CHAPTER TWO

OXIDATION OF MIXTURES OF 3-DIARYLTHIOUREAS
AND THIOUREA
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OXIDATION OF MIXTURES OF 2-DIARYLTHIOUREAS AND THIOUREA

INTRODUCTION

The products of oxidation of arylthioureas are greatly dependent on the polarity of the medium. (vide Chapter One). While oxidation of arylthioureas with bromine in non-polar medium like benzene or chloroform leads to the formation of 2-aminobenzothiazole derivatives (I),\(^{61,91-94}\) oxidation with bromine in polar medium like aqueous ethanol affords mainly thiadiazole (II)\(^{73-90,102,103,106}\) or 2-guanidobenzothiazole (III)\(^{74,93,99,103,112}\) derivatives. The following reaction sequence has been suggested for the oxidation in polar media:\(^{102,103,106,108,114}\)

\[
\begin{align*}
2 \text{ArNH-C-NHR} & \xrightarrow{\text{HX}} \text{ArNH-C-S-S-C-NHR}, \\
& \xrightarrow{\text{2HX}} \text{ArNH-C-S-C-NHR}, \\
& \xrightarrow{\text{isomerisation}} \text{ArNH-C-N-C-NHR}, \\
& \xrightarrow{\text{HX}} \text{ArNH-C-S-C-NHR}
\end{align*}
\]
In these oxidations in polar medium it is found that the final oxidation product (II or III) is built up from two thiourea molecules.\textsuperscript{102,103,103} It therefore appeared possible that either 1,2,4-thiadiazoles (II) or 2-guanidobenzothiazoles (III) could also be obtained by oxidising binary mixtures of thioureas where the final products are built up from the two constituent thioureas.

During the investigation on the structure of Hector's bases (II, Ar = aryl; R=H), the oxidation products of monoarylthioureas, to exclude the possibility of it having a 5-amino-2-aryl-3-arylimino-1,2,4-\textDelta^-thiadiazoline structure (VII), its synthesis was found necessary.\textsuperscript{113} These compounds were obtained by the oxidation of 1-(N,N'-diaryl amidino)-thioureas (VIII).\textsuperscript{113} Amidinothioureas (VIII) were in turn prepared by the interaction of cyanogen bromide with the respective 1,3-diarylguanidines followed by the thiohydrolysis of the resulting N,N'-diaryl-N''-cyanoguanidines (IX).
Oxidation of an equimolar mixture of α-diarylthiourea and thiourea in polar medium appeared to be an alternative and easier route to the thiadiazolene (VII), provided one molecule each of these thioureas was involved in the building up of the final oxidation product. However, the oxidation taking a different course, could lead to the formation of 3-amino-4-aryl-5-arylimino-1,2,4-Δ²-thiadiazolene (X), or N-2-benzothiazolyl-N-arylguanidine (XI) or 3-amidino-2-arylimino-benzothiazolene (XII).

(X - XII, (a) Ar = Phenyl (b) Ar = o-tolyl (c) Ar = p-tolyl)

The intermolecular ionic mechanism of oxidation of thioureas (vide Chapter One) favours the formation of a mixed oxidation product in addition to any independent oxidation products, when
RESULTS AND DISCUSSION

Oxidation of an equimolar mixture of 1,4-diphenylthiourea and thiourea in acid alcoholic medium with hydrogen peroxide yielded mainly a base, m.p. 185°C. The same base was obtained when an ethanolic solution of bromine or iodine was used as the oxidant. However, when iodine was used, the oxidation did not proceed to completion. The base obtained in these oxidations was found to be different from Hugershoff's base (III, $Ar=R=Ph$), the oxidation product of 1,4-diphenylthiourea in polar medium. From elemental analysis and also from the molecular weight (mass spectrum m/e 263) the molecular formula of the base was found to be $C_{14}H_{12}N_{4}S$. The base although isomeric with Necter's base (II, $Ar=Ph$; $R=H$), derived from phenylthiourea, was found to be different. It was also not identical with 5-amino-2-phenyl-3-phenylimino-1,2,4-$\Delta$-thiadiazoline (VII, $Ar=Ph$).

The base formed a monopicate and a monohydrochloride. It formed a nitroso derivative with nitrous acid. But the nitroso derivative decomposed on keeping and it could not be purified by crystallisation. The base did not form any benzoyl derivative under Schotten-Baumann conditions, unlike other aminothiadiazoles. Unlike Necter's bases, the base did not form any condensation product with phenylisocyanate,
phenylisothiocyanate or carbon disulphide even at elevated temperatures. It was found to be stable in boiling 5 N acid and 5 N alkali and could not be desulphurised with alkaline lead acetate. Its reduction with hydrogen sulphide in hydrochloric acid solution gave a pale yellow solution which decomposed on treatment with sodium bicarbonate into phenylguanidine carbonate and phenylisothiocyanate. On concentration under reduced pressure the pale yellow solution gave a sticky solid which formed a crystalline picrate. This picrate when oxidised with hydrogen peroxide yielded the picrate of the original base and when treated with sodium bicarbonate solution and acidified yielded phenylguanidine picrate and phenylisothiocyanate. Hence the reduction product could be formulated as 1-amidino-1,3-diphenylthiourea hydrochloride (XIIa). The facile interconversion between this amidinothiourea salt (XIIia) and the original base leads to the assignment of a 3-amino-4-phenyl-5-phenylimino-1,2,4-\( \Delta^2 \)-thiadiazoline (Xa) or a tautomeric 3-imino-4-phenyl-5-phenylimino-1,2,4-thiadiazolidine (XIVa) structure for the latter.

\[
\begin{align*}
\text{ArNH-S-N-C-NH}_2, \text{HCl} & \xrightarrow{1) \text{H}_2\text{O}_2} \xrightarrow{2) \text{OH}_2\text{O}} \\
\text{XIII} & \xrightarrow{\text{Na}_2\text{CO}_3} \\
\text{ArNOS} + \text{ArNH-C-NH}_2, \text{HCO}_3 & \xrightarrow{\xrightarrow{\text{H}_2\text{S/HCl}}}
\end{align*}
\]
This conclusion is based on the observation that similar reduction of Hector's bases (II) yields 1-aryl-1-arylamidinothiourea salts (XV) which decompose on treatment with alkali into 1,3-diarylguanidine and thiocyanic acid.\(^{102,103}\)

Reduction of the base with alcoholic ammoniacal hydrogen

\[
\text{Ar-N-C=NAr} \xrightarrow{\text{Sn/HCl}} \text{ArNH-C-N-C-NHNR, HCl} \rightarrow \text{ArNH-C-NHAr+HCl}\]

(Ar = aryl
R = hydrogen)

sulphide gave phenylguanidine and phenylthiourea. This also is in accord with the assigned structure Xa or the tautomeric structure XIVa.

Similar oxidation of binary mixtures of 2-di-o-tolyl- and 2-di-p-tolyl-thioureas and thiourea also yielded bases (Xb,c or XIVb,c) analogous to 3-amino-4-phenyl-5-phenylimino-1,2,4-\(\Delta^1\)-thiadiazoline (Xa) or its tautomer (XIVa). Reduction of these bases with hydrogen sulphide in hydrochloric acid solutions yielded 1-amidino-1,3-diarylthiourea hydrochlorides (XIIIb and XIIIc) which could be oxidised back to the original bases. These amidinothiourea hydrochlorides (XIIIb and XIIIc) on treatment with sodium bicarbonate decomposed giving the corresponding arylguanidines and arylisothiocyanates. Reduction of the bases with ammoniacal hydrogen sulphide yielded arylguanidines and arylthioureas, similar to the phenyl analogue.
Fig. 1. Infrared spectrum of 2-phenoxycarbonyl-1-phenylalanine-
1,2,4-6'-trimethoxystilbene in neat.

Fig. 2. N.m.r. spectrum of 2-phenylimidazole-1-phenylalanine-
1,2,4-6'-trimethoxystilbene.
Fig. 3. N.M.R. spectrum of 3-amino-4-µ-tolyl-5-µ-tolylindole.

Fig. 4. N.M.R. spectrum of 3-amino-4-µ-tolyl-5-µ-tolylindole.
In all the three cases, although the thiadiazoline structure (X) as well as the thiadiazolidine structure (XIV) could explain the formation of the reduction products in acidic and ammoniacal media, the spectral data are in conformity with the former.

The i.r. spectra of these bases show great similarity to one another (The i.r. spectrum of the phenyl analogue is given in Fig.1). They show similar finger-print region bands. They do not show any absorption characteristics of benzothiazolylguanidines. The characteristic ring skeletal vibrations of 1,2,4-\(4\)-thiadiazolines are to be found at 1030-1020 cm\(^{-1}\) and 825-310 cm\(^{-1}\) and all these compounds exhibit weak or medium absorptions in the above regions. A large number of medium and weak absorption bands are found in the finger-print regions due to the aromatic substituents. All these compounds show N-H stretching vibration bands of medium intensity around 3400 and 3150 cm\(^{-1}\). The position of these bands and their intensities indicate primary amide-like character which is also suggested by the absence of condensation products of these bases with carbon disulphide and phenylisothiocyanate. The strong absorptions around 1650-1590 cm\(^{-1}\) can be considered due to NH\(_2\) scissoring vibrations. Thus the i.r. spectra favour thiadiazoline (X) rather than thiadiazolidine (XIV) structure. The i.r. data are presented in Table 2A.
Fig. 7. Mass Spectrum of 3-aminobenzyl-3-methylbenzylamine-1,2,5-2-thiodianolane.
Fig. 5. Mass Spectrum of 3-Phenyl-4-phenyl-5-phenyltriazine

Fig. 6. Mass Spectrum of 3-Methyl-5-methyl-5-methyltriazine

3,2,1,4-Phthaldiazine
The n.m.r. spectra (Figs. 2-4) favour the thiadiazoline structure (X) for these bases. The ratio of the amino protons to the aromatic protons (1:5 for the phenyl analogue and 1:4 for the tolyl derivatives) agrees with the thiadiazoline structure (X) and rules out the benzothiazolylguanidine structure (XI).

The mass spectra (Figs. 5-7) of these bases agree with the structures assigned to them. Similar to the $^2\Delta$-thiazolines,$^{121}$ the thiadiazoline system can undergo fragmentation by the following routes (A - E) and the products can be represented as:

\[ \text{Ar-N} \quad \text{C-NH}_2 \quad \rightarrow \quad \text{Ar-N} \quad \text{C=NAr} \quad \rightarrow \quad \text{Ar-N} \quad \text{C-NH}_2 \]

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

\[ \text{Ar-N} \quad \text{C-NH}_2 \quad \rightarrow \quad \text{Ar-N=C=S} \quad + \quad \text{Ar-N} \quad \text{C-NH}_2 \]
Peaks corresponding to all these ions besides the $M^+$ peaks are found in the mass spectra of all these bases (Figs. 5-7). The two peaks with tentative structures $(Ar\text{N}=\text{C}=\text{NH})^{++}$ and $(\text{N}=\text{C}=\text{NH})^{++}$ appear to be of high diagnostic value in assigning the positions of the aryl substituents. In the case of the phenyl analogue the base peak is due to the molecular ion at $m/e$ 263, whereas for the tolyl analogues the base peaks are found at $m/e$ 211. The peaks at $m/e$ 91 in the tolyl bases is due to the formation of the tropilium cation $C_7H_7^+$. The absence of any fragment with $m/e$ 134 in the mass spectrum rules out a benzothiazolyl structure (XIa) for the phenyl derivative, as such a molecule would be expected to give this fragment by the following mode of fragmentation:

$m/e$ 134

\[ \text{XIa} \]

*Fragment ions formed by paths D and E are represented for convenience like this.*
In the spectra of the tolyl analogues also no peak (m/e 148) corresponding to ions formed by fragmentation of a benzo-thio-
zolyl structure (XIIb or XIIc) is observed.

The intermediate oxidation products viz. 1-amidino-
1,3-diaryliourea hydrochlorides (XIIIa-c) were also obtained
1) by the half-way oxidation of equimolar binary mixtures of
3-diaryliourea and thiourea with hydrogen peroxide; 2) by
the interactions of 3-tetraaryldithioformamidine dihydrochlorides
(XVI) with dithioformamidine dihydrochloride (XVII) and with thiourea and 3) by the interactions of dithioformamidine
dihydrochloride (XVII) with 3-diarylioureas.

\[
\begin{align*}
\text{ArNH-C-S-S-C-NHAr, 2HCl} & \quad \text{NH}_2-C-S-S-C-NH_2, 2\text{HCl} \\
\text{XVI} & \quad \text{XVII}
\end{align*}
\]

Although the interaction of 3-tetraaryldithioformamidine
salt (XVI) and dithioformamidine salt (XVII) resulted in the
formation of the mixed amidinothiourea salt (XIII), a similar
interaction between 3-tetraaryldithioformamidine hydrochloride
(XVIII) and thioformamidine dihydrochloride (XIX) failed
to give XIII.

\[
\begin{align*}
\text{ArNH-C-S-S-C-NHAr, HCl} & \quad \text{NH}_2-C-S-S-C-NH_2, 2\text{HCl} \\
\text{XVIII} & \quad \text{XIX}
\end{align*}
\]

Based on the above observations a reasonable mechanism
for the formation of these thiadiazolines is outlined along the
same lines as suggested for the formation of Hock's bases (II) from arylthioureas\textsuperscript{102,103,106} and Hugershoff's bases (III) from $\pi$-diarylthioureas.\textsuperscript{103,114} In the oxidations of binary mixtures of thioureas, the initial product is probably a disulphide of the type (XX) or (XVI) and (XVII). The disulphide (XX) disproportionates into a molecule each of diarylcarbodiimide and thiourea or/and $\pi$-diarylthiourea and cyanamide, besides sulphur and hydrogen chloride (Chart I). The disproportionation of XVI and XVII could result in the formation

**CHART I**

\[
\begin{align*}
\text{ArNH}_2\text{C}=\text{NH}_2 + \text{NH}_2\text{C}=\text{NH}_2 & \xrightarrow{\text{H}_2\text{O}_2} \text{ArNH}_2\text{C}=\text{S}=\text{S}=\text{C}=\text{NH}_2 \cdot 2\text{HCl} \\
\text{ArN}=\text{C}=\text{NAR} + \text{NH}_2\text{C}=\text{NH}_2 + 2\text{HCl} + \text{S} & \xrightarrow{} \text{ArNH}_2\text{C}=\text{NAR} + \text{NH}_2\text{CN} + 2\text{HCl} + \text{S} \\
\text{ArNH}_2\text{C}=\text{S}=\text{S}=\text{C}=\text{NH}_2 & \xrightarrow{\text{HCl}} \text{ArNH}_2\text{C}=\text{NAR} \cdot \text{NH}_2 \\
\end{align*}
\]

**CHART II**

\[
\begin{align*}
2 \text{ArNH}=\text{C}=\text{NHAR} & \xrightarrow{} \text{ArNH}=\text{C}=\text{S}=\text{S}=\text{C}=\text{NHAR} \cdot 2\text{HCl} \\
\text{ArN}=\text{C}=\text{NAR} + \text{ArNH}=\text{C}=\text{NHAR} & \xrightarrow{\text{HCl}} \text{ArNH}=\text{C}=\text{NAR} + \text{NH}_2\text{CN} + 2\text{HCl} + \text{S} \\
2\text{NH}_2\text{C}=\text{NH}_2 & \xrightarrow{} \text{NH}_2\text{C}=\text{S}=\text{S}=\text{C}=\text{NH}_2 \cdot 2\text{HCl} \\
\text{NH}_2\text{C}=\text{NH}_2 + \text{NH}_2\text{CN} + 2\text{HCl} + \text{S} & \xrightarrow{} \text{NH}_2\text{C}=\text{NH}_2 + \text{NH}_2\text{CN} + 2\text{HCl} + \text{S} \\
\text{ArNH}=\text{C}=\text{NAR} + \text{NH}_2\text{CN} & \xrightarrow{\text{HCl}} \text{ArNH}=\text{C}=\text{S}=\text{S}=\text{C}=\text{NH}_2 \cdot \text{HCl} \\
\text{ArN}=\text{C}=\text{NAR} + \text{NH}_2\text{C}=\text{NH}_2 & \xrightarrow{\text{HCl}} \text{ArNH}=\text{C}=\text{S}=\text{S}=\text{C}=\text{NH}_2 \cdot \text{HCl} \\
\end{align*}
\]
of diarylcarbodiimide, \( \text{g-diarylthiourea}, \text{thiourea and cyanamide} \) in the reaction mixture (Chart II). Interaction of \( \text{g-diarylthiourea} \) with cyanamide as well as that of diarylcarbodiimide with thiourea in presence of hydrochloric acid could then lead to the formation of a mixed thioformamidine salt (XXI). The fact that a mixed thioformamidine (XXI) only could yield the mixed amidinothiourea salt (XIII) is in agreement with the intra-molecular mechanism proposed for the rearrangement of the thioformamidine salt (XXI). The thioformamidine (XXI) could undergo rearrangement to amidinothiourea XIII or XXII. XIII alone on further oxidation could give the thiadiazoline (X). Hence the rearrangement proceeds via route (i). If, on the other hand, the rearrangement proceeded via route (ii), it would have given the amidinothiourea salt (XXII) and finally the thiadiazoline (VII) by further oxidation (Chart III). It has always been observed that in such rearrangements of thioformamidines to amidinothioureas, the amidino group migrates preferentially to a nitrogen which bears an aryl group.\(^{110,111,115}\)

**Chart III**

\[
\begin{align*}
\text{ArNH-} & \text{-C-S-C-NH}_2, \text{HCl} \xrightarrow{(1)} \text{ArNH-} & \text{-C-N-C-NH}_2, \text{HCl} \xrightarrow{2)} \text{OH} \\
\text{XXII} \quad [\text{iii}] & \quad \text{XIII} \\
\text{ArNH-C-NH-} & \text{-C-NH}_2, \text{HCl} \xrightarrow{1)} \text{H}_2\text{O}_2 \quad \text{ArN=}& \text{-C}-\text{NH}_2 \\
\text{XXII} \quad \text{VII}
\end{align*}
\]
A synthesis of the thiadiazoline (X) was performed, along the same route by which a synthesis of Hector's base (XII) was achieved. Cyanamides and carbodiimides condensed with thioureas in presence of hydrochloric acid to form the related amidinothiourea salts. Condensations of (i) \( g \)-diaryldithiourea with cyanamide and (ii), diarylcarbodiimide with thiourea should give the same amidinothiourea salt (XIII) via the labile intermediate thioformamidine salt (XXI) if the mechanism envisaged above holds good (Charts II and III). In fact this expectation was realised, since both condensations yielded the same amidinothiourea salt (XIII). Oxidation of the amidinothiourea salts (XIIIa-c) obtained as above gave the thiadiazoline bases (Xa-c). These synthetic products were identical with the products of mixed oxidations.

**EXPERIMENTAL**

The required \( g \)-diaryldithioureas were prepared according to known procedure and the samples purified by recrystallisation from ethanol. The dithioformamidine salts (XVI, and XVII) were prepared by oxidising the appropriate thioureas with thionylchloride in chloroform medium.

The infrared spectra were run on Perkin-Elmer (137 and 700) spectrophotometers and the n.m.r. spectra were taken on a DP 60 Varian model spectrometer using deuterochloroform as the
solvent and tetramethylsilane as the internal standard. Mass spectra were taken on a Varian MAT CH-7 instrument operating at 70 ev. The inlet temperature was below 60°C and direct inlet system was made use of. Melting points were determined on a hot stage and are uncorrected.

II.1. OXIDATION OF BINARY MIXTURES OF 2-DIARYLTHIOUREAS AND THIOUREA: FORMATION OF 3-AMINO-4-ARYL-5-ARYLIMINO-1,2,4-$\Delta^2$-THIADIAZOLINES (Xa-c)

A) WITH HYDROGEN PEROXIDE

A finely powdered mixture of 2-diphenylthiourea (11.4g, 0.05M) and thiourea (3.8g, 0.05M) was suspended in 50% ethanol (200 ml) containing conc. hydrochloric acid (12 ml) and oxidised with hydrogen peroxide (20V, 60-70 ml). During the addition of hydrogen peroxide the reaction mixture warmed up and the thioureas gradually went into solution. It was then allowed to stand for 30 minutes with occasional stirring. Separation of sulphur was found to be complete during this period, which indicated the completion of the reaction. The mixture was then diluted with water (300 ml) and the precipitated sulphur filtered off. On basification of the filtrate a white fluffy precipitate was obtained. It was filtered, washed with water and finally extracted with dilute hydrochloric acid (0.05 M). The residue was mostly sulphur and traces of Hugershoff's base (III, Ar=R=Ph) (on removal of sulphur by
washing with carbon disulphide and recrystallisation from ethanol (m.p. 136°C). The hydrochloric acid extract was then basified and the precipitate (9g., 67%) collected and repeatedly crystallised from ethanol to constant melting point, when white shining plates of 3-amino-4-phenyl-5-phenylimino-1,2,4-Δ²-thiadiazoline (Xa) were obtained m.p. 185°C.*

B) OXIDATION WITH BROMINE

A suspension of 8-diphenylthiourea (11.4g, 0.05 M) and thiourea (3.8g, 0.05 M) in 50% ethanol (200 ml) was warmed to 60-80°C and a solution of bromine (16g, 0.1 M) in ethanol (75 ml) was added gradually with good stirring. During this period sulphur was found to separate slowly. Addition of bromine was stopped when its colour was no longer discharged. The mixture was then diluted with water (200 ml) and treated with sodium bisulphite solution to remove the excess of bromine. The precipitated sulphur was filtered off and the filtrate basified with ammonia. The precipitate formed was filtered and extracted with dilute hydrochloric acid (0.05 M). Basification of this acidic extract with ammonia gave a white fluffy precipitate (9.5g, 71%) which on repeated crystallisation from ethanol gave white shining plates of Xa, m.p. 185°C.

C) OXIDATION WITH IODINE

A suspension of 8-diphenylthiourea (11.4g, 0.05 M) and thiourea (3.8g, 0.05 M) in 50% ethanol (200 ml) containing

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*Purity of this as well as the other bases was confirmed by TLC experiments.
strong hydrochloric acid (12 ml) was warmed to 60-30°C and a solution of iodine (25.4 g, 0.1 M) in ethanol added slowly with stirring till the iodine colour persisted. The mixture was diluted with water and allowed to stand for 30 minutes. Excess iodine was removed by treatment with sodium bisulphite and the solution filtered. The residue contained unreacted 2-di-phenylthiourea (2.5 g) besides sulphur and traces of Bugershoff's base (III). The filtrate was then basified, the precipitate collected and extracted with dilute hydrochloric acid (0.05 N). Basification of the acidic extract gave a white fluffy precipitate (6.1 g, 45.5%) which on crystallisation from ethanol gave shining plates of Xa, m.p. 185°C.

DERIVATIVES:

Picrate - An alcoholic or dilute acid solution of the base when mixed with picric acid immediately formed a picrate. This when recrystallised from ethanol gave shining yellow plates m.p. 227°C (Found: N, 19.9; C₁₄H₁₂N₄S. C₆H₃N₂O₂ requires N, 19.7%).

Nitroso derivative - An ice cold solution of the base in dilute hydrochloric acid was treated with sodium nitrite, when a nitroso derivative was thrown out. This nitroso derivative could not be crystallised from any solvent, as it decomposed gradually. The crude sample after washing successively with dilute acid and water melted with decomposition at 68°C.
Hydrochloride - When dry hydrogen chloride gas was passed through a solution of the base in dry benzene, a monohydrochloride was obtained, m.p. 212°C (Eq. wt. found: 309; C₁₄H₁₂N₄S (HCl requires 304.5)).

Acyl derivative - The base did not form any benzoyl derivative under Schotten-Baumann conditions. Refluxing the base with acetic anhydride and glacial acetic acid did not yield any acetyl derivative also.

The base did not form any condensation product with phenylisocyanate, phenylisothiocyanate or carbon disulphide even after prolonged heating on a steam bath. Heating the base (1g) with hydrochloric acid (5N, 50 ml) for two hours and subsequent working up yielded the starting material only. Similar heating of the base with sodium hydroxide (5N) and working up also gave the starting material only.

Oxidation of binary mixtures of p-di-p-tolyl- and p-di-p-tolyl-thioureas and thiourea under similar conditions gave the corresponding 3-amino-4-aryl-5-arylimino-1,2,4-Δ²-thiadiazolines (Xb,c) which are listed in Table I. I.r. and n.m.r spectral characteristics of these thiadiazolines are given in Tables II A and II B respectively.

II.2. REDUCTION OF 3-AMINO-4-ARYL-5-ARYLIMINO-1,2,4-Δ²-
THIADIAZOLINES (Xa-c) WITH HYDROGEN SULPHIDE IN HYDRO-
CHLORIC ACID SOLUTIONS: FORMATION OF 1-AMINO-1,3-
DIARYLTHIOUREA HYDROCHLORIDES (XIIa-c)

A) REDUCTION OF 3-AMINO-4-PHENYL-5-PHENYLIMINO-1,2,4-Δ²-
THIADIAZOLINE (Xa)

A slow stream of hydrogen sulphide was bubbled through
# Table I

**Oxidation of Binary Mixtures of $s$-Diarylthioureas and Thiourea**

<table>
<thead>
<tr>
<th>No.</th>
<th>Thioureas oxidised</th>
<th>3-Amino-1,2,4-$\Delta^2$-thiadiazolines formed</th>
<th>Yield*</th>
<th>M.p. °C</th>
<th>Analysis</th>
<th>Nitroso derivative m.p. °C</th>
<th>Hydrochloride Equivalent wt.</th>
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<td></td>
<td></td>
<td></td>
<td>Found</td>
<td>Required</td>
<td></td>
<td>M.p. °C</td>
<td>Found Required</td>
</tr>
<tr>
<td>1</td>
<td>$s$-Diphenylthiourea + thiourea</td>
<td>4-Phenyl-5-phenyl-imino-</td>
<td>67</td>
<td>185</td>
<td>0.628, 0.627</td>
<td>227, 68**</td>
<td>212, 309</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>H, 4.6, H, 4.5</td>
<td>N, 20.9, N, 20.9</td>
<td>S, 12.0, S, 11.9</td>
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<tr>
<td>2</td>
<td>$s$-Di-$p$-tolylthiourea + thiourea</td>
<td>4-$p$-tolyl-5-$p$-tolylimino-</td>
<td>67</td>
<td>189</td>
<td>0.651, 0.649</td>
<td>176, 75**</td>
<td>96**, 335</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td>H, 5.3, H, 5.4</td>
<td>N, 19.1, N, 18.9</td>
<td>S, 11.0, S, 10.8</td>
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<tr>
<td>3</td>
<td>$s$-Di-$o$-tolylthiourea + thiourea</td>
<td>4-$o$-tolyl-5-$o$-tolylimino-</td>
<td>71</td>
<td>179</td>
<td>0.648, 0.649</td>
<td>226, 87**</td>
<td>224, 338</td>
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<td>H, 5.2, H, 5.4</td>
<td>N, 19.0, N, 18.9</td>
<td>S, 11.1, S, 10.8</td>
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</table>

*Yields are for oxidation with hydrogen peroxide

**Melts with decomposition.
<table>
<thead>
<tr>
<th>No.</th>
<th>3-Amino-1,2,4-Δ2-thiadiazoline</th>
<th>Absorption peaks (cm⁻¹)</th>
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<tr>
<td>1.</td>
<td>4-phenyl-5-phenylimino</td>
<td>3400m; 3150m; 1640s; 1625s; 1590s; 1550s; 1500m; 1435m; 1300m; 1240m; 1160m; 1145w; 1130m; 1105m; 1075m; 1020m; 995w; 915m; 883w; 850w; 830m; 810w; 775m; 760m; 705m.</td>
</tr>
<tr>
<td>2.</td>
<td>4-2-tolyl-5-2-tolylimino</td>
<td>3400m; 3150m; 1650-1590s; 1490m; 1465w; 1350m; 1300m; 1250w; 1160m; 1120m; 1010m; 990w; 900w; 870w; 825w; 800w; 760m.</td>
</tr>
<tr>
<td>3.</td>
<td>4-p-tolyl-5-p-tolylimino</td>
<td>3400m; 3150m; 1650-1590s; 1500m; 1440b; 1320m; 1250m; 1170w; 1145m; 1115m; 1080m; 1025m; 870m; 790w; 750w; 700m.</td>
</tr>
</tbody>
</table>

s = strong  
m = medium  
w = weak  
b = broad
<table>
<thead>
<tr>
<th>No.</th>
<th>3-Amino-1,2,4-Δ²-thiadiazoline</th>
<th>Chemical shifts in T scale</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>4-phenyl-5-phenylimino-</td>
<td>2.70, C-H aromatic (10 protons); 5.40, N-H (2 protons).</td>
</tr>
<tr>
<td>2.</td>
<td>4-α-tolyl-5-α-tolylimino-</td>
<td>2.76, C-H aromatic (8 protons); 5.20, N-H (2 protons); 7.60, C-H, methyl of 4-α-tolyl (3 protons); 7.80, C-H, methyl of 5-α-tolylimino (3 protons).</td>
</tr>
<tr>
<td>3.</td>
<td>4-α-tolyl-5-α-tolylimino-</td>
<td>2.80, C-H aromatic (8 protons); 5.23, N-H (2 protons); 7.57, C-H, methyl of 4-α-tolyl (3 protons); 7.70, C-H, methyl of 5-α-tolylimino (3 protons).</td>
</tr>
</tbody>
</table>
a solution of the base (2.7 g, 0.01 M) in dilute hydrochloric
acid (0.2 N, 100 ml) for 15 minutes. The precipitated sal
was filtered off and the pale yellow solution concentrated to
about 10 ml by evaporation under reduced pressure at 40-60°C.
On cooling 1-amidino-1,3-diphenylthiourea hydrochloride sepa-
rated as a sticky solid. It could not be crystallised from
any solvent due to its gradual decomposition into phenylisothi-
cyanate and phenylguanidine hydrochloride. The sticky
solid when dissolved in water (25 ml) and treated with aqueous
picric acid gave 1-amidino-1,3-diphenylthiourea picrate (2.7g).
Recrystallisation from ethanol yielded bright yellow needles,
m.p. 196°C (Found: N, 19.9%; C_{14}H_{14}N_{4}S, C_{6}H_{3}N_{0} requires
N, 19.6%).

A portion of the picrate (1g) suspended in water (25 ml)
containing strong hydrochloric acid (1 ml) was treated with hydro-
peroxide (20% 2 ml) and the mixture stirred for 5 minutes.
The picrate was then filtered and crystallised from ethanol when
the picrate of the thiadiazoline Xα (0.7g) was obtained, m.p.
and mixed m.p. 227°C.

The amidinothiourea picrate (1g) when stirred with
excess of saturated sodium bicarbonate solution decomposed
almost instantaneously into phenylisothiocyanate and phenyl-
guanidine. The mixture was then acidified with dilute hydro-
chloric acid and filtered. The yellow residue was washed with
water (50 ml) and then with ether (40 ml) and crystallised
from ethanol (10 ml). It was identified as phenylguanidine picrate, m.p. and mixed m.p. 223°C. The other washings were treated with strong ammonia when colourless crystals of phenylthiourea (m.p. and mixed m.p. 154°C) were obtained.

B) **REDUCTION OF 3-AMINO-4-O-TOLYL-5-O-TOLYLIMINO-1,2,4-Δ2-

THIADIAZOLINE (Xb)**

A solution of the thiadiazoline, Xb, (3g, 0.01 M) in dilute hydrochloric acid (0.2 N, 100 ml) was reduced with hydrogen sulphide as before. When the reduction was complete sulphur formed was filtered off and the solution evaporated to 20 ml under reduced pressure, when 1-amidino-1,3-di-o-tolylnitriourea hydrochloride (XIIIb) started separating. The crystals (1.1g) were collected, dissolved in water (25 ml) and reprecipitated by adding strong hydrochloric acid. The amidinothiourea hydrochloride (XIIIb) was obtained as colourless cubes, m.p. 112°C; picrate, m.p. 135°C (Found: N, 16.5; S, 9.9; Cl, 10.6%. C₁₆H₁₃N₄S·HCl requires N, 16.7; S, 9.6; Cl, 10.6%). Oxidation of an aqueous solution of this amidinothiourea salt (XIIIb) with hydrogen peroxide yielded thiadiiazoline (Xb), m.p. and mixed m.p. 139°C. Decomposition of XIIIb with sodium bicarbonate solution yielded o-tolylisothiocyanate (identified as o-tolylthiourea, m.p. 162°C) and o-tolylguanidine (identified as picrate m.p. and mixed m.p. 223°C).
C) REDUCTION OF 3-AMINO-4-P-TOLYL-5-P-TOLYLIMINO-1,2,4-Δ^2-
THIAZOLINE (Xc)

Reduction of the thiaazoline (Xc) and subsequent work up as in the above case yielded pale yellow cubes of 1-amidino-1,3-di-p-tolylthiourea hydrochloride (XIIIc), m.p. 122°C; picrate, m.p. 185°C (Found: N, 16.5; S, 9.7; Cl, 10.6; \( \text{C}_16\text{H}_{18}\text{N}_4\text{S} \cdot \text{HCl} \) requires N, 16.7; S, 9.6; Cl, 10.6%). Its oxidation gave back the thiaazoline (Xc) and decomposition with sodium bicarbonate gave p-tolylisothiocyanate (identified as p-tolylthioureia, m.p. 183°C) and p-tolylguanidino (identified as p-tolylguanidine picrate, m.p. 229°C).

II.3. REDUCTION OF 3-AMINO-4-ARYL-5-ARYLIMINO-1,2,4-Δ^2-
THIAZOLIDINES (Xa-c) WITH AMMONIACAL HYDROGEN SULPHIDE

Hydrogen sulphide was bubbled through a solution of the thiaazoline, Xa, (2g) in ethanol (150 ml) containing liquor ammonia (50 ml) for about an hour. The mixture was occasionally warmed during the reaction. Ethanol was then evaporated off and the residue extracted with ether. The ethereal extract was evaporated and leached with hot water. The material (0.2g) left behind was found to be unchanged base, m.p. 185°C. The aqueous extract obtained here on treatment with aqueous picric acid, gave phenylguanidine picrate, m.p. and mixed m.p. 223°C. The residue left after extraction with ether was digested with boiling water and
the solution filtered. This filtrate on cooling gave needles of phenylthiourea m.p. 154°C (0.68g).

Reduction of the thiadiazolines (Xb,c) also with ammoniacal hydrogen sulphide gave the corresponding aryl-guanidines and arylthioureas.

II.4. HALF-WAY OXIDATION OF BINARY MIXTURES OF 2-DIARYLTHIOUreas AND THIOUREA: FORMATION OF 1-AMIDINO-1,3-DIARYLTHIOUrea HYDROCHLORIDES (XIIIa-c).

A suspension of finely powdered, 2-diphenylthiourea (11.4g, 0.05 M) and thiourea (3.3g, 0.05 M) in 50% ethanol (200 ml) containing strong hydrochloric acid (12 ml) was treated with hydrogen peroxide (20V; 30 ml) and warmed over a water-bath at 60-80°C. The thioureas went into solution and sulphur gradually separated. After warming for 5-10 minutes, the precipitated sulphur was filtered off. The pale yellow filtrate was concentrated under reduced pressure to 15 ml when a sticky solid separated. It was extracted with cold water. The aqueous extract decomposed into phenylguanidine carbonate and phenylisothiocyanate when treated with sodium bicarbonate. It did not yield any solid hydrochloride on concentration, but yielded a picrate which was identified as crude picrate of 1-amidino-1,3-diphenylthiourea, as there was no depression in melting point when mixed with the picrate obtained in II.2.A.
Similar half-way oxidation of binary mixtures of $a$-di-$o$-tolyl- and $a$-di-$p$-tolyl-thioureas and thiourea with hydrogen peroxide and subsequent work-up gave pale yellow solutions which on concentration under reduced pressure yielded the corresponding 1-amidino-1,3-diarylthiourea hydrochlorides (XIIIb,c).

**II.5. INTERACTIONS OF $a$-TETRAARYL DITHIOFORMAMIDINE DIHYDROCHLORIDES (XVIa-c) WITH DITHIOFORMAMIDINE DIHYDROCHLORIDE (XVII): FORMATION OF 1-AMIDINO-1,3-DIARYLTHIOUREA HYDROCHLORIDES (XIIIa-c)**

An intimate mixture of $a$-tetraphenyl dithioformamidine dihydrochloride, XVIa, (13.2 g, 0.025 M) and dithioformamidine dihydrochloride, XVII, (5.6 g, 0.025 M) was dissolved in ethanol (50 ml) and stirred well. The mixture was allowed to remain for 5 minutes and then warmed over a water-bath at 60-80°C. It was cooled, diluted with water (100 ml) and the precipitated sulphur filtered off. The pale yellow filtrate was concentrated under reduced pressure, when a sticky solid separated. It was extracted with cold water. The aqueous extract showed the presence of 1-amidino-1,3-diphenylthiourea hydrochloride (XIIIa) *(vide Section II.4.)*.

Similar interactions of $a$-tetra-$o$-tolyl dithioformamidine dihydrochloride (XVIb) and $a$-tetra-$p$-tolyl dithioformamidine dihydrochloride (XVIc) with dithioformamidine dihydrochloride (XVII) and subsequent work-up yielded the corresponding 1-amidino-1,3-diarylthiourea hydrochlorides (XIIIb,c).
II.6. INTERACTIONS OF DITHIOFORMAMIDINE DIHYDROCHLORIDE (XVII) WITH 2-DIAZARYLTHIOUREAS: FORMATION OF 1-AMIDINO-1,3-DIARYLTHIOUREA HYDROCHLORIDES (XIIIa-c)

A mixture of dithioformamidine dihydrochloride (5.6g, 0.025 M) and 2-diphenylthiourea (5.7g, 0.025 M) was dissolved in ethanol (50 ml) with vigorous stirring. The mixture was heated on a water bath for 30 minutes, cooled, diluted with water (100 ml) and the precipitated sulphur and unchanged 2-diphenylthiourea filtered off. The pale yellow filtrate was concentrated by evaporation under reduced pressure and the sticky solid that separated was collected and extracted with cold water. The aqueous extract so obtained showed the presence of the amidinothiourea salt (XIIIa) (vide Section II.4).

Similar interactions of dithioformamidine dihydrochloride with 2-di-o-tolylthiourea and 2-di-p-tolylthiourea and subsequent work-up yielded the corresponding 1-amidino-1,3-diarylthiourea hydrochlorides (XIIIb,c).

II.7. INTERACTIONS OF 2-TETRAMETHYLTHIOFORMAMIDINE DIHYDROCHLORIDES (XIVA-c) WITH THIOUREAS: FORMATION OF 1-AMIDINO-1,3-DIARYLTHIOUREA HYDROCHLORIDES (XIIIIa-c)

Interactions of 2-tetraphenyl-, 2-teta-o-tolyl- and 2-teta-p-tolyl- dithioformamidine dihydrochlorides (XVIa-c) with thiourea in ethanol, carried out as in the previous experiments were found to yield the corresponding 1-amidino-1,3-diarylthiourea hydrochlorides (XIIIa-c) in solution. The
amidinothiourea salts (XIIb,c) were isolated as in the previous cases.

II.3. INTERACTION OF 5- TETRA PHENYLTHI OFORMAMIDINE HYDROCHLORIDE (XVIIIa) WITH THIOFORM AMIDINE DIHYDROCHLORIDE (XIX)

A mixture of 5-tetraphenylthioformamidine hydrochloride (11.5g, 0.025 M) and thiourea hydrochloride (1.53g, 0.025 M) was stirred with ethanol (50 ml) for 5 minutes and then warmed at 60-80°C over a water-bath for another 5 minutes. It was diluted with water (100 ml) and filtered. The filtrate decomposed on evaporation under reduced pressure giving phenylisothiocyanate and triphenylguanidine. Oxidation of a portion of the filtrate with hydrogen peroxide and subsequent basification yielded N-2-benzothiazolyl-N""-triph enylguanidine (III, Ar=Phenyl), m.p. and mixed m.p. 136°C.

II.4. SYNTHESIS OF 3-AMINO-4-ARYL-5-ARYLIMINO-1,2,4-Δ²-
THIADIAZOLINES (Xa-c)

A) 3-AMINO-4-PHENYL-5-PHENYLIMINO-1,2,4-Δ²-THIADIAZOLINE (Xa)

A solution of 5-diphenylthiourea (10g) in dry acetone (200 ml) was dehydro sulphurised with lead monoxide to diphenylcarbodiimide. Thiourea (3g) was then added to the acetone solution and dry hydrogen chloride passed through it. The sticky solid that separated was collected and extracted with cold water. The pale yellow aqueous extract on treatment with
picric acid afforded the picrate of 1-amidino-1,3-diphenylthiourea, m.p. 194-196°C (undepressed on mixing with the picrate obtained in Section II.2.A). This picrate on oxidation with hydrogen peroxide gave the picrate of 3-amino-4-phenyl-5-phenylimino-1,2,4-Δ²-thiadiazoline (Xa), m.p. and mixed m.p. 227°C.

A solution of cyanamide obtained by the dehydrotrisulphurisation of thiourea (4g) was mixed with s-diphenylthiourea (1g) in dry acetone (100 ml) and treated with dry hydrogen chloride. The solid products separated were collected and extracted with water. The pale yellow aqueous extract when treated with picric acid yielded the picrate of 1-amidino-1,3-diphenylthiourea, m.p. and mixed m.p. 194-196°C. Oxidation of the picrate with hydrogen peroxide gave the picrate of 3-amino-4-phenyl-5-phenylimino-1,2,4-Δ²-thiadiazoline (Xa), m.p. and mixed m.p. 227°C.

B) 3-AMINO-4-O-TOLYL-5-O-TOLYLIMINO-1,2,4-Δ²-THIADIAZOLINE (Xb)

Similar to the above reaction a solution of di-o-tolyl-carbodiimide and thiourea in acetone was treated with hydrogen chloride. The solid products obtained were extracted with water. The aqueous extract on concentration under reduced pressure yielded colourless cubes of 1-amidino-1,3-di-o-tolylthiourea hydrochloride (XIIIb). Condensation of s-di-o-tolylthiourea and cyanamide also yielded the same amidinothiourea salt (XIIIb).
Oxidation of this amidinothiourea salt (XIIIb) afforded 3-amino-3'-a-tolyl-3'-tolylimino-1,2,4,6-tetra-thiadiazolino.

C) 3-AMINO-4-P-TOLYL-5-P-TOLYLIMINO-1,2,4,6-TETRA-ThIADIAZOLINE (Xc)

Condensation of di-p-tolylicarbodiimide and thiourea, as well as, that of a-di-p-tolythiourea and cyanamide in presence of hydrochloric acid yielded 1-amidino-1,3-di-p-tolylthiourea hydrochloride (XIIIC). Oxidation of this amidinothiourea salt (XIIIc) as before yielded 3-amino-4-p-tolyl-5-p-tolylimino-1,2,4,6-tetra-thiadiazolino (Xc).