphur and yield 1-aryl-1-arylamidinothiourea salts (36).\(^{88}\) Oxidative cyclisation\(^{83}\) of these amidinothioureas was shown to yield the related Hector's bases. These amidinothioureas (36) were also obtained by the interaction of arylcyanamide and arylthiourea in acetone in presence of acid\(^j^{40}\) by the partial oxidation of 1-arylthioureas in ethanol\(^{88}\) and by the interaction of 2-chlorobenzothiazole (37) with 1-arylthioureas.\(^{94}\)

\[
\begin{align*}
\text{ArNH-} & \text{S-S-} \equiv \text{NHAr.2HX} \rightarrow S \\
(35) \\
\text{ArNH-} & \equiv \text{NAr-} \equiv \text{NH}_2 \text{.HX} \xrightarrow{\text{HCl}} \text{ArNH-} \equiv \text{NH}_2 + \text{ArNHCN} \\
(36) \\
\text{ArN} & \equiv \text{C}=\text{NAr} \\
(32) \\
\text{ArN} & \equiv \text{C}=\text{NAr} + \text{N}_2 \text{C-Cl} \\
(37)
\end{align*}
\]

Based on these results, Kurzer\(^{88}\) suggested the following reaction sequence for the oxidation of 1-arylthiourea. This pathway is identical to the one suggested by Pandeya\(^{74,95}\) and Srivastava\(^{41,75,96}\) except for the absence of a bis(formamidino) sulphide intermediate (38). The formation of this sulphide salt as an intermediate has been suggested on the basis of the formation and isolation of
bis(formamidino) sulphides from other similar oxidations. These salts rapidly undergo isomerisation to the amidino-thiourea in protic media.

$$2\text{ArNH-S-NH}_2 \rightarrow \text{ArNH-S-S-NHAr.}_2\text{HX}$$  \hspace{1cm} (35)

$$\text{ArNH-S-NH}_2+\text{ArNHCN} \xrightarrow{\text{HX}} \text{ArNH-S-S-NHAr.}_2\text{HX} \rightarrow$$  \hspace{1cm} (38)

$$\text{H}_2\text{N-S-N-NHAr.HX} \rightarrow \text{ArN-}C=\text{NaNar}$$  \hspace{1cm} (32)

The oxidative cyclisation involving two molecules of aromatic thioureas to the 1,2,4-thiadiazole derivatives can be performed by means of a variety of oxidising agents. These are hydrogen peroxide, nitrous acid, ferric chloride, cupric salts, iodine, bromine, thionyl chloride, and oxygen.

4. Oxidation of 1-alkyl-1-aryltioureas and 1,1-diarylthioureas

The oxidation of 1-alkyl-1-aryltioureas (39; \( R^1 = \text{alkyl}, R^2 = \text{aryl} \)) in polar media yields 3,5-bis(alkyl arylamino)-1,2,4-thiadiazole (40; \( R^1 = \text{alkyl}, R^2 = \text{aryl} \))
Bis(formamidino) disulphide has been suggested as the first intermediate during the oxidation of these thioureas also. The bis(N-alkyl-N-arylamidino) disulphide salts (41; \( R^1 = \text{alkyl}, R^2 = \text{aryl} \)) were formed\(^{39,41} \) when 1,1-alkyaryl-thioureas were oxidised with thionyl chloride or bromine in benzene or chloroform. These disulphide salts when trituated with ethanol extruded sulphur and yielded the amidinothiourea\(^{41} \) (43; \( R^1 = \text{alkyl}, R^2 = \text{aryl} \)). During this change, the intermediate formation of bis(formamidino) sulphide salts (42) has been suggested.\(^{38,41} \) These amidinothioureas (43) then underwent oxidative cyclisation to yield 3,5-bis(alkylarylamino)-1,2,4-thiadiazoles (40).\(^{108} \)

\[
\begin{align*}
R^1R^2N-C-NH_2 & \rightarrow R^1R^2N-C-S-S-NR^1R^2.2HX \rightarrow S \\
(39) & \quad (40)
\end{align*}
\]

\[
\begin{align*}
R^1R^2N-C-S-C-NR^1R^2.2HX & \rightarrow R^1R^2N-C-NH-C-NR^1R^2.HX \\
(42) & \quad (43)
\end{align*}
\]

The amidinothiourea (43; \( R^1 = \text{Me}, R^2 = \text{Ph} \)) has been synthesised by the condensation of 1,1-methylphenylcyanamide and 1,1-methylphenylthiourea in presence of acid. This
amidinothiourea on oxidation was found to yield the thiadiazole\(^{108}\) \((40; R^1 = \text{Me}, R^2 = \text{Ph})\). A comparison of its u.v. and i.r. spectra with those of 3,5-diamilino derivative\(^{109,110}\) supports the 3,5-bis(alkylarylamino)-1,2,4-thiadiazole structure. Also, it has been found that the thiadiazole obtained thus is identical with the product obtained by the interaction of 3-imino-5-methylphenylamino-2,3-dihydro-1,2,4-dithiazole with N-methylaniline.\(^{107}\) In this reaction, the initial formation of 1,5-di(methylphenyl)amidinothiourea and its in situ oxidation by sulphur formed during the reaction to 3,5-bis(methylphenylamino)-1,2,4-thiadiazole has been suggested.

3,5-Bis(diarylamino)-1,2,4-thiadiazoles \((40; R^1 = R^2 = \text{aryl})\) have also been prepared by the oxidation of 1,1-diarylthioureas \((39; R^1 = R^2 = \text{aryl})\). Presumably these compounds also are formed by the above mechanism and the structures have been assigned on similar grounds.\(^{100,109,110}\)

5. Oxidation of 1,3-diarylthioureas and 1-alkyl-3-arylthioureas

The oxidation product of 1,3-diphenylthiourea in polar medium, called Hugershoff's base after its discoverer, has been earlier assigned a thiadiazole structure \((44; \text{Ar} = \text{Ph})\).\(^{48,55}\)
Later, Suresh\textsuperscript{109-111} suggested \(N\)-(benzothiazol-2-yl)\(\cdot\)\(N\),\(N'\),\(N''\)-triphenyl guanidine structure (45) for this base and this has been confirmed later by its synthesis\textsuperscript{112} from 2-anilino-benzothiazole (46) and diphenylcarbodiimide (47).

\[
\begin{align*}
\text{PhN\textsuperscript{--}} & \quad \text{N\textsuperscript{--}} \\
\text{C-NHPh} + \text{PhN=C=NPh} & \quad \rightarrow \\
\text{N\textsuperscript{--}} & \quad \text{C-N\textsuperscript{--}} \\
\text{NPh} & \quad \text{NPh}
\end{align*}
\]

(46) \hspace{1cm} (47) \hspace{1cm} (45)

Srivastava\textsuperscript{41} prepared bis\((N,\text{N'}\text{-diarylaminodio})\) disulphide salts (47) by the treatment of 1,3-diarylthiourea with equimolar quantity of thionyl chloride in benzene or chloroform. These disulphide salts on treatment with ethanol have been found to yield the related sulphide salts (48) by the extrusion of sulphur. These sulphides have been alternatively prepared by the condensation of diarylcarbodiimide with diarylthiourea; by the oxidation of diarylthiourea with bromine or hydrogen peroxide in aqueous ethanol and also by the interaction of 2-chlorobenzothiazole with diarylthiourea\textsuperscript{94}.

Srivastava and Saleem\textsuperscript{113} later isolated the salt of 1,3-diphenyl-3-(\(N,\text{N'}\)-diphenylamidino)thiourea (49) by the rearrangement of the bis\(-(\text{N,\text{N'}-diphenylamidino})\) sulphide
salt (48). Further oxidation of this amidinothiourea using bromine yielded the benzothiazolyl guanidine (45).

\[
\text{ArNH}_2\text{-N}-\text{Ar} \xrightarrow{\text{bromine}} \text{ArNH}_2\text{-S} \text{-S} \text{-N}-\text{Ar} \cdot 2\text{HX}
\]

(47)

\[
\text{ArNH}_2\text{-C} \text{-N} \text{-Ar} \xrightarrow{\text{Ox}} \text{ArN} \equiv \text{C} \equiv \text{N} \text{-Ar}
\]

(45)

On investigating the oxidation of 1-methyl-3-phenylthiourea with alcoholic bromine, Srivastava observed that the final product formed was \(\text{N}-(\text{benzothiazol-2-yl})-\text{N},\text{N}'-\text{dimethyl-N''-phenylguanidine} \) (50). The bis(\(\text{N}-\text{methyl-N'}-\text{phenylamidino}\)) disulphide salt (51), obtained by the oxidation of 1-methyl-3-phenylthiourea in chloroform with thionyl chloride, when treated with aqueous ethanol yields the related sulphide (52) by the extrusion of sulphur. This sulphide, as in the other cases, was found to undergo isomerisation to 1-methyl-3-(\(\text{N}-\text{methyl-N'}-\text{phenylamidino}\))-3-phenylthiourea (53). The amidinothiourea has also been prepared by the interaction of methylphenylcarbodiimide with 1-methyl-3-phenylthiourea and by the interaction of
2-chlorobenzothiazole with 1-methyl-3-phenylthiourea. The amidinothiourea on careful oxidation was reported to yield 3-(N-methyl-N'-phenylamidino)-2-methylimino-2,3-dihydrobenzothiazole (54) which then rearranged to N-(benzothiazol-2-yl)-N,N'-dimethyl-N''-phenylguanidine (50).

![Chemical structures and reactions]

MeNH-C-NHPh + Br₂ → MeNH-C-NHPh

MeNH-C-S-S-C-NHMe.2HX → MeNH-C=NPh

MeNH-C-S-C-NHMe.2HX → MeNH-C=NPh

MeNH-C=NPh + MeNH-C-NHPh

PhN-C=NPh

PhN-C=NMe

(55)  (56)
Srivastava assigned structure (54) for the oxidation product of amidinothiourea (53) in preference to the thiadiazolidine structures (55) and (56) because the oxidation product underwent easy reduction to $N,N'$-diphenyl-$N''$-methylguanidine and easily isomerised to $N$-(benzothiazol-2-yl)-$N,N'$-dimethyl-$N''$-phenylguanidine (50).

Recently the oxidation of 1-alkyl-3-arylthioureas with nitrous acid as the oxidant has been reported by Christophersen$^{115}$ et al. They have shown with the aid of X-ray crystallographic studies that the products thus obtained are 2,4-dialkyl-3,5-bis(arylimino)-1,2,4-thiadiazolidines (57).

\[
\begin{align*}
2RNH-C-NHAr & \rightarrow \quad \text{RN} \begin{array}{c} \text{S} \\ \text{ArN=C-NR} \end{array} \\
\text{(57)}
\end{align*}
\]

Kinoshita$^{80}$ and co-workers who examined the oxidation of 1-alkyl-3-arylthioureas and 1,3-diphenylthiourea with benzoyl peroxide in dichloromethane also obtained 2,4-dialkyl-3,5-bis(arylimino)-1,2,4-thiadiazolidine (57) and 2,4-diphenyl-3,5-bis(phenylimino)-1,2,4-thiadiazolidine (57; $R = Ar = Ph$).

In yet another study of the oxidation of 1-alkyl-3-arylthioureas in polar media using hydrogen peroxide$^{116}$ it has been found that in fact both the thia(diazole (57) and
benzothiazolylguanidines such as (50) are formed simultaneously. The benzothiazolylguanidines have however been shown to be formed from the thiadiazoles (57) by the acid induced isomerisation. Another interesting finding in this connection was that the amidinothiourea (58) obtained by the reduction of the thiadiazole (57) is different from the one (59) obtained by the condensation of carbodiimide and thiourea or by the half-way oxidation of 1-methyl-3-phenylthiourea. The authors envisaged an isomeric change of a labile thiadiazolidine (60) to the more stable thiadiazolidine (57). The scheme is depicted below:

\[
\begin{align*}
\text{ArNH=CN}_R & \text{NR} + \text{ArNH}-\text{C}\_S\_\text{NHar} \text{NR} \rightarrow \text{ArNH}\_\text{C}\_S\_\text{NHar} \text{NR} \_2\text{HX} \stackrel{\text{half-way oxidation}}{\longrightarrow} \text{ArNH=CN}_R \text{NHar} \\
\rightarrow \text{RNH}\_\text{C}\_\text{NAr} \text{NHar} \text{HX} & \rightarrow \text{RN=CN}_R \text{NAr} \\
\text{rn=CN}_R \text{NAr} & \rightarrow \text{ArNH}\_\text{C}\_\text{NHar} \text{HX} \\
\end{align*}
\]

6. Oxidation of mixtures of thioureas

Recently by the oxidation of binary mixtures of thioureas, several 3-amino (or substituted amino)-4-aryl-
5-aryl(alkyl)imino-4,5-dihydro-1,2,4-thiadiazoles have been prepared. One molecule each of the component thioureas in the binary mixture take part in the reaction. The oxidation of a mixture of 1,3-diarylthiourea and thiourea in acidic ethanol with hydrogen peroxide yields 3-amino-4-aryl-5-arylmino-4,5-dihydro-1,2,4-thiadiazoles (61). Substituting thiourea with 1-alkylthiourea in the binary mixture yields 3-alkylamino-4-aryl-5-arylmino-4,5-dihydro-1,2,4-thiadiazoles (62) and with 1-aryltiourea yields 4-aryl-3-arylamino-5-arylmino-4,5-dihydro-1,2,4-thiadiazole (63). The use of 1-alkyl-3-aryltiourea and thiourea mixture gives 5-alkylimino-3-amino-4-aryl-4,5-dihydro-1,2,4-thiadiazoles (64; R = alkyl).

\[
\text{ArNH-C-NHar} + \text{H}_2\text{N-C-NH}_2 \rightarrow \text{ArN=C-NH}_2
\]

(61)

\[
\text{ArNH-C-NHar} + \text{RNH-C-NH}_2 \rightarrow \text{ArN=C-NHR}
\]

(62)

\[
\text{ArNH-C-NHar} + \text{ArNH-C-NH}_2 \rightarrow \text{ArN=C-NHar}
\]

(63)
In these oxidations also, the intervention of bis(formamidino) disulphide salt (65), bis(formamidino) sulphide salt (66) and amidinothiourea salt (67) has been separately established. The reaction of bis(formamidino) disulphide salt obtained from one component of the mixture with the other thiourea in ethanol also yields the intermediate amidinothiourea salt. During the oxidation the initially formed disulphide salt decomposes to a molecule each of thiourea, cyanamide or carbodiimide and sulphur. The thiourea and cyanamide or carbodiimide and thiourea recombines in the presence of acid to form a 'mixed' sulphide which undergoes isomerisation to the related amidinothiourea (67). The amidinothiourea is also obtained from the corresponding carbodiimide or cyanamide, prepared from either one constituent of the binary mixture when treated with the other thiourea in presence of acid. This is indicative of the intermediacy of such sulphides in the oxidation reaction as well.

\[
\text{ArNH-C-NR}^1 + \text{NH}_2\text{-C-NHR}^2 \rightarrow \text{ArNH-C-S-S-C-NHR}^2 \cdot 2\text{HX and/or}
\]

(65)
The reduction of 5-alkyl(or aryl)imino-3-amino-4-aryl-1,2,4-thiadiazoles with hydrogen sulphide in acid has been found to yield the amidinothiourea (67). This amidinothiourea has also been obtained by the partial oxidation of the mixtures of thiourea. The amidinothiourea so formed, decomposes on warming with sodium bicarbonate solution giving an isothiocyanate and a guanidine. The identification of the isothiocyanate has been made use of in the assignment of the structure for the amidinothiourea. The structural assignments have been confirmed by a study of the mass spectra of these thiadiazoles. 

\[ \text{ArNH-C-S-C-NHAr}.2\text{HX} + \text{R}^2\text{NH-C-S-C-NHR}^2.2\text{HX} \]

\[ \xrightarrow{\text{ArN=C=NR}^1 + \text{R}^2\text{NH-C-NH}_2} \]

\[ \xrightarrow{\text{R}^2\text{NHCN} + \text{ArNH-C-NHR}^1} \]

\[ \text{ArNH-C-S-C-NHR}^2.2\text{HX} \xrightarrow{\text{R}^1\text{NH-C-N-C-NHR}^2.\text{HX}} \text{ArN=C-NHR}^2 \]

(R\(^1\) = alkyl or aryl; R\(^2\) = alkyl, aryl or H)

\[ \text{R}^1\text{NCS} + \text{ArNH-C-NH}_2 \xrightarrow{\text{NaHCO}_3} \text{R}^1\text{NH-C-NAr-C-NHR}^2 \xrightarrow{(\text{ox})} \text{ArN=C-NHR}^2 \]

R\(^1\) = alkyl or aryl; R\(^2\) = alkyl, aryl or H
Results obtained from the oxidations of thioureas show that the product determining steps are (i) the rearrangement of monosulphide salt into the amidinothiourea salt and (ii) the oxidative ring closure. The substitution pattern in the amidinothiourea determines the position of the various substituents in the final base. During the intramolecular rearrangement of the sulphide to amidinothiourea, the unsubstituted or the alkyl substituted amidino group was found to migrate to the aryl substituted nitrogen of the other amidino group. It has also been found that if the aryl substituents in a sulphide are different, the amidino group which migrates preferentially goes to the nitrogen which bears the more electron releasing aryl group\textsuperscript{122,123}. Besides, the migrating group is found to be either a monosubstituted or an unsubstituted one and never a disubstituted one.

As further information could be obtained and migratory patterns established, oxidations of binary mixtures dialkyl substituted thioureas and thioureas, 1-alkyl/aryl-3-benzylthioureas and thioureas were carried out and the products examined. This work constitutes the main body of the present thesis.
III. OXIDATION OF COMPOUNDS CONTAINING THIOAMIDO AND AMIDINOPTHIONO SYSTEMS

Since the work described in the thesis is also connected with the oxidation of certain thioamides and amidinothioureas, the oxidations of these compounds are reviewed here.

1. Oxidation of thioamides

A variety of oxidising agents have been used to oxidise thioamides (69) and it has been found that the related 3,5-disubstituted-1,2,4-thiadiazole (70) is the product formed in each case. Thus when thiobenzamide was oxidised with iodine the product formed was found to be 3,5-diphenyl-1,2,4-thiadiazole (70; \( R = \text{Ph} \)).

\[
\begin{align*}
2R-C\text{-}\text{NH}_2 + 2(0) \rightarrow & \quad N\overline{\text{C}}\text{-}R \quad \rightarrow \quad \text{HN}\overline{\text{C}}\text{-}R \\
(69) & \quad (70) & \quad (71)
\end{align*}
\]

The 3,5-disubstituted structure (70) has been assigned to these products on the basis of its non-identity with related 2,5-disubstituted-1,3,4-thiadiazole and its easy reduction to N-benzyl benzamidine (71; \( R = \text{Ph} \)).

Several other oxidising agents have also been used for the oxidation. Sulphur monochloride, thionyl chloride, phosphorus pentachloride, ammonium persulphate,
hydrogen peroxide, ozone, nitrous acid in various solvents, N,N-dichloromethyl carbamate, sodium-N-chloromethyl carbamate and 2-bromoindane-1,3-dione are among them. During the oxidation with chlorine, bromine and nitric acid, it has been found that they also cause substitution on the aryl ring.

The reaction has been extended to the preparation of 3,5-diaryl (or alkyl)-1,2,4-thiadiazoles and the heteryl analogs including 3,5-difuryl and 3,5-diL-(or 4)-pyridyl-1,2,4-thiadiazoles.

The formation of thioacrylamidines by the condensation of nitriles with thioamides and their oxidation to 3,5-disubstituted-1,2,4-thiadiazoles is a general method for the preparation of these 1,2,4-thiadiazoles. An intermediate formation of a diimide sulphide has been suggested.

\[
\text{RCN} + \text{R}_2\text{C}-\text{NH}_2 \rightarrow \text{R}_2\text{C-S-C-R} \rightarrow \text{R}-\text{C-NH-} \rightarrow \text{R}_2\text{C-NH-S-C-R}
\]

(72) (73)

During studies on the oxidation of thioamides, Kitamura has been able to isolate the intermediate S-oxides. These were found useful for the preparation of 3,5-dialkyl (or aryl) analogs with unlike substituents. Thus treatment of phenyl thioacetamide-S-oxide with
thiobenzamide (75) gives\textsuperscript{130,144,145} 3-benzyl-5-phenyl isomer (77). The thioamides are considered to be converted to thioacylamidine (76) by the S-oxide which formally functions as an imidoacylating agent. The intermediate thioacylamidino then undergoes oxidative cyclisation to the 1,2,4-thiadiazole (77) as shown below.

\[
\text{PhH}_2\text{C}-\text{C-NH}_2 + \text{Ph-}C-\text{NH}_2 \xrightarrow{\text{SO}^+} \text{Ph-}C-\text{NH}+\text{C-CH}_2-\text{Ph} \xrightarrow{\text{SO}^-} (74) \quad (75) \quad (76)
\]

\[
\text{Ph-C-S-N} \quad \text{S-C-CH}_2\text{Ph} \\
\text{Ph-C-S-N} \\
(77)
\]

The role of thioamide-S-oxides in the formation of 1,2,4-thiadiazoles have been further examined by Walter and co-workers.\textsuperscript{147-150} The detailed mechanism put forward by them for the oxidation is depicted below:

\[
\text{R-C-NH}_2 \xrightarrow{\text{S-ox}} \text{R-C-NH}_2 \xrightarrow{\text{H}^+} \text{R-C=NH}^+ \xrightarrow{\text{SO}^-} (78)
\]
2. Oxidation of amidinothioureas

(a) 3,5-diamino-1,2,4-thiadiazole

The conversion of amidinothioureas to thiadiazoles involves the oxidative cyclisation of an amidinothiono system. The formation of a sulphenic acid derivative has been suggested as an intermediate\textsuperscript{38} in this cyclisation. The parent compound of this series, the 3,5-diamino-1,2,4-thiadiazole (79) is readily obtained\textsuperscript{73} by the oxidative cyclisation of amidinothiourea (78). At higher temperatures, oxidation with 30% hydrogen peroxide has been found to give amidinourea (80).

\[
\begin{align*}
\text{NH}_2\text{-C-NH-S-NH}_2 & \xrightarrow{\text{oxidation}} \text{NH}_2\text{-C-NH-S-NH}_2 \\
(78) & \hspace{10cm} (79) \\
& \text{NH}_2\text{-C-NH-S-NH}_2 \\
(80)
\end{align*}
\]
On reduction, generally the 3,5-diamino-1,2,4-thiadiazole and its derivatives are converted to the corresponding amidinothiourea. The ready interconvertibility has been suggested as evidence for the structure assignment of the oxidation products as 3,5-diamino-1,2,4-thiadiazole derivatives.

Variously substituted thiadiazoles have been prepared by the cyclisation of the corresponding amidinothioureas.

(b) 3-amino-5-aryl(or alkyl)amino-1,2,4-thiadiazoles

3-amino-5-aryl(or alkyl)amino-1,2,4-thiadiazoles (82) are obtained\textsuperscript{151,152} by the oxidative cyclisation of the 1-alkyl(aryl)-3-amidinothioureas (81; \( R = \text{alkyl or aryl} \)) which in turn are prepared by the condensation of isothiocyanates with guanidines. The reduction of the thiadiazole with hydrogen sulphide is found to regenerate the amidinothiourea (81).

\[
\text{RNCS} + \text{NH}_2\text{C-\( \overline{\text{\text{-}}} \)NH}_2 \rightarrow \text{H}_2\text{N-C-\( \overline{\text{\text{-}}} \)NH-C-NHR} \leftrightarrow \text{RNH-C-S-N-C-NH}_2
\]

(c) 5-amino-3-arylamino-1,2,4-thiadiazole

5-Amino-3-arylamino-1,2,4-thiadiazoles (85) have been prepared recently\textsuperscript{153} by the oxidative cyclisation of
1-arylamidinothioureas (84). The alternative formulation viz. 5-amino-2-aryl-3-imino-1,2,4-thiadiazoline (86) has been ruled out based on earlier observations\textsuperscript{154} that the cyclisations involving an unsubstituted amino group in the oxidation of amidinothiourea is not generally encountered.

1-N-arylamidinothioureas are prepared in good yield by the reaction between 3,5-diimino-1,2,4-dithiazolidine (83) and arylamine in refluxing ethanol. The thiadiazole is reconverted to the amidinothiourea on reduction using hydrogen sulphide.

\[ \text{(83)} \]

\[ \begin{align*}
\text{HN} & \quad \text{C}=\text{NH} \\
\text{HN}=\text{C} & \quad \text{S=S} \\
\text{HN} & \quad \text{C}=\text{NH}
\end{align*} \]

+ ArNH\textsubscript{2} \quad \rightarrow \quad \text{ArNH} \quad \text{C}=\text{NH} \quad \text{C}=\text{NH}_2 \quad \text{NH} \quad \text{S}

\[ \text{(84)} \]

\[ \text{Red} \quad \text{Ox} \]

\[ \text{(85)} \]

\[ \begin{align*}
\text{HN} \quad & \quad \text{C}=\text{NH} \\
\text{HN} & \quad \text{C=S} \\
\text{HN} & \quad \text{C}=\text{NH}_{\text{Ar}}
\end{align*} \]

\[ \text{(86)} \]

(a) 3-Amino-4-aryl-5-imino-4,5-dihydro-1,2,4-thiadiazole

The oxidation of the amidinothioureas\textsuperscript{95}(87) gives 3-amino-4-aryl-5-imino-4,5-dihydro-1,2,4-thiadiazoles (88). The amidinothioureas (87) have been prepared by the interaction of arylcyanamide with thiourea in presence of acid. There are two other possible alternative structures (89) and (90), for the amidinothiourea. But these represent known
compounds are different from the one formed. Therefore the amidinothiourea obtained has been assigned the structure (87).

\[
\begin{align*}
\text{H}_2\text{N-C-NH}_2 & \rightarrow \text{H}_2\text{N-C-NAr-C-NH}_2 \\
+ \quad \text{ArNHCN} & \quad \rightarrow \quad \text{HN=C-S-N}
\end{align*}
\]

The decomposition of the amidinothiourea (87) to arylguanidine and thiocyanic acid is offered as further support for the assigned structure. The thiaiazole (88) also on reduction gives the same degradation products.

(e) 3,5-Bis(substituted amino)-1,2,4-thiadiazoles

The 1-substituted-3-(substituted amidino)thiooureas (91; R = alkyl or aryl) are obtained by the condensation of isothiocyanate and monosubstituted guanidines. On oxidation, these amidinothioureas yield the 3,4-bis(substituted amino)-1,2,4-thiadiazoles (92). The reaction between aromatic amines and appropriate 3,5-diimino-1,2,4-dithia-zolidine hydrohalides (93) has also been used as an alternative route to the amidinothioureas (91).
(f) 2-Aryl-3-arylimino-5-imino-1,2,4-thiadiazolidines

The addition of hydrogen sulphide to the cyano­
guanidines (94) is reported\textsuperscript{158} to give 1-(N,N'-diarylamidino)-

\[
\text{ArNH-} \text{C-} \text{NH-} \text{C-NHAr} \rightarrow \text{ArNH-} \text{C-} \text{NH-} \text{HNCN} \rightarrow \text{ArNH-} \text{C-} \text{NH-} \text{C-NH}_{2} \rightarrow \text{HN-} \text{C-} \text{NHAr}
\]

(94)  (95)  (96)

These amidinothioureas (95) on oxidation with hydrogen
peroxide gives the thiadiazolidines (96).

(g) 3-Alkylimino-4-aryl-5-imino-1,2,4-thiadiazolidines

1-Aryl-1-(N-alkylamidino)thioureas (98) on oxidation
are found to yield 3-alkylimino-4-aryl-5-imino-1,2,4-thia-
diazolidines (99). These amidinothioureas are formed\textsuperscript{94} in
the reaction between arylcyanamides and alkylthioureas.
In the isomerisation of the sulphide (97) to the amidino-thiourea (98), the amidino group migrates to the nitrogen carrying an aryl group.

\[
\text{ArNHCN} + \text{RNH-C-NH}_2 \rightarrow \text{ArNH-C-S-C-NH}_2 \cdot \text{HX} \tag{97}
\]

\[
\rightarrow \text{H}_2\text{N-C-N-C-NHR} \rightarrow \text{ArN-C=NR} \tag{98}
\]

These thiadiazolidines have been reported to have properties which are similar to those of Hector's bases.

(h) 2-Aryl-5-arylamino-3-arylimino-2,3-dihydro-1,2,4-thiadiazoles

The 2-aryl-5-arylamino-3-arylimino-2,3-dihydro-1,2,4-thiadiazoles (101) have been obtained by the oxidation of 1-aryl-3-(N,N'-diarylamidino)thioureas (100), which have been prepared by the condensation of aryl isothiocyanates with N,N'-diarylguanidines.\textsuperscript{154} The thiadiazoles give back the amidinothioureas on reduction. These thiadiazoles are stable only in the form of their salts. On basification of their salts, the thiadiazoles irreversibly isomerise to benzothiazolylguanidines (102).
3. Oxidation of imidoylthioureas

3-Substituted-5-substituted amino-1,2,4-thiadiazoles\(^{159}\) (104; \(R^1 = \) alkyl or aryl, \(R^2 = \) alkyl or aryl) were obtained by the oxidative cyclisation of imidoylthioureas (103); which were prepared from the corresponding amidines and isothiocyanates following Pinner's method.\(^ {160}\)

2,3-Di-substituted-5-imino-2,5-dihydro-1,2,4-thiadiazoles (106; \(R^1, R^2\) and \(R^3 = \) alkyl or aryl) were thus obtained from the corresponding \(N,N',N''\)-trisubstituted imidoylthioureas (105; \(R^1, R^2\) and \(R^3 = \) alkyl or aryl).
4. Oxidation of thioacylguanidines

Thioacylguanidines (108) have been cyclised to 5-substituted-3-substituted amino-1,2,4-thiadiazoles (109; \( R^1 = \text{alkyl or aryl}; \ R^2 = \text{alkyl or aryl} \)). The procedure adopted involves the treatment of acylguanidines (107) with phosphorus pentasulphide and the in situ cyclisation of the thioacylguanidine (108).

\[
\begin{align*}
\text{R}^1\text{NH-C=N-C-R}^2 \xrightarrow{\text{P}_2\text{S}_5} \text{R}^1\text{NH-C=N-C-R}^2 \\
(107) & \quad (109)
\end{align*}
\]

Conversion of guanidine using ethylthiobenzoate to thiobenzoylguanidine (110) and its oxidation to 3-amino-5-phenyl-1,2,4-thiadiazole (111) have also been reported.

5. Oxidation of 2,4-dithiobiurets and related compounds

3-Alkyl(or aryl)thio-5-substituted amino-1,2,4-thiadiazoles (113) have been obtained from 1-substituted-4-\( S \)-alkyl(or aryl)iso-2,4-dithiobiurets (112) by oxidative cyclisation with bromine in ethanol or hydrogen peroxide. Oxidation of (112) using dilute solutions of bromine in
chloroform also gives the same product, but when the oxidation is effected with concentrated solution of bromine in chloroform, S-debenzylation and deallylation occur where the S-alkyl groups in (112) are benzyl and allyl, and 1,2,4-dithiazolidines are formed (114). The 1,5-diaryl-2-S-alkylisodithiobiurets (115) on oxidation yield only the related benzothiazolylisothioureas (116). In 1,5-dialkyl-2-S-alkylisodithiobiurets (112; \( R^1 = R^2 = R^3 = \text{alkyl} \)), oxidation causes debenzylolation and formation of dithiazolidines (114; \( R^1 = R^2 = \text{alkyl} \)). The 4-O-alkyl-1-aryl(or alkyl)-2-thioisobiurets (117) can be ring-closed with bromine or hydrogen peroxide into 3-alkoxy-5-alkyl(or aryl)amino-1,2,4-thiadiazoles (118). Similarly the oxidation of 1-substituted-2-thiobiurets (119) and 1,5-diaryl-2-thiobiuret (121) yields 3-hydroxy-1,2,4-thiadiazole (120) and 2-aryl-5-arylmino-1,2,4-thiadiazolidin-3-one (122; \( \text{Ar} = \text{Ph} \)).
6. Oxidation of dithiobiureas and amidinothiosemicarbazides

The oxidation of 1-phenyldithiobiurea\(^{176}\) (123) and a few 1,6-diaryldithiobiureas\(^{177}\) (125) with hydrogen peroxide give 2-amino-5-phenylamino-1,3,4-thiadiazole (124) and 2-amino-5-substituted amino-1,3,4-thiadiazoles (126). Recently the oxidation of 1-(N,N'-diarylamidino)thiosemicarbazide (127) to 3-amino-4-aryl-5-arylaminoo-1,2,4-triazole (128) has also been reported.\(^{178}\)
In this thesis a few oxidations of related S-alkyl-isodithiobiureas and a few 1-aryl- and alkylthiobiureas are also reported.

Incidentally the alkylation studies of a few dithiobiureas also had to be carried out and the results of these alkylations are also included in the thesis.