CHAPTER II

OXIDATION OF MIXTURES OF 1,3-DIALKYLTHIOUREAS AND THIOUREA

INTRODUCTION

The oxidation of thioureas in polar media generally leads to 1,2,4-thiadiazole derivatives and in non-polar media to 2-aminobenzothiazole derivatives. Two molecules of thiourea are involved in the formation of thiadiazoles, whereas in the formation of benzothiazoles, only an intramolecular oxidative cyclisation of a single thiourea molecule alone occurs. The oxidation of binary mixtures of 1,3-disubstituted thioureas and thiourea is found to give 3-amino-4-substituted-5-substitutedimino-4,5-dihydro-1,2,4-thiadiazoles. In the formation of these heterocycles, one molecule each of the two different thioureas used found to be incorporated. Thus 3-amino-4-aryl-5-arylimino, 5-alkylimino-3-amino-4-aryl and 3-arylamino-4-aryl-5-arylimino-4,5-dihydro-1,2,4-thiadiazoles have been prepared by the oxidation of binary mixtures of 1,3-diarylthioureas and thiourea, 117,123 1,3-diarylthioureas and 1-alkylthioureas 118 1-alkyl-3-aryltioureas and thiourea, 120 and 1,3-diarylthioureas and 1-aryltioureas 119 respectively.
The substitution pattern in the thiadiazole formed is determined by that of the intermediate amidinothiourea which is formed by the isomerisation of the intermediate bis(formamidino) sulphide in which the two amidino groups are respectively from each of the two thioureas used (see Chapter I, page 27). During this rearrangement, the migration terminus of one of the amidinopart was always found to be a nitrogen bearing an aryl group and the migrating group, an unsubstituted \(\text{aryl} \text{ group} \text{ and} \text{ the migrating group, an unsubstituted} \text{ amidino group of the bis(formamidino) sulphide. Further it was also observed that the electron releasing nature of the substituents on the aryl group in the bis(formamidino) sulphide also influences the outcome of the isomerisation. As diarylthiourea and thiourea systems have been studied, a feasible extension for the further study of the reaction mechanism appeared to be one containing only alkyl functions. These oxidations were expected to throw further light on the migratory aptitudes of the different amidino groups during the isomerisation of bis(formamidino) sulphide to amidinothiourea. For this purpose, \(1,3\)-dialkylthiourea and thiourea system was chosen. Here, the 'mixed' bis(formamidino) sulphide (1) which might be formed during the oxidation would contain two amidino groups; one carrying two alkyl functions and the other an unsubstituted one. The 'mixed' sulphide (1) then could rearrange to either of the amidinothioureas (2) or
(3) or both. These then could cyclise to the thiadiazoles (4) and (5) respectively.

\[
R\text{NH} \quad \begin{array}{c} \text{S} \quad \text{C} \quad \text{NH} \\ \text{R'}\text{N'} \end{array} \quad \begin{array}{c} \text{NH} \quad \text{NH}_2 \\
\text{R}\text{N} = \text{C} \quad \text{S} \quad \text{N}
\end{array}
\]

\( (1) \)

\[
\begin{array}{c}
R\text{NH} - \text{C} - \text{NH} - \text{C} - \text{NH}_2 \\
\text{S} \quad \text{NH}
\end{array} \quad \begin{array}{c}
H_2\text{N} - \text{C} - \text{NH} - \text{C} - \text{NHR} \\
\text{S} \quad \text{NR}
\end{array}
\]

\( (2) \) \( \quad (3) \)

\[
\begin{array}{c}
R\text{N} - \text{C} - \text{NH}_2 \\
\text{R}\text{N}=\text{C} \quad \text{S} \quad \text{N}
\end{array}
\]

\( (4) \)

\[
\begin{array}{c}
H_2\text{N} - \text{C} - \text{S} \quad \text{NR} \\
\text{N} \quad \text{C}=\text{NR}
\end{array}
\]

\( (5) \)

RESULTS AND DISCUSSIONS

An equimolecular mixture of 1,3-diethylthiourea and thiourea in acidic aqueous ethanol was oxidised with hydrogen peroxide. As observed in the cases of aryl derivatives, \(^{11,20,122,1}\) rapid separation of sulphur did not occur in this case. The bis(diethylamidino)\(_\text{d}^\text{i}\) sulphide and bis(amidino)\(_\text{d}^\text{i}\) sulphide are known to be stable in polar solutions at room temperature.\(^{75}\) Therefore the solution obtained after addition of hydrogen peroxide was heated on a water bath to make these disulphides decompose into cyanamide and thiourea or carbodiimide and thiourea. Gradual separation of sulphur was observed and
it was found to be complete after about two hours.

After cooling the solution was filtered and basified. A turbid solution resulted which gradually became clear with the separation of an oily substance and sulphur.

The basified solution was extracted with benzene. A comparison of the chromatogram of this extract with that of the products obtained by the oxidation of 1,3-diethylthiourea alone showed an intense additional spot in the former. The only other major spot was probably due to the 2,4-diethyl-3,5-diethylimino-1,2,4-thiadiazolidine which is the sole product formed when 1,3-diethylthiourea alone is oxidised. The additional product formed in the oxidation of the binary mixture of thioureas could easily be separated from other side products (see experimental). The basic compound was found to have a molecular formula \( C_6H_{12}N_4S \). It did not yield any condensation product with phenyl isothiocyanate. Nor did it undergo desulphurisation with boiling alkaline lead acetate solution. The base was found to be stable in 3N acid and alkali. These observations were parallel to those made for 3-amino-4-aryl-5-arylimino-4,5-dihydro-1,2,4-thiadiazoles.\(^{117}\)

The base shows strong absorptions resulting from C=N and NH stretching modes of vibration in its i.r. spectrum
at 1610 cm⁻¹ and 3150 cm⁻¹. N.m.r. spectrum shows a broad signal due to -NH₂ at δ 4.46; one quartet at δ 3 due to one CH₂ another at δ 3.74 due to the other CH₂ and a multiplet of 6H due to two methyl groups in the range of δ 1.05 to δ 1.4. The mass spectrum of the compound shows a peak due to a fragment C₂H₅NH=C≡N⁻ at m/e 71. Such fragments are suggested to be characteristic of 3-amino or substituted amino-4-substituted-5-substituted imino-4,5-dihydro-1,2,4-thiadiazoles. The above ion could only be formed by the cleavage of ring as shown below.

\[ \text{C}_2\text{H}_5\text{N} = \text{C} = \text{N} \rightarrow \text{C}_2\text{H}_5\text{NH} = \text{C} = \text{NC}_2\text{H}_5 \]

\[ (4, R = \text{Et}) \]

Hence the base may be 3-amino-4-ethyl-5-ethylimino-4,5-dihydro-1,2,4-thiadiazole as surmised from spectral data.

Reduction of a solution of the base in dilute hydrochloric acid with hydrogen sulphide yielded an amidinothiourea in solution which could be oxidised back to the base. The amidinothiourea formed in this reduction when warmed with sodium bicarbonate yielded ethyl isothiocyanate. If the base formed had structure (5), then the decomposition
products of the amidinothiourea would have been diethylguanidine and thiocyanic acid. The fact that it decomposed to yield isothiocyanate and probably ethylguanidine (which could not be isolated) shown that the amidinothiourea has structure (2) and the base, because of their easy interconvertibility, structure (4). Further, in structure (5) the presence of imino or amino group (tautomeric possibility) at position five suggested a possible reaction with phenyl isothiocyanate or carbon disulphide since in 4-aryl-3-aryl-amino-5-imino-4,5-dihydro-1,2,4-thiadiazoles, 79 5-arylaminio-4,5-dihydro-1,2,4-thiadiazoles, 3-arylaminio-4-aryl-5-imino-4,5-dihydro-1,2,4-thiadiazoles, 4-benzyl-3-benzyl-amino-5-imino-4,5-dihydro-1,2,4-thiadiazole or in 2-aryl-3-arylimino-5-amino-2,3-dihydro-1,2,4-thiadiazoles, 158 the
5-imino or the amino group is fairly reactive towards such additions. Since the base did not yield any condensation product with isothiocyanate or carbon disulphide, structure (5) can be ruled out for the base. Thus the spectral and chemical evidences suggest a 3-amino-4-ethyl-5-ethyl:mino-4,5-dihydro-1,2,4-thiadiazole structure for the base.

Oxidations of mixtures of 1,3-di-n-propylthiourea and thiourea, 1,3-di-n-butylthiourea and thiourea were also carried out under identical conditions. In each case a thiadiazole derived from 1,3-dialkylthiourea and thiourea was isolated. In all these oxidations, two bases were formed - the tetraalkyl substituted and dialkyl substituted derivatives - which could be separated by their difference in solubility in dilute hydrochloric acid. The tetraalkyl substituted thiadiazoles are insoluble in dilute acid, whereas the dialkyl substituted one was found to be very soluble.

Hydrogen sulphide in acidic solution was found to open the thiadiazoles mentioned above. The reduction products, viz., the amidinothiourea, could not be isolated in any of these cases even on careful manipulation. Therefore their behaviour was studied with the solution obtained after the reduction. The solution was found to decompose when warmed with sodium bicarbonate solution to the related alkyl isothiocyanate and probably alkylguanidine. Alkyl isothiocyanates
were identified in each case but the alkylguanidines could not be isolated and identified. It is likely that the guanidines underwent rapid decomposition. The amidino-thioureas may therefore, have the structure (2). Oxidation of the solution obtained after reduction yielded the related thiadiazoles back. This easy interconvertibility indicates, again, that in each of these cases the base formed has a 3-amino-4-alkyl-5-alkylimino-4,5-dihydro-1,2,4-thiadiazole structure.

N.m.r. spectra of the compounds obtained from the oxidation of 1,3-di-n-propylthiourea and thiourea and 1,3-di-n-butylthiourea and thiourea show two triplets due to the two -CH₂CH₂CH₃ methylene groups at δ 3.0 and 3.7 for the propyl derivative and two triplets due to the -CH₂CH₂CH₂CH₃ groups at δ 3.0 and 3.6 for the butyl derivative besides the signals due to the other protons of the alkyl substituents. The δ value of the two -CH₂ signal is not considerably shifted from those of the -CH₂ protons of ethyl derivatives (δ 3.0 and 3.74). This shows that in all these cases the alkyl groups occupy similar positions and thus these compounds possess similar structures.

Oxidation of a mixture of 1,3-diisopropylthiourea and thiourea with hydrogen peroxide and subsequent work-up did not yield any thiadiazole. 1,3-Diisopropylurea was formed
in large quantities. It is possible that in the isomerisation of the sulphide to amidinothiourea, the bulk of the isopropyl group prevented the migration of the amidino part onto the nitrogen which carried the isopropyl group. This is also supported by the observation that the derivative of bis(formamidino) sulphide salt obtained by the condensation of cyanamide and 1,3-diisopropylthiourea or thiourea and diisopropylcarbodiimide did not undergo isomerisation to the amidinothiourea even on prolonged heating. Addition of hydrogen peroxide to a solution of the above sulphide salt resulted in the formation of 1,3-diisopropylurea.

Oxidation of a binary mixture of 1,3-dibenzylthiourea and thiourea yielded a base with molecular formula $\text{C}_{16}\text{H}_{16}\text{N}_{4}\text{S}$. This base was found to be different from 3,5-bis(benzylamino)-1,2,4-thiadiazole (6) and 3-benzylamino-4-benzyl-5-imino-4,5-dihydro-1,2,4-thiadiazole (7).

Reduction of its solution in aqueous acid with hydrogen sulphide followed by its decomposition yielded benzyl isothiocyanate and benzylguanidine. Hence the thiadiazole formed in this oxidation has a substitution pattern similar to that in the other cases earlier discussed.

The i.r. spectrum of the compound shows characteristic absorptions of C=N, C=C and NH stretching vibrations. The mass spectrum of this base was compared with those of
3,5-bis(benzylamino)-1,2,4-thiadiazole (6) and 3-benzylamino-4-benzyl-5-imino-4,5-dihydro-1,2,4-thiadiazole (7).

In the mass spectrum of compound (6), a peak due to $\text{C}_6\text{H}_5\text{CH}_2\text{NCS}^+$ ion is observed. It is probably formed from the molecular ion by the following fragmentations (see Figs. 1, 2 and 3).

$$\text{N} = \text{C-NHBz}$$

$\text{BzNH-C-S-N}$

$\text{BzN-C-NHBz}$

$\text{+} \rightarrow \text{BzNCS} + \text{HN=C-NHBz}$

The loss of elements corresponding to $\text{C}_7\text{H}_7\text{N}$ gives the ion at m/e 191 (metastable peak at 123.2) from the molecular ion. In the spectrum of 3-benzylamino-4-benzyl-5-imino-4,5-dihydro-1,2,4-thiadiazole (7) also, loss of $\text{C}_7\text{H}_7\text{N}$ lead to the ion at m/e 191. Besides, both the compounds (6) and (7) give ions at m/e 106 (formulated as $\text{C}_7\text{H}_7\text{NH}$). This seems to indicate that 3-benzylamino substituent in (6) and (7) is cleaved giving rise to the peak at m/e 106. The same substituent could be involved in the formation of $\text{M-C}_7\text{H}_7\text{N}$ ion in compounds (6) and (7). The compound obtained from the oxidation of 1,3-dibenzylthiourea and thiourea does not show $\text{M-C}_7\text{H}_7\text{N}$ or $\text{C}_7\text{H}_7\text{NH}$ ions. From this it can be
Fig. 1

![Figure 1: Mass spectrum of compound (4d).]

Fig. 2

![Figure 2: Mass spectrum of compound (7).]

Fig. 3

![Figure 3: Mass spectrum of compound (6).]
concluded that the base obtained now may not have a benzyl substituent on 3-amino or imino group.

The compound (7) shows M-91 ion, so does the base obtained from the oxidation of 1,3-dibenzylthiourea and thiourea. But compound (6) does not yield such a fragment. This indicates the presence of a N4 benzyl group in the present base. Thus the mass spectral data also seems to favour a 3-amino-4-benzyl-5-benzylimino-4,5-dihydro-1,2,4-thiadiazole structure rather than a 2,3-dibenzyl substituted thiadiazole structure (5; R = benzyl).

The suggested sequence of reactions during oxidation of thioureas involves the formation of a bis(formamidino) sulphide from thiourea and the cyanamide or carbodiimide. The bis(formamidino) sulphide hydrochlorides have been isolated from the reaction of cyanamide with 1,3-dialkyl-thiourea as well as dialkylicarbodiimide and thiourea in presence of hydrochloric acid. These compounds were characterised as bis(formamidino) sulphide hydrochlorides because hydrogen sulphide readily reduced them to the corresponding substituted thioureas. Further, the solutions of these salts did not undergo oxidation on treatment with hydrogen peroxide.

The bis(formamidino) sulphides underwent isomerisation to the related amidinothioureas on refluxing in ethanol. These amidinothioureas could not be isolated in
crystalline form from the ethanolic solution. However their formation was indicated by their decomposition with sodium bicarbonate to alkyl isothiocyanate and their oxidation to the corresponding thiadiazoles.

The reaction pathway is outlined along the lines suggested earlier for oxidations of thioureas (see Chapter I page 27).

\[
\begin{align*}
R'\text{-NH-C-NHR} + H_2N-C-NH_2 & \rightarrow R'\text{NH-C-S-S-C-NH}_2 \\
\text{and/or} & \\
R'\text{NH-C-S-S-C-NHR} \cdot 2\text{HCl} + H_2N-C-S-S-C-NH_2 \cdot 2\text{HCl} & \rightarrow R'\text{NH-C-S-S-C-NH}_2 \cdot 2\text{HCl}
\end{align*}
\]

(8)

(9)

(10)

\[R = \text{alkyl}\]

\[
\begin{align*}
\fbox{
\begin{array}{c}
\text{RN=C-NR} + H_2N-C-NH_2 \\
\text{HCl}
\end{array}
}\quad & \quad \fbox{
\begin{array}{c}
\text{RNH-C-NHR} + NH_2\text{CN}
\end{array}
}\bigg)
\end{align*}
\]

(1)

(2)

\[
\begin{align*}
\fbox{
\begin{array}{c}
\text{RN=C-NH}_2
\end{array}
}\quad & \quad \fbox{
\begin{array}{c}
\text{RN=C-S-NH}_2
\end{array}
}\bigg)
\end{align*}
\]

(4)

a. \(R = \text{C}_2\text{H}_5\)  
b. \(R = \text{CH}_3\text{CH}_2\text{CH}_2\)  
c. \(R = \text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\)  
d. \(R = \text{C}_6\text{H}_5\text{CH}_2\)  
e. \(R = \text{CH}_3(\text{CH})\text{CH}_3\)

SCHEME 1
The formation of the sulphide (1) representing the second stage of the reaction is preceded by the oxidation of thiourea to the corresponding disulphide (9) and (10) or to a 'mixed' disulphide (8). The disulphide decomposes under the reaction conditions to carbodiimide or cyanamide and thiourea. In the presence of hydrochloric acid these products react further to form the sulphide (1). This intermediate product then isomerises to the amidinothiourea (2) which in turn undergoes oxidative cyclisation to the thiadiazole (4).

In conclusion it is now seen that the bases obtained presently are formed from the oxidation of 1-amidino-1,3-dialkylthiourea. This amidinothiourea is formed as a result of isomerisation of amidino-(N,N'-dialkyl)amidino sulphide salt. The migration of the unsubstituted amidino part onto the other disubstituted amidino part is the important step. This preferential migration is possibly controlled by polar effect of the substituents involved.

The rearrangement of the sulphide to the amidinothiourea has been shown to be an intramolecular one. In the bis(formamidino) sulphide salt formed, both the amidino parts are monoprotonated. The amidinothiourea formed by the isomerisation is a monoacid salt. Hence the controlling factor may be the deprotonation of the bis(formamidino) sulphide dihydrochloride in one of the amidino
part and this could preferably be occurring in the unsubstituted part.

\[
\begin{align*}
R-\text{NH} & \quad \text{C-S-C} \quad \text{NH} \\
+ \quad \text{RNH} & \quad \text{NH} \\
\text{RNH} & \quad \text{C-S-C} \quad \text{NH}_2
\end{align*}
\]

The result of the oxidations of 1,3-diisopropylthiourea and thiourea mixture shows that along with the electronic effects steric factor may also assume importance. The bulkiness of the group, viz., isopropyl would be preventing the rearrangement. Admittedly, the dialkyl substituted amidino part could as well migrate to the unsubstituted amidino part to yield an amidinothiourea. However it did not happen. In fact the only reported case where the amidino group migrated to an unsubstituted amidino part in bis(formamidino) sulphide is that of the parent bis(formamidino) sulphide salt. Here again it was an unsubstituted amidino part which migrated and that too under basic conditions. In this case, the necessity of the basic condition appears to point to a possible role of deprotonation as a factor promoting rearrangement. It has been observed in these laboratories that the use of a lesser quantity of acid during the oxidation of thioureas assists the reaction as reflected in the increased yield of the thiadiazole formed. Lower concentration of acid
probably brings about only monoprotonation of the bis(formamidino) sulphide salt. When such is the case the usual deprotonation step becomes unnecessary and the rearrangement proceeds faster.

EXPERIMENTAL

GENERAL

Melting points were determined on a Thomas Hoover Unimelt apparatus and are uncorrected. The purity of the products was ascertained in each case by thin layer chromatography using Kieselgel-G (Merck) HF-354 and benzene-ethyl acetate (3:1) as solvent.

Infrared spectra were taken on Perkin Elmer 257 and 700 spectrophotometers. N.m.r. spectra were recorded on Varian A-60 or Varian XL-100 instruments using tetramethylsilane as the internal standard and the mass spectra were run on a Varian MAT-CH7 spectrometer.

All the reagents used were of commercial grade. The required 1,3-dialkylthioureas were prepared following known procedure. Dialkylcarbodiimides were prepared adopting methods reported for diaryl derivatives. Isothiocyanates were prepared by reported methods.
I. OXIDATION OF MIXTURES OF 1,3-DIALKYLTHIOUREAS AND THIOUREA: Formation of 4-alkyl-5-alkylimino-3-amino-4,5-dihydro-1,2,4-thiadiazoles

(a) 3-Amino-4-ethyl-5-ethylimino-4,5-dihydro-1,2,4-thiadiazoles (4a)

To a solution of 1,3-diethylthiourea (13.2g, 0.1 mol) and thiourea (7.6g, 0.1 mol) in 1:1 ethanol-water mixture (150 ml) containing concentrated hydrochloric acid (23 ml, 32%, 0.2 mol) hydrogen peroxide (24 ml, 30%, 0.2 mol) was added gradually with stirring. The reaction mixture was then kept on a boiling water-bath for 2 hrs. Then the solution was cooled, diluted with water (100 ml) and the precipitated sulphur removed by filtration. The filtrate on basification with aqueous ammonia formed a turbid solution which gradually became clear on keeping. An oily layer and a small amount of sulphur separated out. It was extracted repeatedly with benzene (50 ml x 4). Using a drop of this extract a chromatogram was developed. Benzene was then distilled off from the extract and the oily residue left behind extracted with very dilute hydrochloric acid. A major part of the oily substance (see below) remained undissolved. The aqueous acidic extract when basified did not yield any precipitate and hence was extracted again with benzene. The benzene extracts on concentration and dilution with petroleum ether afforded colourless shining plates.
These crystals were collected (2.8g), washed with petroleum ether and dried, m.p. 112°. Recrystallisation from benzene-petroleum ether mixture to constant melting point gave shining plates of 3-amino-4-ethyl-5-ethylimino-4,5-dihydro-1,2,4-thiadiazole, m.p. 114°. (Found: C, 41.8; H, 7.1; N, 32.7; S, 19.0. $C_6H_{12}N_4S$ requires C, 41.9; H, 7.0; N, 32.6; S, 18.6%).

$\nu_{\text{max (KBr)}}$: 3400s, 3200s (NH); 1625s (C=N); 1475m (C-H alkyl) cm$^{-1}$. N.m.r. (CDCl$_3$): $\delta$ 1.06-1.4, m, 6 aliphatic H; 3.0, quartet, 2 methylene H of N4-C$_2$H$_5$; 3.74, quartet, 2 methylene H of C5-C$_2$H$_5$N; 4.7, broad s, 2 amino H. Mass spectrum: m/e (%): 172(68); 157(72.4); 144(37.2); 129(26.9); 100(16.7); 101(15.4); 99(10.3); 87(7.7); 74(37.2); 71(62.8); 55(21.2); 43(100). The base formed a monopicrate, needles from ethanol, m.p. 156° (Found: N, 23.7; S, 7.6. $C_6H_{12}N_4S$. $C_6H_{3}N_3S_7$ requires N, 24.4; S, 7.9%).

To verify whether the products obtained in the above oxidation contained any products of the oxidation of 1,3-diethylthiourea, the oxidation of 1,3-diethylthiourea in aqueous acid solution was done under similar conditions and the products thus formed was analysed by t.l.c. The chromatogram was compared with the one obtained in the previous experiment. The products obtained from the oxidation of a mixture of 1,3-diethylthiourea and thiourea contained only one additional intense spot, which was due to the thiadiazole derived from 1,3-diethylthiourea and thiourea. The undissolved oily residue formed in the
oxidation of the binary mixture was found to be formed in the oxidation of 1,3-diethylthiourea also. It was probably 2,4-diethyl-3,5-diethylimino-1,2,4-thiadiazolidine. No attempts were made to characterise this as this is a known compound.

In another experiment 3-amino-4-ethyl-5-ethylimino-4,5-dihydro-1,2,4-thiadiazole was separated from the mixture adopting the following procedure. The solution obtained after the oxidation was basified and kept aside. When the turbid solution became clear, it was reacidified. The oily matter which remained undissolved was removed by extraction with benzene and the remaining acidic solution treated with picric acid. The picrate thus precipitated was collected (5.3g, 40%) and crystallised from ethanol when shining yellow needles were obtained, m.p. 156°. (Found: N,23.5, S,8.3; C₆H₁₂N₄S. C₆H₃N₃O₇ requires N,24.4; S,7.9%).

This picrate was decomposed by trituration with 40% aqueous sodium hydroxide. The pasty mass so formed was repeatedly extracted with benzene. The benzene extract on concentration and dilution with petroleum ether afforded colourless crystals of 3-amino-4-ethyl-5-ethylimino-4,5-dihydro-1,2,4-thiadiazole, m.p. 114°.

When this base was refluxed in benzene with phenyl
isothiocyanate or carbon disulphide, no condensation product was formed. The base did not undergo desulphurisation even in boiling alkaline lead acetate solution. These negative results were also shown by the other thiadiazoles described below:

(b) 3-Amino-4-\textit{n}-propyl-5-\textit{n}-propylimino-4,5-dihydro-1,2,4-thiadiazole (4b)

A mixture of 1,3-di-\textit{n}-propylthiourea (8g, 0.05 mol) and thiourea (3.8g, 0.05 mol) was oxidised as detailed in the case described above. Sulphur was removed by filtration and the reaction mixture was poured into ice-cold ammonia solution. After some time, it was reacidified and the undissolved oily layer was extracted with benzene. The aqueous acidic solution on basification afforded a white precipitate (5g, 50%) which was collected and crystallised from benzene-petroleum ether mixture to constant m.p. 108°.

(Found: C,47.6; H,7.7; N,27.9; S,15.6. C\textsubscript{8}H\textsubscript{16}N\textsubscript{4}S requires C,48.0; H,8.1; N,28.0; S,15.9%). \textit{$\nu$} \textsubscript{max} (KBr): 3150m (NH); 1670m (NH\textsubscript{2}def); 1620s, 1580s (C=N); 1460s (C-H alkyl);

N.m.r. (CDCl\textsubscript{3}). δ 0.72-1.2, m, 6 aliphatic H; 1.4-2, m, 4 aliphatic H; 3.0, t, 2 methylene H of N4-CH\textsubscript{2}CH\textsubscript{2}CH\textsubscript{3}; 3.7, t, 2 methylene H of C5-CH\textsubscript{2}CH\textsubscript{2}CH\textsubscript{3}; 4.9, s, 2 amino H.

Picrate, needles from ethanol, m.p.150°. (Found: N,21.6; S,7.0. C\textsubscript{8}H\textsubscript{16}N\textsubscript{4}S. C\textsubscript{6}H\textsubscript{3}N\textsubscript{3}O\textsubscript{7} requires N,22.8; S,7.5%).
(c) 3-Amino-4-n-butyl-5-n-butylimino-4,5-dihydro-1,2,4-thiadiazole (4c)

A solution of 1,3-di-n-butylthiourea (9.4g, 0.05 mol) and thiourea (3.8g, 0.05 mol) in aqueous ethanol was oxidised and worked up as in the case of (4b). The product (3.8g, 35%) crystallised from benzene-petroleum ether mixture as colourless shining plates m.p. 98°.\( ^\circ \) (Found: C,52.6; H,8.5; N,24.5; S,13.7. \( \text{C}_{10}\text{H}_{20}\text{N}_{4}\text{S} \) requires C,52.6; H,8.7; N,24.6; S,14.0%). \( \nu \) max (KBr): 3350m, 3250m, 3150s (NH); 2850s (C-H stretch), 1660s (NH\(_2\) def); 1620s, 1580s (C=N); 1460s (C-H alkyl) cm\(^{-1}\). N.m.r. (CDCl\(_3\)): 0 0.7-1.1, m, 6 aliphatic H; 1.1-2.1, m, 8 aliphatic H; 3.0, t, 2 methylene H of N4 CH\(_3\)CH\(_2\)CH\(_2\)CH\(_2\)-; 3.6, t, 2 methylene H of C5-NCH\(_2\)CH\(_2\)CH\(_2\)CH\(_3\); 4.8, s, 2 amino H. Picrate, needles from ethanol, m.p. 99°. (Found: N,21.0; S,6.8 \( \text{C}_{10}\text{H}_{18}\text{N}_{4}\text{S} \). \( \text{C}_{6}\text{H}_{2}\text{N}_{3}\text{O}_{7} \) requires N,21.4; S,7.0%).

(d) 3-Amino-4-benzyl-5-benzylimino-4,5-dihydro-1,2,4-thiadiazole (4d)

The oxidation of 1,3-dibenzylthiourea (12.8g, 0.05 mol) and thiourea (3.8g, 0.05 mol) yielded (4d) (9g, 61.0%) which on crystallisation from ethanol gave shining needles, m.p. 124°. (Found: C,65.1; H,5.6; N,19.2; S,10.5. \( \text{C}_{16}\text{H}_{16}\text{N}_{4}\text{S} \) requires C,64.8; H,5.4; N,18.9; S,10.8%). \( \nu \) max (KBr): 3150s (NH); 1660m (NH\(_2\) def); 1620s (C=N); 1580s, 1480s
(C=C aryl); 1460s (C-H alkyl); 700m, 740m (Ph) cm⁻¹.
N.m.r. (CDCl₃); δ 4.3, s, 2 methylene H of C₅-NCH₂C₆H₅; 4.5, s, 2 amino H; 5.05, s, 2 methylene H of N₄-CH₂C₆H₅; 7.1-7.5, m, 10 aromatic H. Picrate, needles from ethanol, m.p. 148°. (Found: N, 17.9; S, 6.2; C₁₆H₁₆N₄S. C₆H₃N₃O₇ requires N, 18.7; S, 6.1%).

(e) Oxidation of a mixture of 1,3-diisopropylthiourea and thiourea

The oxidation of 1,3-diisopropylthiourea (8g, 0.05 mol) and thiourea (3.8g, 0.05 mol) was carried out as described for the earlier cases. After dilution and removal of sulphur, the solution slowly deposited crystals which were collected after cooling. The product (5g, 71%) was crystallised from ethanol to give colourless shining needles of 1,3-diisopropylthiourea, m.p. and m.m.p. 192°. To one portion of the filtrate, aqueous ammonia was added and to the remaining portion picric acid. No precipitation could be observed in either case indicating that thiadiazole was not formed.

II. REDUCTION OF 4-ALKYL-5-ALKYLIMINO-3-AMINO-4,5-DIHYDRO-1,2,4-THIADIAZOLES

The details of a typical reduction and degradation procedure are given below.

Through a solution of 3-amino-4-ethyl-5-ethylimino-
4,5-dihydro-1,2,4-thiadiazole (4a) (3.4g, 0.02 mol) in dilute hydrochloric acid, hydrogen sulphide was bubbled until sulphur separation was complete. Removal of sulphur, subsequent concentration of the solution and cooling did not afford any crystalline material and hence it was diluted with water and examined as follows:

i) Treatment with sodium bicarbonate

To a portion of the solution obtained after reduction, saturated aqueous sodium bicarbonate solution was added and warmed. It was subsequently acidified and steam distilled. The oily droplets which were found in the distillate was extracted into ether and then treated with ammonia. Ethylthiourea was isolated and identified, m.p. and m.m.p. 113°C. The residual solution left behind in the flask after steam distillation did not afford any picrate when treated with picric acid. It is possible that ethylguanidine which should have been the other product decomposed during steam distillation.

ii) Oxidation with hydrogen peroxide

To another portion of the solution hydrogen peroxide (1 ml, 30%) was added. After a while, addition of picric acid to this solution afforded a picrate which crystallised from ethanol as shining needles, m.p. 156°C. It did not show
any depression in m.p. when mixed with the picrate of an authentic sample of 3-amino-4-ethyl-5-ethylimino-4,5-dihydro-1,2,4-thiadiazole.

Similarly the other 1,2,4-thiadiazoles (4b-d) were also reduced and the alkyl isothiocyanates formed were identified by converting them to the corresponding thioureas. (4d) gave benzylguanidine picrate, m.p. 186°.

III. A. FORMATION OF BIS(FORMAMIDINO) SULPHIDE DIHYDROCHLORIDES

a) Interaction of cyanamide with 1,3-dialkylthiourea

In a typical experiment, 1,3-diethylthiourea (6.6g, 0.05 mol) and cyanamide (2.1g, 0.05 mol) were mixed in acetone (200 ml) and dry hydrogen chloride gas was passed through the solution. A colourless crystalline material which separated was filtered, washed with dry acetone and dried (9.8g) m.p. 169°.

Other sulphide salts were also prepared in a similar fashion and they are listed in Table I.

b) Interaction of 1,3-dialkylcarbodiimides with thiourea

In a representative experiment, 1,3-diethylthiourea (6.6g, 0.05 mol) in acetone was dehydrsulphurised with yellow lead oxide. After filtration to remove lead sulphide
and unreacted lead oxide, thiourea (3.8g, 0.05 mol) was added to the filtrate. On passing dry hydrogen chloride gas through the solution, a white crystalline substance was obtained. It was collected, washed with dry acetone and dried (7.2g) m.p. 169°. It did not show any depression in melting point when mixed with the bis(formamidino) sulphide salt obtained in the above experiment.

Other similar compounds were obtained following the same procedure. In each case, the product was identical with the corresponding one obtained from the cyanamide-thiourea reaction.

B. CHEMICAL BEHAVIOUR OF BIS(FORMAMIDINO) SULPHIDE SALTS

1. Reduction

Amidino - (1,3-diethyl)amidino sulphide hydrochloride (3g) was dissolved in ethanol and hydrogen sulphide was bubbled through the solution for 3 hours. The solution was well concentrated, diluted with water (10 ml) and cooled in ice. The colourless shining crystals which separated (1.2g) were collected and identified as 1,3-diethylthiourea by determination of m.m.p. 72°. The unsubstituted thiourea formed in the solution was not isolated and identified, but its presence in the solution was detected by t.l.c.
The other monosulphides also behaved similarly in that they gave the corresponding dialkylthioureas (80% yield) when reduced with hydrogen sulphide in ethanolic solution.

2. Oxidation

A solution of the sulphide salt (3g) in aqueous ethanol was mixed with hydrogen peroxide and kept aside for two hours. Working up this did not yield any thia-diazole.

3. Decomposition in presence of sodium bicarbonate

On treatment with aqueous sodium bicarbonate solution the above sulphide hydrochloride, decomposed to give an oil with a pleasant odour. It was extracted with ether and after removal of ether, the oil which remained was treated with ammoniacal ethanol saturated with hydrogen sulphide. After 4 hr, excess hydrogen sulphide was boiled off and the alcoholic solution concentrated. The solid formed on cooling was crystallised from dilute ethanol, m.p. 72°. This was 1,3-diethylthiourea m.p. and m.m.p. 72°. 

4. Isomerisation of bis(formamidino) sulphide: Formation of 1-amidino-1,3-dialkylthiourea

The above amidino sulphide salt (3g) was refluxed
in ethanol (20 ml) for 3 hrs. The solution was then concentrated under reduced pressure and cooled. No crystalline material could be separated from the solution. The solution was decomposed with sodium bicarbonate solution to yield ethyl isothiocyanate. It was identified by its conversion to 1-ethylthiourea, m.p. and m.m.p. 113°.

C. CONVERSION TO 4-ALKYL-5-ALKYLIMINO-3-AMINO-4,5-DIHYDRO-1,2,4-THIADIAZOLE

In an experiment, the solution obtained after refluxing the sulphide in ethanol for 3 hrs was oxidised with hydrogen peroxide (2 ml, 30%). After a while, picric acid was added to this solution. The picrate formed was crystallised from ethanol as shining needles, m.p. 156°. It did not show any depression in melting point when mixed with the picrate of an authentic sample of 3-amino-4-ethyl-5-ethylimino-4,5-dihydro-1,2,4-thiadiazole.

All the other bis(formamidino) sulphide salt showed similar behaviour and the thiadiazoles were obtained following the above procedure.
### TABLE I

**CONDENSATION OF CARBODIIMIDES OR CYANAMIDES WITH THIOUREAS**

<table>
<thead>
<tr>
<th>Reactants</th>
<th>Sulphide salt formed</th>
<th>M.P. °C</th>
<th>Element analysis</th>
</tr>
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<tbody>
<tr>
<td>1,3-Diethylthiourea + cyanamide</td>
<td>C₆H₁₄N₄S.2HCl</td>
<td>169</td>
<td>Found N%</td>
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<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>22.5 13.2</td>
</tr>
<tr>
<td>1,3-Diethylcarbodiimide + thiourea</td>
<td>&quot;</td>
<td>169</td>
<td>Required N%</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td>22.7 13.0</td>
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<tr>
<td>1,3-Di-n-propylthiourea + cyanamide</td>
<td>C₈H₁₈N₄S.2HCl</td>
<td>170</td>
<td>Found S%</td>
</tr>
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<td></td>
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<td>11.4 20.4</td>
</tr>
<tr>
<td>1,3-Di-n-propylcarbodiimide + thiourea</td>
<td>&quot;</td>
<td>173</td>
<td>Required S%</td>
</tr>
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<td></td>
<td></td>
<td>11.6 20.4</td>
</tr>
<tr>
<td>1,3-Di-n-butylthiourea + cyanamide</td>
<td>C₁₀H₂₂N₄S.2HCl</td>
<td>171</td>
<td>Found N%</td>
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<td>18.1 18.5</td>
</tr>
<tr>
<td>1,3-Di-n-butylcarbodiimide + thiourea</td>
<td>&quot;</td>
<td>172</td>
<td>Required N%</td>
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<td></td>
<td></td>
<td>10.3 18.5</td>
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<tr>
<td>1,3-Dibenzylthiourea + cyanamide</td>
<td>C₁₆H₁₈N₄S.2HCl</td>
<td>185</td>
<td>Found S%</td>
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<td>8.5 15.1</td>
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<td>1,3-Dibenzylcarbodiimide + thiourea</td>
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<td>182</td>
<td>Required S%</td>
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<td></td>
<td>8.6 15.1</td>
</tr>
<tr>
<td>1,3-Diisopropylthiourea + cyanamide</td>
<td>C₈H₁₈N₄S.2HCl</td>
<td>168</td>
<td>Found N%</td>
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<td>20.5 20.4</td>
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<td>1,3-Diisopropylcarbodiimide + thiourea</td>
<td>&quot;</td>
<td>169</td>
<td>Required N%</td>
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<td>20.4 11.6</td>
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