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I hereby recommend that the thesis prepared under my supervision by Clarence A. Rosen

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An Alternative Reaction Mechanism for the Synthesis of Disubstituted Thioureas

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by

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INTRODUCTION AND HISTORICAL

The classic synthesis of disubstituted thioureas, both in time and in simplicity, is that of Hoffman (1). He obtained diphenyl thiourea (thiocarbanilide) by refluxing aniline with carbon disulphide. The equation for this reaction is the simplest possible to yield the product obtained:

$$2\ RNH_2\quad CS_2 \longrightarrow RNH\text{-}CS\text{-}NHR\quad H_2S.$$

Most of the procedures for the synthesis of thioureas developed since Hoffman's method are concerned with a means of promoting the elimination of hydrogen sulphide.

There being a variety of reaction mechanism schemes proposed for the synthesis of disubstituted thioureas, the purpose of this thesis is to present another reaction mechanism scheme, based upon some new experimental evidence. It is applicable to those procedures which use an oxidizing agent to promote the condensation of primary amines with carbon disulphide. The steps of this mechanism consist of: (1) the reaction of primary amine and carbon disulphide to form the amine salt of a dithio carbamic acid ($RNH\text{-}CS\text{-}SH \cdot H_2NR$), (2) the oxidation of two moles of the dithio carbamic salt to one mole of the corresponding thiuram disulphide ($RNH\text{-}CS\text{-}S\text{-}S\text{-}CS\text{-}RNH$), (3) the decomposition by heat of the thiuram disulphide to the corresponding mustard oil ($R\text{-}N{=}C{=}S$) and thiourea, and (4) the reaction of the mustard oil of step (3) with part of the original amine, forming the thiourea.

In this reaction mechanism scheme, a differentiation is made between those procedures which use catalysts or basic substances to remove hydrogen sulphide and those which eliminate hydrogen sulphide by oxidizing it to free sulphur.

Accordingly, the various thiourea syntheses enumerated in this historical section will be classified on the same basis.

Inasmuch as the thiourea reaction and its mechanism have been the subject of a number of papers issued from this laboratory, this historical section will avoid unnecessary duplication of bibliographies already available. Other literature references may be found in the earlier papers (2), (3), (4). The history of this subject is considered according to the following outline:

I. Synthesis of Thioureas, by
    a. Non-oxidizing reagents,
    b. Oxidizing reagents,
    c. Methods other than condensation of amine and carbon disulphide.

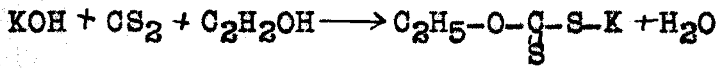
II. Dithio Carbamic Acids

III. Thiuram Disulphides.

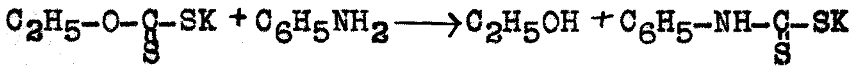
I. Synthesis of Thioureas

(a) Non-oxidizing condensing agents:

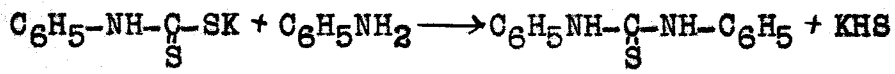
Weith (6), in 1873, used alcoholic potassium hydroxide to take up the hydrogen sulphide formed in the synthesis of diphenyl thiourea. In an attempt to elucidate the mechanism of Weith's reaction, Rathke (7) was able to effect the synthesis of diphenyl thiourea through the preliminary preparation of potassium ethyl xanthate, which was then converted to the potassium salt of phenyl dithio carbamic acid. This compound was subsequently reacted with aniline to yield diphenyl thiourea. The equations for each separate step of the synthesis are as follows:



$$KOH + CS_2 + C_2H_2OH \longrightarrow C_2H_5\text{-}O\text{-}\underset{\overset{\|}{S}}{C}\text{-}S\text{-}K + H_2O \qquad (1)$$



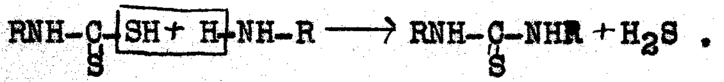
$$C_2H_5\text{-}O\text{-}\underset{\overset{\|}{S}}{C}\text{-}SK + C_6H_5NH_2 \longrightarrow C_2H_5OH + C_6H_5\text{-}NH\text{-}\underset{\overset{\|}{S}}{C}\text{-}SK \qquad (2)$$



$$C_6H_5\text{-}NH\text{-}\underset{\overset{\|}{S}}{C}\text{-}SK + C_6H_5NH_2 \longrightarrow C_6H_5NH\text{-}\underset{\overset{\|}{S}}{C}\text{-}NH\text{-}C_6H_5 + KHS \qquad (3)$$

$$\sum (1),(2),(3):\ 2\ C_6H_5NH_2 + CS_2 + KOH \longrightarrow C_6H_5NH\text{-}CS\text{-}NHC_6H_5 + KHS + H_2O\ .$$

Rathke then suggested that, in the absence of an inorganic base, equimolecular quantities of the amine and carbon disulphide combined to form the corresponding dithio carbamic acid, $RNH\text{-}\underset{\overset{\|}{S}}{C}\text{-}SH$, which combined with another molecule of the amine to produce the thiourea:



$$RNH\text{-}\underset{\overset{\|}{S}}{C}\text{-}\boxed{SH + H}\text{-}NH\text{-}R \longrightarrow RNH\text{-}\underset{\overset{\|}{S}}{C}\text{-}NHR + H_2S\ .$$

This was a possible mechanism for the Hoffman reaction.

It was supported by Rathke's synthesis of phenyl dithio carbamic acid, which reacted with aniline, yielding hydrogen sulphide and thiocarbanilide as the product.

In 1899? Hugershoff (8) suggested the use of sulphur as a catalyst for the elimination of hydrogen sulphide in Hoffman's reaction. The yields of the corresponding thiourea were almost quantitative. Two years previously, Billetier had widened the range of thioureas by preparing unsymmetrical di-, tri-, and *tetrasubstituted* thioureas through the reaction of thiophosgene, $CSCl_2$, on a variety of *primary and secondary* amines. It is proper to add at this point that no thioureas have been prepared by the action of carbon disulphide on *secondary* amines. In 1913, Krulla (10) returned to the use of metallic bases for the purpose of removing hydrogen sulphide. He used the oxides of lead and tin (PbO and SnO), but only the latter was satisfactory. His mechanism was based on the intermediate formation of stannous dithio carbamate, which reacted further with the amine to yield the thiourea, in accordance with the following series of consecutive reaction equations:

$$2\ RNH_2 + SnO + 2\ CS_2 \longrightarrow (RNH\text{-}CS\text{-}S\text{-})_2Sn + H_2O \qquad (1)$$

$$\begin{array}{l} RNH\text{-}CS|S \\ RNH\text{-}CS|S \end{array}\!\!>Sn + \begin{array}{l} H|NHR \\ H|NHR \end{array} \longrightarrow 2\ (RNH)_2CS + SnS + H_2S \qquad (2)$$

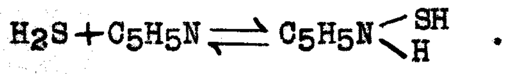
$$SnO + H_2S \longrightarrow SnS + H_2O \qquad (3)$$

$\sum$ (1),(2),(3) :

$$4\ RNH_2 + 2\ SnO + 2\ CS_2 \longrightarrow 2\ H_2O + 2\ SnS + 2\ (RNH)_2CS$$

This mechanism resembles that of Rathke in that it presupposes the formation of a dithio carbamic salt, an assumption for which further support will be produced in the following pages.

In 1913, Fry (4) returned to the use of a catalyst for the elimination of hydrogen sulphide in the synthesis of symmetrical thioureas. For this purpose, pyridine was utilized as a hydrogen sulphide carrier, in conformity with the reversible reaction:



$$H_2S + C_5H_5N \rightleftharpoons C_5H_5N{<}\begin{smallmatrix}SH\\H\end{smallmatrix} \; .$$

After the excess carbon disulphide and pyridine were removed by steam distillation, the thiourea remained in quite pure form and frequently in theoretical yields.

Losanitsch (11) observed that the ammonium salt of phenyl dithio carbamic acid, $C_6H_5NH{-}CS{-}SH \cdot NH_3$, decomposed spontaneously to yield, among other products, diphenyl thiourea. This observation was similar to one of Rathke (7), who obtained the same product, thiocarbanilide, on heating the potassium salt of the same dithio carbamic acid to decomposition. The equation for this type of reaction follows:

$$2\ C_6H_5NH{-}CS{-}SK \xrightarrow{\Delta} (C_6H_5NH)_2CS + K_2S + CS_2 \; .$$

A procedure quite analogous to that of Weith is Dennstedt's (12) which requires the addition of a few cc. of concentrated sodium hydroxide solution to the amine and carbon disulphide dissolved in alcohol.

(b) Oxidizing condensing agents:

Use has been made of oxidizing condensing agents to aid in the elimination of hydrogen sulphide in the thiocarbanilide reaction, according to the equations which follow. It was to elucidate the mechanism of these procedures that this work was undertaken. The simplest equation is:

$H_2S + (O) \longrightarrow H_2O + S.$

With iodine as the oxidizing agent, the equation is:

$H_2S + I_2 \longrightarrow 2\ HI + S.$

Claus and Krall (13), (14) used sulphur monochloride to destroy the hydrogen sulphide formed in Hoffman's reaction. They represented the mechanism as:

$CS_2 + 2\ C_6H_5NH_2 \longrightarrow (C_6H_5NH)_2CS + H_2S$ (1)

$H_2S + S_2Cl_2 \longrightarrow 2\ HCl + 3\ S$ (2)

$2\ C_6H_5NH_2 + 2\ HCl \longrightarrow 2\ C_6H_5NH_2 \cdot HCl$ (3)

Σ (1),(2),(3):

$CS_2 + 4\ C_6H_5NH_2 + S_2Cl_2 \longrightarrow (C_6H_5NH)_2CS + 3S + 2\ C_6H_5NH_2 \cdot HCl$

The side products obtained were triphenylguainidine hydrochloride and phenyl mustard oil:

$2\ (C_6H_5NH)_2CS + S_2Cl_2 \rightarrow C_{19}H_{17}N_3 \cdot HCl + C_6H_5NCS + HCl + 3S.$

Losanitsch reacted the ammonium salt of phenyl dithio carbamic acid with iodine as the oxidizing agent (11), obtaining as the organic product Hoffman's thiocarbanilide. His equations were:

$2\ NH_3 + 2\ CS_2 + 2\ C_6H_5NH_2 \longrightarrow 2\ C_6H_5\text{-}NH\text{-}CS\text{-}S\text{-}NH_4$ (1)

$2\ C_6H_5\text{-}NH\text{-}CS\text{-}S\text{-}NH_4 + I_2 \longrightarrow (C_6H_5NH)_2CS + 2\ NH_4I + CS_2 + S$ (2)

Side reactions produced small amounts of phenyl mustard oil and triphenylguanidine hydro-iodide, an occurrence similar to that observed by Claus and Krall.

The very first attempt at the use of oxidizing agents was made by Hoffman only a year after his discovery of the thiocarbanilide reaction (15). Without closely controlling the conditions, he obtained an indeterminate mixture containing phenyl mustard oil and triphenylguanidine. In 1878, Rudneff (16) elucidated the work of Hoffman by showing that, with ethylamine, the action of iodine on the dithio carbamate gives as principle products, in alcoholic solution, the corresponding mustard oil, thiourea, hydriodide of the amine, sulphur, and carbon disulphide.

In 1900, Von Braun (17) showed that <u>aromatic</u> amines, but not <u>aliphatic</u>, will react in the presence of the theoretical amount of carbon disulphide at ordinary temperature with oxidizing agents (iodine, potassium persulphate, potassium percarbonate, hydrogen peroxide, etc.) to yield the corresponding disubstituted thiourea. This reaction was elucidated in a later work.

Thirteen years later, Krulla (10) returned to the use of oxidizing agents to hasten the thiourea reaction. He considered hydrogen peroxide unsatisfactory because its use entailed two liquid phases. He next considered the use of an aromatic nitro-compound, nitrobenzene, as the oxidizing agent for the condensation of aniline:

$6\ C_6H_5NH_2 + 3\ CS_2 \longrightarrow 3\ (C_6H_5NH)_2CS + 3\ H_2S$ (1)

$3\ H_2S + C_6H_5NO_2 \longrightarrow C_6H_5NH_2 + 2\ H_2O + 3\ S$ (2)

Σ (1),(2):

$5\ C_6H_5NH_2 + 3\ CS_2 + C_6H_5NO_2 \longrightarrow 3(C_6H_5NH)_2CS + 2\ H_2O + 3S$.

This method was found to be satisfactory.

The most uniformly efficient [1] procedure for the synthesis of disubstituted thioureas from primary amines and carbon disulphide, both with regard to time and extent of reaction, is that of Fry (4). It is based on the elimination of hydrogen sulphide in Hoffman's equation by the use of a carbon disulphide solution of iodine:

$H_2S\ \ I_2 \longrightarrow 2\ HI + S$.

Sufficient pyridine is added to the reaction mixture to remove the hydrogen iodide through the formation of the CS_2- insoluble pyridonium iodide, $C_5H_5N \cdot HI$:

$HI + C_5H_5N \longrightarrow C_5H_5N \cdot HI$.

To a solution of the amine and pyridine in excess carbon disulphide, heated to refluxing, is added the calculated weight of iodine required for the formation of the thiourea, also dissolved in carbon disulphide. Refluxing is continued until the iodine color is removed, whereupon the solvent and pyridine are removed by steam distillation, followed by recovery and suitable purification of the thiourea. Fry obtained 75 % to 99 % yields with primary aromatic amines. The complete equation for this method

[1] As shown by the work of Raiford and McNulty. (18)

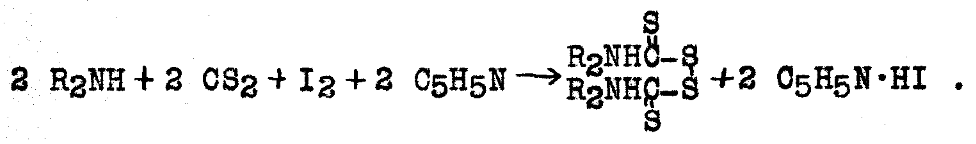
is as follows:

$$2\ C_5H_5N + 2\ RNH_2 + CS_2 + I_2 \longrightarrow (RNH)_2CS + S + 2\ C_5H_5N\cdot HI.$$

If, however, aniline dissolved in a mixture of carbon disulphide and pyridine is titrated with a standard solution of iodine at room temperature, the molecular ratio, $C_6H_5NH_2:I_2$, is 1:1, and not 2:1, as with the thiourea equation above. In this manner the formation of phenyl isothiocyanate (phenyl mustard oil) results according to the equation:

$$RNH_2 + CS_2 + I_2 + 2\ C_5H_5N \longrightarrow RNCS + 2\ C_5H_5N\cdot HI + S.$$

Ten years later, Fry and Culp (5) attempted to extend the use of the pyridine - iodine method to the synthesis of symmetrical tetrasubstituted thioureas. Instead, compounds of the *thiuram disulphide* type were obtained, with both *aromatic* and *aliphatic secondary* amines. The type equation is:



$$2\ R_2NH + 2\ CS_2 + I_2 + 2\ C_5H_5N \longrightarrow \begin{matrix} R_2NH\overset{S}{\overset{\|}{C}}-S \\ R_2NH\underset{S}{\underset{\|}{C}}-S \end{matrix} + 2\ C_5H_5N\cdot HI\ .$$

A short time later, Farquhar and Fry (2), in a study of the inhibitory effects of substituents in the nucleus of aromatic amines, continued the same work, showing that the speed and extent of the reactions involved are increased by using a 100 % excess of pyridine. They also showed that the organic base, quinoline, may be substituted, mole-for-mole, for pyridine in Fry's method, without noticeably affecting the yield of thiourea. To the time of the present research, no trial of Fry's method had been made on primary aliphatic amines.

(c) Methods other than condensation of amine and carbon disulphide.

Naunton (19) has stated that any thiourea which can be prepared by the action of a condensing agent can also be formed by the action of carbon disulphide with the corresponding amine alone. Other reactants must be used for the synthesis of those thioureas which do not result from the reaction of amines and carbon disulphide.

The method of Billetier (9) using thiophosgene, $CSCl_2$, has already been cited. The reaction proceeds in two steps:

$$2\ RNH_2 + CSCl_2 \longrightarrow RNH{-}CS{-}Cl + RNH_2 \cdot HCl \tag{1}$$

$$RNH{-}CS{-}Cl + 2\ R_2NH \longrightarrow RNH{-}CS{-}NR_2 + R_2NH \cdot HCl \tag{2}$$

Any combination of primary and secondary amines may be used to yield di-, tri-, and tetra-substituted thioureas (20).

At the same time Hoffman published his work on the thiocarbanilide reaction (1), he also presented the synthesis of a thiourea by the reaction of a mustard oil with the corresponding amine:

$$C_6H_5N{=}C{=}S + C_6H_5NH_2 \longrightarrow C_6H_5NH{-}CS{-}NHC_6H_5.$$

By the use of different primary and secondary amines with each mustard oil, a variety of thioureas have since been obtained (21). Since no mustard oils can be prepared from secondary amines, it is evident that this method does not apply to the synthesis of tetra-substituted thioureas; Methods of doubtful practical value are those which react mustard oils with ketoximes and aldoximes (22) and with hydrogen sulphide (23), obtaining thioureas in each case. The respective equations are not clear.

Mono- and di-acyl thioureas have been prepared by heating thiourea with the corresponding acid anhydride (24),(25),(26). According to this method, diacetyl thiourea has been synthesized:

$$NH_2\text{-}CS\text{-}NH_2 + 2(CH_3\text{-}CO\text{-})_2O \rightarrow (CH_3\text{-}CO\text{-}NH\text{-})_2CS + 2\ CH_3CO_2H.$$

Monosubstituted thioureas have also been obtained by the isomerization of thiocyanic acid salts of primary amines (22),(27),(28) :

$$RNH_2 \cdot HNCS \longrightarrow RNH\text{-}CS\text{-}NH_2.$$

An unique method for preparing symmetric diaryl thioureas reacts aromatic nitroso compounds with an aqueous solution of sodium trithiocarbonate (29):

$$Na_2CS_3 + 2\ RNO + H_2O \longrightarrow (RNH)_2CS + Na_2S_2O_3\ .$$

A 75 % yield is claimed for this method.

II. Dithio Carbamic Acids

Since dithio carbamic acids are the first intermediate products formed in the synthesis of thioureas, a historical survey of their preparation is pertinent to subsequent discussion of reaction mechanisms.

In 1834, Zeise (30) prepared ammonium dithio carbamate, the parent compound of the dithio carbamic acid salts, by the interaction of ammonia and carbon disulphide:

$$2\ NH_3 + CS_2 \longrightarrow NH_2\text{-}CS\text{-}S\text{-}NH_4\ .$$

However, he did not establish the identity of his product. Twenty-six years later, Debus (31) resumed this work and isolated the product, without identifying it. At higher reaction temperatures, he observed a decomposition to a compound of formula N_2H_4CS , which he considered to be ammonium thiocyanate, NH_4NCS, but which may have been thiourea, NH_2CSNH_2, as pointed out by Hoffman (27). His suggested equation is:

$$NH_2\text{-}CS\text{-}S\text{-}NH_4 \longrightarrow NH_2\text{-}CS\text{-}NH_2 + H_2S.$$

Later. He showed that the same type of equation applied to the amine salt of ethyl dithio carbamic acid (32) and to aromatic dithio carbamic salts (15):

$$RNH\text{-}CS\text{-}SH\cdot H_2NR \xrightarrow{\Delta} RNH\text{-}CS\text{-}NHR + H_2S\ .$$

The work of Rathke (Page 3) and Losanitsch (Page 5) on dithio carbamic salts has already been cited. In 1902, Delepine (21) presented an extensive study of the preparation of dithio carbamic salts, acids, and esters. By this time, it had become accepted that the normal course of reaction of primary and secondary amines with carbon disulphide leads to the formation of dithio carbamic acids or salts. Thus, in 1881, Grodzki (33) had shown that both primary and secondary amines react with carbon disulphide to form dithio carbamates, but that this reaction can not occur with tertiary amines. He also showed that primary amine dithio carbamates can react to yield thioureas, according to Hoffman's equation (page 12), but that secondary amines do not show this reaction. Even the much less basic amino-acids have yielded dithio carbamates, as for example, glycine (34), (35), (36) :

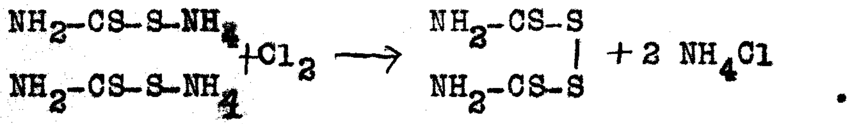
$$HOOC\text{-}CH_2\text{-}NH_2 + CS_2 + 2\ KOH \longrightarrow KOOC\text{-}CH_2\text{-}NH\text{-}CS\text{-}SK + 2\ H_2O.$$

From the time of Hoffman and Rathke, the assumption of the intermediate formation of dithio carbamic acids or salts has been implicit in most work on thioureas and similar compounds.

III. Thiuram Disulphides

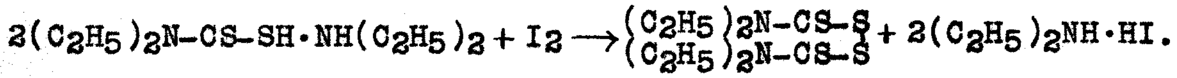
The chief purpose of this thesis has been stated to be the consideration of a method for the synthesis of thioureas, based upon the intermediate formation of thiuram disulphides. Accordingly, a survey of the preparation and properties of thiuram disulphides is presented here.

The first synthesis of a thiuram disulphide was performed in 1850 by Debus (31). He treated ammonium dithio carbamate with halogens, and obtained a compound with the formula $C_2S_4N_2H_4$, which he could not identify. It was later shown by Von Braun (37) to be thiuram disulphide, $NH_2CS{-}S{-}S{-}CSNH_2$, formed by the equation (here recorded as a simplification of the earlier double formulae):



$$\begin{array}{l} NH_2{-}CS{-}S{-}NH_4 \\ NH_2{-}CS{-}S{-}NH_4 \end{array} + Cl_2 \longrightarrow \begin{array}{l} NH_2{-}CS{-}S \\ \qquad\qquad\;\, | \\ NH_2{-}CS{-}S \end{array} + 2\ NH_4Cl \quad .$$

In 1881, Grodzki (33) prepared tetraethyl thiuram disulphide, by oxidizing a solution of the dithio carbamate of diethyl amine with iodine:



$$2(C_2H_5)_2N{-}CS{-}SH\cdot NH(C_2H_5)_2 + I_2 \longrightarrow \begin{array}{l} (C_2H_5)_2N{-}CS{-}S \\ (C_2H_5)_2N{-}CS{-}S \end{array} + 2(C_2H_5)_2NH\cdot HI.$$

The molecular ratio of amine to iodine was 4:1, in accordance with the above equation. The name, "thiuram disulphide", had been suggested in 1873 (38). In an analogous way, the thiuram disulphide of piperidine was synthesized (39). Freund (40) used bromine water in the synthesis of dimethyl and diethyl thiuram disulphide.

Von Braun has made a thorough study of the behavior of primary and secondary amine dithiocarbamates on oxidation. In a preliminary publication on the preparation of thiocarbanilide by the use of oxidizing condensing agents (17), he presented a mechanism based on the intermediate formation of the dithiocarbamate, followed by the formation of an unstable thiuram disulphide:

$$\begin{matrix}C_6H_5NH\text{-}CS\text{-}SH\cdot NH_2C_6H_5\\ C_6H_5NH\text{-}CS\text{-}SH\cdot NH_2C_6H_5\end{matrix} \xrightarrow{(O)} \left.\begin{matrix}C_6H_5NH\text{-}CS\text{-}S\\ C_6H_5NH\text{-}CS\text{-}S\end{matrix}\right| + 2\ C_6H_5NH_2 + H_2O.$$

This r

$$\begin{matrix}C_6H_5NH\text{-}CS\text{-}SH\cdot NH_2C_6H_5\\ C_6H_5NH\text{-}CS\text{-}SH\cdot NH_2C_6H_5\end{matrix} \xrightarrow{(O)} \left.\begin{matrix}C_6H_5NH\text{-}CS\text{-}S\\ C_6H_5NH\text{-}CS\text{-}S\end{matrix}\right| + 2\ C_6H_5NH_2 + H_2O.$$

section.

A few years later, he further confirmed the nature of this reaction by synthesizing the thiuram disulphides of a large number of primary and secondary amines (37). He showed that when two moles of any <u>primary aliphatic</u> or <u>aromatic-aliphatic</u> amine, or any <u>secondary</u> amine, are dissolved with one mole of carbon disulphide in alcohol, the product of oxidation at low temperatures is always a <u>thiuram disulphide</u>. On the other hand, <u>primary aromatic</u> amines invariably yield <u>thioureas</u>, with traces of mustard oil.

Tetra-substituted thiuram disulphides, resulting from secondary amines, are stable to heat and chemical reagents. On the other hand, the disubstituted thiuram disulphides which are the reaction product of primary amines are decidedly unstable to heat. The information derived from a study of the decomposition reactions of these latter thiuram disulphides suggested to Von Braun a revision of his previous reaction mechanism scheme for the synthesis of thioureas by the use of oxidizing condensing agents. This revised scheme will also be considered in the theoretical section.

More recently, the application of Fry's iodine - pyridine method for the synthesis of thioureas to secondary amines has resulted in the formation of thiuram disulphides. Fry and Culp obtained the thiuram disulphides of methyl and ethyl aniline, ethyl alpha and beta naphthylamine, dimethylamine, and diethylamine. This was followed by the work of Fry and Farquhar, on diphenylamine, methyl ortho-, meta-, and para-toluidine, and meta- and para-nitro methylaniline. In their work, the inhibitory effect on speed and extent of reaction of various substituents in the ring or on the nitrogen atom were determined. Their conclusions on the effect of nitrogen substituents were that the inhibitory effect increases with the weight of the substituent.

In recent years interest has been evinced in thiuram disulphides because of their value as vulcanization aids in the rubber industry. Consequently, a number of variations for their synthesis have appeared in the patent literature. They call for a number of oxidizing agents, such as a mixture of nitrogen oxides and air (41), nitric oxide and air (42), chlorine passed through an aqueous solution of the amine with carbon disulphide (43), sodium hypochlorite solution (44), and aqueous hydrogen peroxide with excess carbon disulphide (45). The efficacy of these latter methods have not been disclosed and are therefore questionable.

THEORETICAL

Since Hoffman's first work on the thiocarbanilide reaction, a variety of reaction mechanism schemes have been proposed. The first one, presented by Hoffman in 1847 (1), was based on the simplest possible equation for the complete reaction:

$$2\ RNH_2 + CS_2 \longrightarrow RNH\text{-}CS\text{-}NHR + H_2S.$$

In making use of sulphur monochloride, Claus and Krall (Page 6) assumed that the fundamental equation involved was identical with Hoffman's. The subsequent equations were merely concerned with the reaction between the hydrogen sulphide evolved and the sulphur chloride, as outlined in the historical section. But two years previous to the work of Claus and Krall, Hoffman (Page 12) had already suggested a more probable mechanism for his original condensation of amines with carbon disulphide, involving the intermediate formation of dithio carbamic salts:

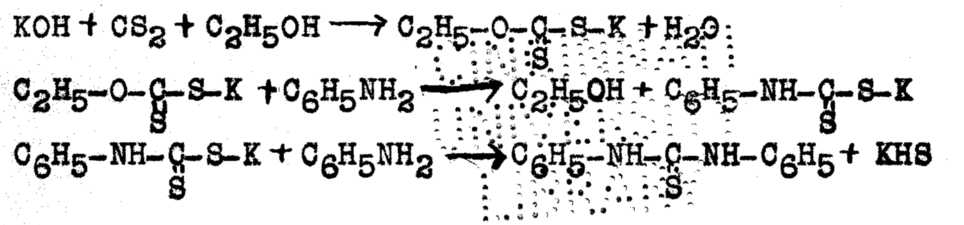
$$2\ RNH_2 + CS_2 \longrightarrow RNH\text{-}CS\text{-}SH \cdot H_2NR \qquad (1)$$

$$RNH\text{-}CS\text{-}SH \cdot H_2NR \xrightarrow{\Delta} RNH\text{-}CS\text{-}NHR + H_2S \qquad (2)$$

$$\Sigma(1),(2):\quad 2\ RNH_2 + CS_2 \longrightarrow RNH\text{-}CS\text{-}NHR + H_2S.$$

The summation is Hoffman's original equation.

In 1878, Rathke (7) established the series of reactions invloved in the use of an alkaline condensing agent, such as potassium hydroxide. They are based on the reaction of aniline with carbon disulphide, in an alcoholic potassium hydroxide solution.

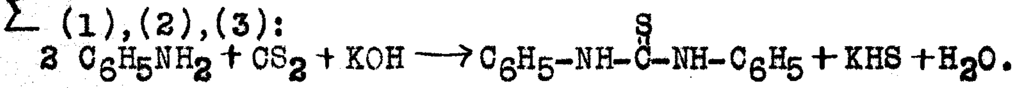


$$KOH + CS_2 + C_2H_5OH \longrightarrow C_2H_5\text{-}O\text{-}\underset{S}{C}\text{-}S\text{-}K + H_2O \qquad (1)$$

$$C_2H_5\text{-}O\text{-}\underset{S}{C}\text{-}S\text{-}K + C_6H_5NH_2 \longrightarrow C_2H_5OH + C_6H_5\text{-}NH\text{-}\underset{S}{C}\text{-}S\text{-}K \qquad (2)$$

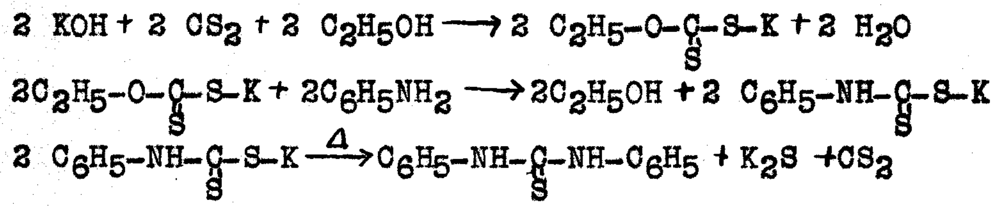
$$C_6H_5\text{-}NH\text{-}\underset{S}{C}\text{-}S\text{-}K + C_6H_5NH_2 \longrightarrow C_6H_5\text{-}NH\text{-}\underset{S}{C}\text{-}NH\text{-}C_6H_5 + KHS \qquad (3)$$

Σ (1),(2),(3):



$$2\ C_6H_5NH_2 + CS_2 + KOH \longrightarrow C_6H_5\text{-}NH\text{-}\overset{S}{C}\text{-}NH\text{-}C_6H_5 + KHS + H_2O.$$

He stated also that at high temperatures, the potassium dithio carbamate is unstable and decomposes, according to the following series of equations:

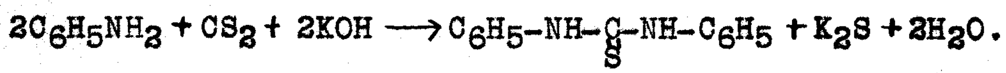


$$2\ KOH + 2\ CS_2 + 2\ C_2H_5OH \longrightarrow 2\ C_2H_5\text{-}O\text{-}\underset{S}{C}\text{-}S\text{-}K + 2\ H_2O \qquad (1)$$

$$2C_2H_5\text{-}O\text{-}\underset{S}{C}\text{-}S\text{-}K + 2C_6H_5NH_2 \longrightarrow 2C_2H_5OH + 2\ C_6H_5\text{-}NH\text{-}\underset{S}{C}\text{-}S\text{-}K \qquad (2)$$

$$2\ C_6H_5\text{-}NH\text{-}\underset{S}{C}\text{-}S\text{-}K \xrightarrow{\Delta} C_6H_5\text{-}NH\text{-}\underset{S}{C}\text{-}NH\text{-}C_6H_5 + K_2S + CS_2 \qquad (3)$$

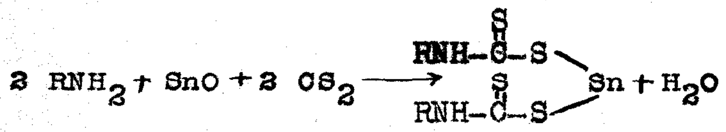
Σ (1),(2),(3):



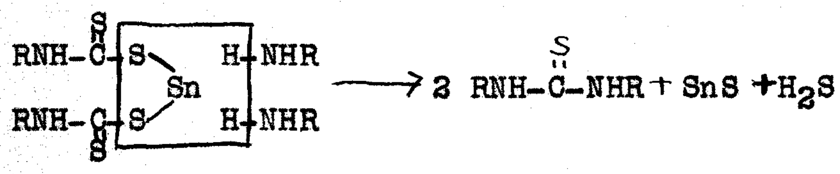
$$2C_6H_5NH_2 + CS_2 + 2KOH \longrightarrow C_6H_5\text{-}NH\text{-}\underset{S}{C}\text{-}NH\text{-}C_6H_5 + K_2S + 2H_2O.$$

Though the two reaction mechanism schemes are quite different, the final equations are almost identical, differing only in whether the acid or nuetral potassium sulphide is obtained.

The reactions proposed by Krulla (10) to explain the condensing action of stannous oxide are similar to Rathke's first series, presented above. They are also based on the metal dithio carbamate:



$$2\ RNH_2 + SnO + 2\ CS_2 \longrightarrow \begin{array}{l} RNH\text{-}\overset{S}{C}\text{-}S \\ RNH\text{-}\overset{S}{C}\text{-}S \end{array} \!\!> Sn + H_2O \qquad (1)$$



$$\begin{array}{l} RNH\text{-}\overset{S}{C}\text{-}S \quad H\text{-}NHR \\ \qquad\qquad\quad Sn \\ RNH\text{-}\underset{S}{C}\text{-}S \quad H\text{-}NHR \end{array} \longrightarrow 2\ RNH\text{-}\overset{S}{C}\text{-}NHR + SnS + H_2S \qquad (2)$$

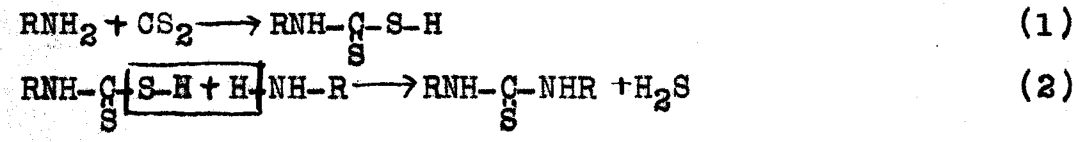
$$SnO + H_2S \longrightarrow SnS + H_2O \qquad (3)$$

$\sum(1),(2),(3)$:

$$4\ RNH_2 + 2\ SnO + 2\ CS_2 \longrightarrow 2\ H_2O + 2\ SnS + 2\ (RNH)_2CS.$$

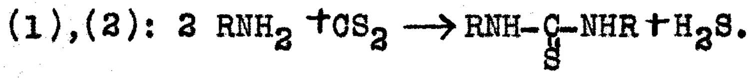
The similarity between the two final equations is very evident. Krulla offered no mechanism for the synthesis making use of the condensing action of nitrobenzene. He presented merely the empirical equations noted on Page 7, to explain the products observed.

In extending his work on the potassium salt of phenyl dithio carbamic acid, Rathke presented a mechanism for Hoffman's reaction (in the absence of condensing agents) which has enjoyed the widest acceptance. The reaction mechanism consists of the following consecutive equations:



$$RNH_2 + CS_2 \longrightarrow RNH-\underset{S}{C}-S-H \qquad (1)$$

$$RNH-\underset{S}{C}-\boxed{S-H + H}-NH-R \longrightarrow RNH-\underset{S}{C}-NHR + H_2S \qquad (2)$$



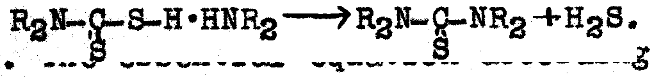
$$(1),(2):\ 2\ RNH_2 + CS_2 \longrightarrow RNH-\underset{S}{C}-NHR + H_2S.$$

This last equation is, of course, identical with that of Hoffman.

Each of the reaction mechanism schemes enumerated thus far has failed to explain the fact, first stated by Grodzki (33), that thioureas have never been synthesized from carbon disulphide and a <u>secondary</u> amine. The empirical equation for such a reaction would be:

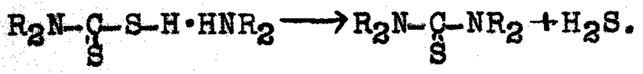
$$2\ R_2NH + CS_2 \longrightarrow R_2N-CS-NR_2 + H_2S.$$

According to each of the mechanism theories presented in the foregoing pages, such a reaction should be able to



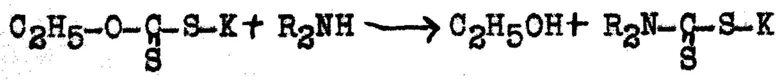
$$R_2N-\underset{\underset{S}{\|}}{C}-S-H\cdot HNR_2 \longrightarrow R_2N-\underset{\underset{S}{\|}}{C}-NR_2 + H_2S.$$

occur. [illegible] to Hoffman would be:

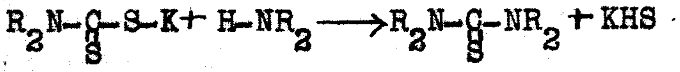


$$R_2N-\underset{\underset{S}{\|}}{C}-S-H\cdot HNR_2 \longrightarrow R_2N-\underset{\underset{S}{\|}}{C}-NR_2 + H_2S.$$

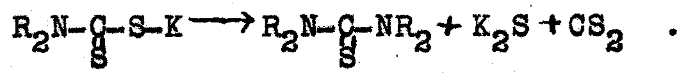
Rathke's theory would be embodied in the following equations:



$$C_2H_5-O-\underset{\underset{S}{\|}}{C}-S-K + R_2NH \longrightarrow C_2H_5OH + R_2N-\underset{\underset{S}{\|}}{C}-S-K \qquad (1)$$

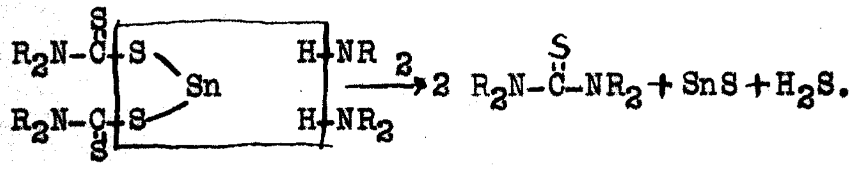


$$R_2N-\underset{\underset{S}{\|}}{C}-S-K + H-NR_2 \longrightarrow R_2N-\underset{\underset{S}{\|}}{C}-NR_2 + KHS \qquad (2)$$

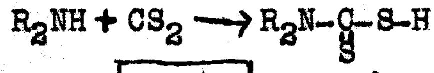


$$\text{or: } 2\ R_2N-\underset{\underset{S}{\|}}{C}-S-K \longrightarrow R_2N-\underset{\underset{S}{\|}}{C}-NR_2 + K_2S + CS_2 \ . \qquad (3)$$

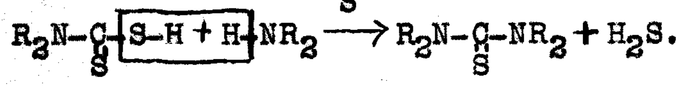
Similarly, the essential reaction of Krulla's mechanism should be:



And in the same way, an adaptation could also be made of Rathke's reaction mechanism scheme for the case of a secondary amine with carbon disulphide, in the absence of condensing agents:



$$R_2NH + CS_2 \longrightarrow R_2N-\underset{\underset{S}{\|}}{C}-S-H \qquad (1)$$



$$R_2N-\underset{\underset{S}{\|}}{C}-\boxed{S-H + H}-NR_2 \longrightarrow R_2N-\underset{\underset{S}{\|}}{C}-NR_2 + H_2S.$$

On the basis of the theories involved, the reactions embodied in each of the above equations should be capable of occurrence. But the fact that such reactions have never been observed suggests a weakness in the corresponding theories, in their failure to differentiate between the behavior of primary and secondary amines.

Snedker (46) has attempted to explain the failure of secondary amines to yield thioureas with carbon disulphide.

For aromatic amines, he postulated that the first reaction with carbon disulphide forms the dithio carbamic acid, RNH-CS-S-H, which then decomposes to form the mustard oil:

$$RNH\text{-}CS\text{-}S\text{-}H \longrightarrow R\text{-}N{=}C{=}S + H_2S.$$

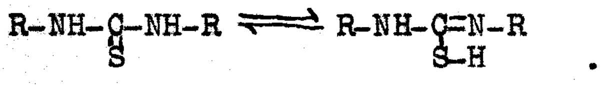
The mustard oil formed then combines with more of the amine to form the thiourea:

$$R\text{-}N{=}C{=}S + RNH_2 \longrightarrow RNH\text{-}CS\text{-}NHR.$$

Secondary amines form dithio carbamic acids of the type $R_2N\text{-}CS\text{-}S\text{-}H$, which lack the amino- hydrogen atom necessary for the formation of the mustard oil intermediate to the thiocarbanilide. Snedker applied this explanation only to aniline and its derivatives, omitting reference to aliphatic amines.

More recently, a reaction mechanism scheme has been presented by Fry and Culp (4) which for the first time explained the difference in reaction of all primary and secondary amines with carbon disulphide. A complete exposition of this theory is available in the thesis of Farquhar (2).

It is applicable to both aliphatic and aromatic amines and is based on the tautomerism of thiourea and its substitution products between the thioketo- (<u>thiocarbamide</u>) and thioenol- (<u>thiocarbimide</u>) forms:



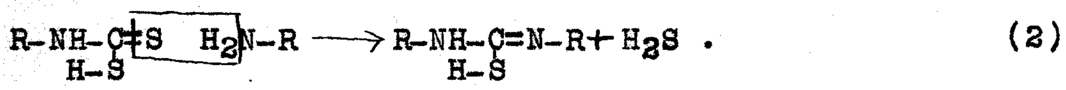
$$R\text{-}NH\text{-}\underset{\displaystyle S}{\overset{}{C}}\text{-}NH\text{-}R \rightleftharpoons R\text{-}NH\text{-}\underset{\displaystyle S\text{-}H}{C}{=}N\text{-}R \quad .$$

Sufficient evidence exists to warrant the wide acceptance this assumption has received.

The first reaction involved in their theory is identical with that proposed by Rathke (Page 20):

$$RNH_2 + CS_2 \longrightarrow R\text{-}NH\text{-}\underset{S}{\underset{\|}{C}}\text{-}S\text{-}H \qquad (1)$$

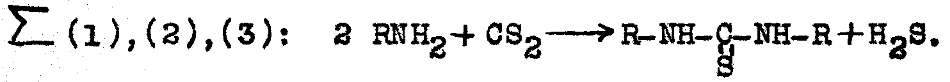
But the novelty of the newer mechanism scheme is embodied in the second equation, in which condensation can only occur between the thiono-sulphur of the dithio carbamic acid and the two amino hydrogen atoms of a second molecule of the primary amine, yielding as products a molecule of hydrogen sulphide and a molecule of the enol- form of the disubstituted thiourea. The equation is:



$$R\text{-}NH\text{-}\underset{H\text{-}S}{C}\boxed{\cancel{=}S \quad H_2}N\text{-}R \longrightarrow R\text{-}NH\text{-}\underset{H\text{-}S}{C}{=}N\text{-}R + H_2S\ . \qquad (2)$$

The enol-form of the thiourea then rearranges, presumably under the influenc of heat, to form the keto (thiocarbamide) modification, according to the third equation:

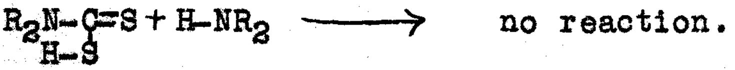
$$R\text{-}NH\text{-}\underset{H\text{-}S}{C}{=}N\text{-}R \longrightarrow R\text{-}NH\text{-}\underset{S}{\underset{\|}{C}}\text{-}NH\text{-}R \qquad (3)$$



$$\sum (1),(2),(3):\quad 2\ RNH_2 + CS_2 \longrightarrow R\text{-}NH\text{-}\underset{S}{\underset{\|}{C}}\text{-}NH\text{-}R + H_2S.$$

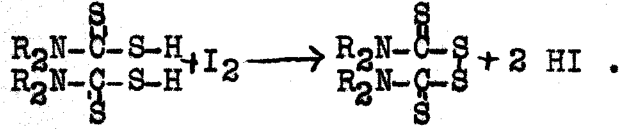
The final equation is thus identical with those proposed by Hoffman and Rathke, as noted on earlier pages of this section.

On the same basis, the fact that secondary amines do not yield thioureas is explained by the absence of two amino hydrogen atoms to react with the thiono-sulphur of the dithio carbamic acid.



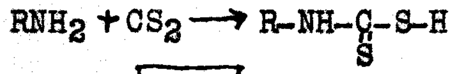
$$R_2N\text{-}\underset{H\text{-}S}{C}{=}S + H\text{-}NR_2 \longrightarrow \quad \text{no reaction.}$$

While a thiourea can not thus be formed from a secondary amine, it is quite possible that, in the presence of an oxidizing agent such as iodine, the dithio carbamic acid of the secondary amine can be oxidized to the corresponding thiuram disulphide.

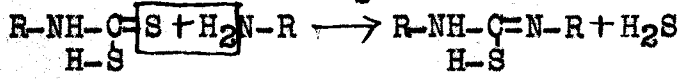


$$\begin{matrix} R_2N-\overset{S}{\overset{\|}{C}}-S-H \\ R_2N-\underset{S}{\underset{\|}{C}}-S-H \end{matrix} + I_2 \longrightarrow \begin{matrix} R_2N-\overset{S}{\overset{\|}{C}}-S \\ R_2N-\underset{S}{\underset{\|}{C}}-S \end{matrix} + 2\ HI\ .$$

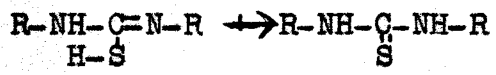
In summary, on the basis of the foregoing reaction mechanism scheme, Fry's pyridine - iodine method for thioureas involves these equations:



$$RNH_2 + CS_2 \longrightarrow R-NH-\underset{S}{\underset{\|}{C}}-S-H \qquad (1)$$



$$R-NH-\underset{H-S}{C}=\boxed{S+H_2}N-R \longrightarrow R-NH-\underset{H-S}{C}=N-R+H_2S \qquad (2)$$



$$R-NH-\underset{H-S}{C}=N-R \longrightarrow R-NH-\underset{S}{\underset{\|}{C}}-NH-R \qquad (3)$$

$$H_2S + I_2 \longrightarrow 2\ HI + S \qquad (4)$$

$$2\ C_5H_5N + 2\ HI \longrightarrow 2\ C_5H_5N\cdot HI \qquad (5)$$

$\sum$ (1),(2),(3),(4),(5),:

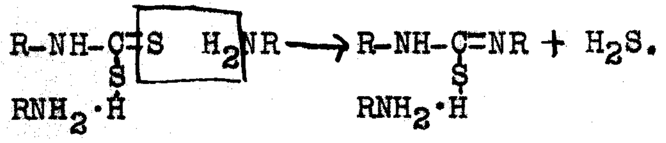
$$CS_2 + 2\ RNH_2 + I_2 + 2\ C_5H_5N \longrightarrow (RNH)_2CS + S + 2\ C_5H_5N\cdot HI.$$

In the mechanism of Fry and Culp, the iodine reacts with the hydrogen sulphide evolved from the primary amine and the dithio carbamic acid.

The theory of Fry and Culp may be questioned from several points of view. For example, let it be assumed first that in equation (2) of the above mechanism, the dithio carbamic acid and the amine react to form the dithio carbamic salt:

$$R-NH-\underset{S}{\underset{\|}{C}}-S-H + H_2NR \longrightarrow RNH-\underset{S}{\underset{\|}{C}}-S-H\cdot H_2NR,$$

which interacts with another molecule of the amine, as follows:



$$R-NH-\underset{\substack{| \\ S \\ RNH_2\cdot H}}{C}-\boxed{S\quad H_2}NR \longrightarrow R-NH-\underset{\substack{| \\ S \\ RNH_2\cdot H}}{C}=NR + H_2S.$$

If this salt formation does occur, then the rearrangement from the *enolic* to the *keto* form of the thiourea would be precluded. Yet most primary amines form the dithio carbamic *salt*, not *acid*, with carbon disulphide. Even if the acid were formed, pyridine, if present, would combine with it to form the pyridine salt:

$$R-NH-\underset{\substack{\| \\ S}}{C}-SH + C_5H_5N \longrightarrow R-NH-\underset{\substack{\| \\ S}}{C}-SH\cdot C_5H_5N\ .$$

Then the presence of pyridine in the reaction mixture should hinder the reaction, yet Farquhar has shown that the speed and yield increases with the pyridine concentration. Such an observation is more compatible with a reaction mechanism scheme based on the dithio carbamic *salt*, rather than the *acid*. The mechanism in support of which this research was undertaken fulfills that requirement.

Fry and Culp have considered the thiuram disulphide reaction as being distinct from the thiourea reaction, occurring only when, for any reason, the latter reaction is inhibited. Even when an oxidizing condensing agent is employed, it was held that the only connection between the two reactions is that both require the intermediate formation of the dithio carbamic acid (or salt). Their theory does not satisfactorily explain the fact that the same *primary* amine may react to form a *thiourea or a* thiuram disulphide, depending only on the temperature of the reaction. The reaction mechanism scheme to be presented in the following pages explains this fact by assuming that the formation of a thiourea is dependent upon the previous intermediate formation of a thiuram disulphide, which in turn may decompose directly to give a thiourea, or may react with the primary amine, when present, to give a thiourea.

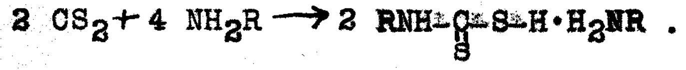
Incident to his use of iodine as the condensing agent in the preparation of thiocarbanilide, Losanitsch (11) presented a series of two equations:

$$2\ NH_3 + 2\ CS_2 + 2\ C_6H_5NH_2 \longrightarrow 2\ C_6H_5NH\text{-}CS\text{-}S\text{-}NH_4 \qquad (1)$$

$$2\ C_6H_5NH\text{-}CS\text{-}S\text{-}NH_4 + I_2 \longrightarrow (C_6H_5NH)_2CS + 2\ NH_4I + CS_2 + S \qquad (2)$$

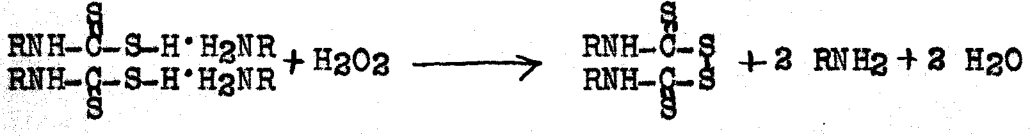
It is evident that the second equation actually covers more than one reaction, the natures of which were unknown to Losanitsch.

In 1900, Von Braun (17) offered a reaction mechanism scheme for his use of hydrogen peroxide in the synthesis of thioureas from aromatic amines, which also applies to the conditions of Losanitsch's synthesis. The first reaction involved is the formation of the amine dithio carbamate:



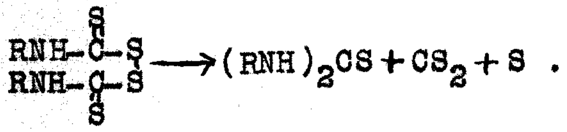
$$2\ CS_2 + 4\ NH_2R \longrightarrow 2\ RNH\text{-}\underset{\overset{\|}{S}}{C}\text{-}S\text{-}H\cdot H_2NR\ . \qquad (1)$$

The next equation was suggested by the works of Debus, Freund, and others on thiuram disulphides:



$$\begin{array}{l} RNH\text{-}\overset{\overset{S}{\|}}{C}\text{-}S\text{-}H\cdot H_2NR \\ RNH\text{-}\underset{\overset{\|}{S}}{C}\text{-}S\text{-}H\cdot H_2NR \end{array} + H_2O_2 \longrightarrow \begin{array}{l} RNH\text{-}\overset{\overset{S}{\|}}{C}\text{-}S \\ \qquad\quad\ \ | \\ RNH\text{-}\underset{\overset{\|}{S}}{C}\text{-}S \end{array} + 2\ RNH_2 + 2\ H_2O \qquad (2)$$

The thiuram disulphide has only transitory existence, since it is very unstable, and decomposes:



$$\begin{array}{l} \text{RNH}-\overset{\overset{S}{\|}}{C}-S \\ \text{RNH}-\underset{\underset{S}{\|}}{C}-S \end{array} \longrightarrow (\text{RNH})_2\text{CS} + \text{CS}_2 + \text{S} \;. \qquad (3)$$

If iodine is used as condensing agent instead of hydrogen peroxide, then no water is produced in equation (2), and the amine is not obtained free, but as the hydriodide. The production of free sulphur, and carbon disulphide in half the quantity originally used, as observed by Losanitsch, is explained by the third equation of Von Braun; the sum of the three equations is:

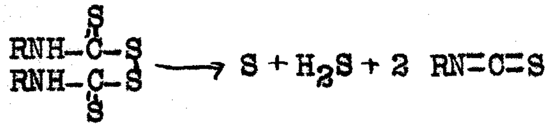
Σ (1),(2),(3):

$$\text{CS}_2 + 2\ \text{RNH}_2 + \text{H}_2\text{O}_2 \longrightarrow (\text{RNH})_2\text{CS} + \text{S} + 2\ \text{H}_2\text{O} \;, \quad \text{or}$$

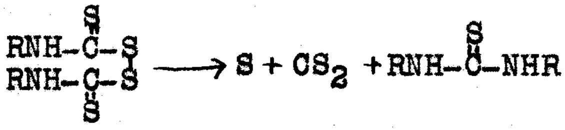
$$\text{CS}_2 + 4\ \text{RNH}_2 + \text{I}_2 \longrightarrow (\text{RNH})_2\text{CS} + 2\ \text{RNH}_2\cdot\text{HI} + \text{S} \;.$$

The difference between the two final equations is based on whether iodine or hydrogen peroxide is the condensing agent. In either case, they apply only to the use of <u>primary aromatic</u> amines.

Two years later, Von Braun (37) substantiated this mechanism, in the case of all primary amines other than the aromatic, by actually isolating the disubstituted thiuram disulphides under suitable conditions. All secondary amines, aliphatic or aromatic, yielded only the corresponding thiuram disulphides. While the thiuram disulphides obtained from secondary amines are stable, those obtained from primary amines decompose on long standing or on being heated. This decomposition was shown to follow two courses:

A. 

$$\begin{matrix}\mathrm{RNH{-}\overset{S}{\overset{\|}{C}}{-}S} \\ \mathrm{RNH{-}\underset{S}{\underset{\|}{C}}{-}S}\end{matrix} \longrightarrow \mathrm{S + H_2S + 2\ RN{=}C{=}S}$$

B. 

$$\begin{matrix}\mathrm{RNH{-}\overset{S}{\overset{\|}{C}}{-}S} \\ \mathrm{RNH{-}\underset{S}{\underset{\|}{C}}{-}S}\end{matrix} \longrightarrow \mathrm{S + CS_2 + RNH{-}\overset{S}{\overset{\|}{C}}{-}NHR}$$

Equation B. is the essential part of the mechanism on the preceding page. Three of the decomposition products, sulphur, thiourea, and mustard oil (isothiocyanate), could be isolated almost quantitatively. From the quantities obtained, the relative extents of reactions A. and B. were determined, and it was shown that the extent of reaction B. increases with the molecular weight of the amine used. Reaction A. is preponderant in the case of the lower homologs in the series of aliphatic amines.

Although no thiuram disulphides of aromatic amines were isolated, Von Braun modified his previous reaction mechanism to allow for both courses of decomposition of the hypothetical diaryl thiuram disulphide. When hydrogen peroxide is used for the formation of the thiuram disulphide, half of the original quantity of amine is freed, according to equation (2) on Page 26. It is postulated that this amine condenses with the mustard oil formed by the decomposition of the thiuram disulphide according to equation A.; forming the thiourea. This is Von Braun's modified mechanism for the synthesis of thiocarbanilide by the action of hydrogen peroxide or other oxidizing agent. It is partially supported, in the case of aniline, by the fact that the reaction of aniline and carbon disulphide with iodine has yielded phenyl mustard oil, one of the intermediate products of this reaction mechanism scheme.

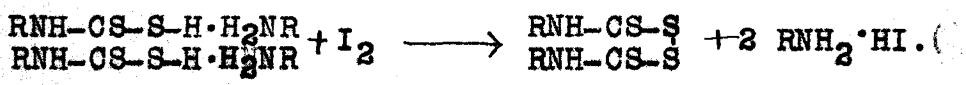
Von Braun's work had been limited to those conditions in which the proportions of amine and carbon disulphide is the exact one needed for the formation of the amine dithio carbamate, i.e., two moles of amine to one mole of carbon disulphide. In acquiring further evidence in this research for the reactions discovered by Von Braun, the range of application was extended to include any excess of carbon disulphide. The reactions of ethanolamine, cyclohexylamine, benzylamine, and isopropylamine were found to subatantiate the equations proposed by Von Braun. In the reaction mechanism scheme which follows, based on those equations, an explanation is offered for the fact that the condensation of primary amines with carbon disulphide, according to Fry's and similar methods, yields thioureas, while secondary amines yield thiuram disulphides.

The following paragraphs present the development of the alternative reaction mechanism proposed for the formation of thioureas from primary amines, and a reason why thiuram disulphides, and not thioureas, are obtained from secondary amines.

As has been shown by Grodzki (33) and others, the first reaction which occurs when a primary or secondary amine reacts with carbon disulphide is the formation of the amine dithio carbamate:

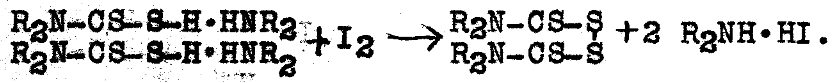
$$2\ RNH_2\quad CS_2\qquad RNH\text{-}CS\text{-}S\text{-}H\cdot H_2NR \qquad (1)$$

This equation has been substantiated in this research by the actual precipitation and isolation of the dithio carbamic salts of cyclohexylamine and benzylamine. When an oxidizing agent is allowed to act on the dithio carbamate at temperatures near 0°, the thiuram disulphide is formed:



$$\begin{array}{l}RNH\text{-}CS\text{-}S\text{-}H\cdot H_2NR\\ RNH\text{-}CS\text{-}S\text{-}H\cdot H_2NR\end{array} + I_2 \longrightarrow \begin{array}{l}RNH\text{-}CS\text{-}S\\ RNH\text{-}CS\text{-}S\end{array} + 2\ RNH_2\cdot HI. \qquad (2)$$

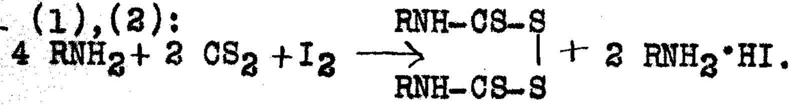
The disubstituted thiuram disulphide is obtained from a primary amine. If a secondary amine were used, the tetrasubstituted thiuram disulphide would result:



$$\begin{array}{l}R_2N\text{-}CS\text{-}S\text{-}H\cdot HNR_2\\ R_2N\text{-}CS\text{-}S\text{-}H\cdot HNR_2\end{array} + I_2 \longrightarrow \begin{array}{l}R_2N\text{-}CS\text{-}S\\ R_2N\text{-}CS\text{-}S\end{array} + 2\ R_2NH\cdot HI. \qquad (2a)$$

The sum of the two equations, (1) and (2), involves a ratio of four moles of amine to one mole of iodine:

Σ (1),(2):



$$4\ RNH_2 + 2\ CS_2 + I_2 \longrightarrow \begin{array}{l}RNH\text{-}CS\text{-}S\\ \qquad\quad\ |\\ RNH\text{-}CS\text{-}S\end{array} + 2\ RNH_2\cdot HI.$$

This ratio of moles of amine to moles of iodine holds for both primary and secondary amines.

When a secondary amine is used as the reactant, then the tetrasubstituted thiuram disulphide obtained is quite stable, even at high temperatures. It does not undergo decomposition; therefore it can be isolated even when the conditions of formation have been drastic.

But when a primary amine has been used as the reactant, then a disubstituted thiuram disulphide is obtained as the product of oxidation. It is very unstable, undergoing slow spontaneous decomposition, or rapidly by a moderate rise in temperature. The reaction temperatures employed in the present thiourea syntheses are sufficiently high to cause this decomposition. The two decomposition courses noted by Von Braun were both observed:

$$\left.\begin{matrix}\text{RNH-CS-S}\\ \text{RNH-CS-S}\end{matrix}\right| \longrightarrow 2\ \text{R-N=C=S} + H_2S + S\ ,\ \text{and} \qquad (3A)$$

$$\left.\begin{matrix}\text{RNH-CS-S}\\ \text{RNH-CS-S}\end{matrix}\right| \longrightarrow \text{RNH-}\underset{\overset{\|}{S}}{C}\text{-NHR} + CS_2 + S. \qquad (3B)$$

In this research, the decompositions of the pure thiuram disulphides were found to vary widely between the two reactions. Thus the extent of reaction (A) in the case of ethanolamine was almost 95 %, while with benzylamine it was only 10 %. As Von Braun stated, the extent of reaction (B) increases with the molecular weight of the amine used.

The mustard oil formed by the reaction of equation (3A) will react with free amine present to form a thiourea:

$$2\ \text{RN=C=S} + 2\ \text{RNH}_2 \longrightarrow 2\ (\text{RNH})_2\text{CS}. \qquad (4A)$$

It is thus evident that the intermediately formed thiuram disulphide may decompose directly to yield a thiourea, as in equation (3B), or may on decomposition yield a mustard oil, which in turn reacts with the amine (equation 4A), also to yield a thiourea.

It can be seen that tetrasubstituted thiuram disulphides can not decompose in this manner, since they lack the amino- hydrogen atoms necessary for the formation of hydrogen sulphide. Mustard oils can not be formed from secondary amines. Therefore the formation of thioureas from secondary amines is impossible by equation (3A) and can not occur according to equation (3B) because of the stability of the thiuram disulphide. Thus, an explanation has been offered to account for the fact that thioureas are not obtained from secondary amines. This explanation applies only to methods wherein oxidizing condensing agents are employed.

It has been noted that the decomposition of thiuram disulphides may, on the one hand, lead to the formation of mustard oils (equation 3A) which in turn combine with primary amines to yield thioureas, or, on the other hand, may decompose directly to yield thioureas (equation 3B). Accordingly, the foregoing description may be summarized in two separate reaction mechanism schemes.

A: $4\ RNH_2 + 2\ CS_2 \longrightarrow 2\ RNH\text{-}CS\text{-}SH \cdot H_2NR$ (1)

$2\ RNH\text{-}CS\text{-}SH \cdot H_2NR + I_2 \longrightarrow (RNH\text{-}CS\text{-}S\text{-})_2 + 2\ RNH_2 \cdot HI$ (2)

$(RNH\text{-}CS\text{-}S\text{-})_2 \longrightarrow 2\ RN{=}C{=}S + H_2S + S$ (3)

$2\ RN{=}C{=}S + 2\ RNH_2 \longrightarrow 2\ (RNH)_2CS$ (4)

$H_2S + I_2 \longrightarrow 2\ HI + S$ (5)

$2\ HI + 2\ RNH_2 \longrightarrow 2\ RNH_2 \cdot HI$ (6)

$\sum$ A:(1),(2),(3),(4),(5),(6):

$8\ RNH_2 + 2\ CS_2 + 2\ I_2 \longrightarrow 2\ (RNH)_2CS + 4\ RNH_2 \cdot HI + 2\ S$

B: $4\ RNH_2 + 2\ CS_2 \longrightarrow 2\ RNH\text{-}CS\text{-}SH \cdot H_2NR$ (1)

$2\ RNH\text{-}CS\text{-}SH \cdot H_2NR + I_2 \longrightarrow (RNH\text{-}CS\text{-}S\text{-})_2 + 2\ RNH_2 \cdot HI$ (2)

$(RNH\text{-}CS\text{-}S\text{-})_2 \longrightarrow (RNH)_2CS + CS_2 + S$ (3)

$CS_2 + 2\ RNH_2 \longrightarrow (RNH)_2CS + H_2S$ (4)

$H_2S + I_2 \longrightarrow 2\ HI + S$ (5)

$2\ HI + 2\ RNH_2 \longrightarrow 2\ RNH_2 \cdot HI$ (6)

B: (1),(2),(3),(4),(5),(6) :

$8\ RNH_2 + 2\ CS_2 + 2\ I_2 \longrightarrow 2\ (RNH)_2CS + 4\ RNH_2 \cdot HI + 2\ S.$

It is evident that the final equations, regardless of the manner of decomposition of the thiuram disulphide, are identical. This equation is the same as Von Braun's (page 27), multiplied by two. Fry's equation for his method is also identical, except for the multiplication by two and the substitution of pyridine, mole-for-mole, for half of the primary amine in the above equation. Thus, according to either or both reaction mechanism schemes, it is conceivable that the formation of thiuram disulphides precedes that of thioureas.

EXPERIMENTAL

Reagents:

The reagents used in this research were of the purity and grade as follows:

absolute methanol: Merck's C.P.
carbon disulphide: Malinckrodt's C.P.
iodine: Coleman and Bell's resublimed
pyridine: Coleman and Bell's and Merck's, dried over NaOH and redistilled, B.P.: 113-115°.
ethanolamine: Eastman's C.P., redistilled, B.P.:168.5°
cyclohexylamine: Eastman's, B.P. 133-135°
benzylamine: Eastman's , B.P.:70-71°/10 mm.
isopropylamine: Kahlbaum's
aniline: Kahlbaum's, redistilled, B.P.:186.5-187°.

General procedure for the formation of a disubstituted thiuram disulphide:

The equation for the formation of a disubstituted thiuram disulphide from a primary amine has been shown to be (page 30):

$$4\ RNH_2 + 2\ CS_2 + I_2 \longrightarrow \begin{array}{l} RNH{-}CS{-}S \\ RNH{-}CS{-}S \end{array} + 2\ RNH_2 \cdot HI.$$

For every mole of iodine used in this reaction four moles of amine must react to form one mole of the thiuram disulphide. It was found that this ratio could be experimentally determined, in the case of the amines studied in this research, by reacting a solution of a known weight of the amine in a mixture of absolute methanol and carbon disulphide, with a standard solution of iodine in absolute methanol. From the quantities of amine and iodine solution which were equivalent at the recognizable end point, the molecular ratio, amine:iodine, was determined. The details of the method are described in the following pages. Where the product was soluble, it was recovered by evaporating the solution almost to dryness, when the thiuram disulphide crystallized out.

With each of the compounds investigated - (I.) Ethanolamine, (II.) Cyclohexylamine, (III.) Benzylamine, (IV.) Isopropylamine,- the first experiments conducted were designed to determine the molecular ratios in which the amine and the iodine interacted in the in the presence of carbon disulphide, using methyl alcohol as a solvent.

The products of these reactions were disubstituted thiuram disulphides. After determining the percent theory yield of the thiuram disulphides, the nature and extent of the decompositions of the various thiuram disulphides were next investigated.

Finally, definite quantities of each of the thiuram disulphides were reacted with slightly excess quantities of the corresponding amine, in order to determine to what extent the thiuram disulphides reacted with the amines to yield thioureas.

In preparing thiuram disulphides, about 20 grams of the amine was accurately measured from a burette into a solvent consisting of 75 cc. of methanol and 25 cc. of carbon disulphide. This mixture was then reacted at 0° with a solution of iodine in a mixture of two volumes of methanol and one volume of carbon disulphide. The concentration was approximately 20 grams of iodine per 100 cc. of the mixed solvents. Completion of the reaction was indicated by a permanent iodine color, which was discharged by an additional small drop of the amine.

The thiuram disulphide of ethanolamine was sufficiently insoluble to isolate it by filtration, as a white, powdery precipitate. The thiuram disulphides of the other amines investigated were too soluble to isolate in this manner. They were recovered by blowing air over the solution, evaporating it almost to dryness, then disintegrating the solid residue with water. The suspension of thiuram disulphide was filtered, washed repeatedly with more distilled water, then dried. The product was purified still further by grinding and washing with solvents such as methanol, carbon disulphide, or ether. From the weight of thiuram disulphide recovered, the percent theoretical yield was calculated, on the basis of the equation already stated.

This method for determining the molecular ratio of amine to iodine in the thiuram disulphide reaction, and the method of preparing the thiuram disulphide, as first developed for ethanolamine, were subsequently applied to cyclohexylamine, benzylamine, and isopropyl amine.

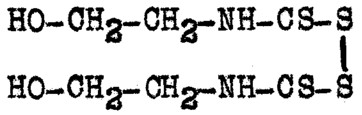
I. Ethanolamine

Preliminary trial of method:

Repeated attempts to react ethanolamine according to Fry's method with carbon disulphide as the only solvent resulted in yellow to brown pasty products. Even when large quantities of reactants were used, no definite org- organic products could be isolated in quantities sufficient for identification. In an endeavor to modify the conditions of this method by making use of variations in temperature and solvents, it was found that a definite crystalline product was obtained when the reaction was performed in a medium of carbon disulphide and anhydrous methyl alcohol.

Approximately ten drops of ethanolamine were dissolved in 10 cc. of a mixture of about equal volumes of absolute methyl alcohol and carbon disulphide. The solution, cooled in an ice bath, was treated with a solution of iodine in carbon disulphide, titrating to a sharp end point, shown by the permanence of the iodine color. A powdery white precipitate separated rapidly from the colorless solution. It was filtered off and found to contain no iodine but a large quantity of sulphur. It melted at 98°, with decomposition. When the filtrate was evaporated, it gave a yellow oil containing much iodine (presumably the hydriodide of the amine), but no free sulphur.

From the fact that a large quantity of iodine was consumed but no free sulphur was formed, it was suggested that the white precipitate containing sulphur is the thiuram disulphide of ethanolamine:

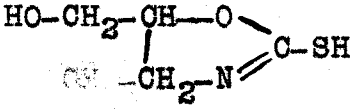


$$\begin{array}{l} HO-CH_2-CH_2-NH-CS-S \\ \qquad\qquad\qquad\qquad\quad\;\; | \\ HO-CH_2-CH_2-NH-CS-S \end{array} .$$

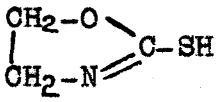
Earlier work on ethanolamine:

In 1899, Gabriel (47) reacted bromoethyl amine with carbon disulphide and sodium hydroxide. He considered that the mixture of bromo-amine and base was equivalent to nascent ethanolamine. The product melted at 106-7°, and was identified as mercapto-thiazoline:

Knorr and Roessler (48) obtained the same product by reacting ethanolamine with carbon disulphide and potassium hydroxide. But with amino-polyols, of the type $HOCH_2-CH(OH)-CH_2NH_2$, the reaction under the same consitions yields a mercapto-oxazoline (49):



This latter reaction has never been shown to apply to ethanolamine. The mercapto-oxazoline which would be formed by the reaction has not been reported in the literature. Its formula is:



The dithio carbamic acid derived from ethanolamine has been isolated as the barium salt (50).

Molecular ratio, ethanolamine : iodine :

Since in the above preliminary experiment, there was a very distinct and sharp reaction, the following experiment was designed to determine the molecular ratio in which ethanolamine and iodine interacted with carbon disulphide in the methyl alcohol medium.

From a burette, a 12 cc. sample of ethanolamine was accurately measured into a cold mixture of 20 cc. methanol and 20 cc. carbon disulphide. The solution was kept at 0° and titrated to an exact end point with a 0.7829 N. solution of iodine in absolute methanol. The slight iodine color at the end point was removed by adding a fraction of a drop of the amine. The density of ethanolamine is given by the Handbook of Chemistry and Physics (51) as 1.018, hence the weight and number of moles of ethanolamine used could be calculated from the observed volume. In the same way, the number of moles of iodine consumed was determined from the normality and volume of the iodine solution used in the titration. From these values, the ratio of moles of ethanolamine to moles of iodine was computed, and compared with the theoretical value of 4 : 1 , called for by the equation. Duplicate determinations of the ratio were made. The results are listed in Table I.

Table I

Determination of Ratio, 4 $HO(CH_2)_2NH_2/I_2$, as based on equation:

$$4\ HOCH_2CH_2NH_2 + 2CS_2 + I_2 \rightarrow (HOCH_2CH_2NHCS{-}S{-})_2 + 2\ HO(CH_2)_2NH_2 \cdot HI$$

Run	$HO(CH_2)_2NH_2$ used (moles)	I_2 used (moles)	Molar ratio $\frac{HO(CH_2)_2NH_2}{I_2}$ found	Molar ratio $\frac{HO(CH_2)_2NH_2}{I_2}$ theory
I.	0.2102	0.05238	4.013 : 1	4.000 : 1
II.	0.1893	0.04703	4.026 : 1	"
Aver.			4.019 : 1	4.000 : 1

The data of Table I shows that the actual molecular ratio of ethanolamine to iodine for the thiuram disulphide reaction, with methanol as solvent, agrees very closely with the theory for the reaction. The same method was applied to cyclohexylamine and benzylamine, with results idicated on subsequent pages.

<u>Yield of diethanol thiuram disulphide</u>:

Two sets of duplicate determinations were made of the percent theoretical yield of diethanol thiuram disulphide. The procedure followed was that already described in this section under <u>general procedure</u>, using 20 gram samples of ethanolamine. The filtered thiuram disulphide was washed several times with cold methanol, to remove any carbon disulphide or ethanolamine hydriodide, and air-dried at room temperature. The data obtained in these determinations is listed in Table II.

Table II

Determination of Percent Theoretical Yield of Diethanol Thiuram Disulphide:

Run	$HO(CH_2)_2NH_2$ used (grams)	$(HOCH_2CH_2NHCS_2-)_2$ found (grams)	% Theory yield
I.	19.69	18.47	89.69
II.	21.57	20.31	89.64
Aver.			89.66
III.	25.37	24.8	87.66
IV.	24.85	25.3	91.26
Aver.			89.46

The recovery of practically 90 % of the theoretical yield of the thiuram disulphide indicated that the predominant reaction which occurs at this temperature is the formation of the thiuram disulphide.

Analysis of diethanol thiuram disulphide:

The diethanol thiuram disulphide is a white powder, decomposing sharply at 98°, with evolution of hydrogen sulphide. When boiled with water, it forms a precipitate of free sulphur, followed by the separation of a yellow tar. From the methanol - carbon disulphide filtrate there was obtained on evaporation a quantity of impure ethanolamine hydriodide, in the form of large quartz-like crystals. The ethanolamine hydriodide, $HOCH_2CH_2NH_2 \cdot HI$, was recrystallized from absolute methanol, forming small white needles, melting at 84°. The melting point of this compound has not previously been recorded.

Pure samples of the thiuram disulphide were analyzed in duplicate for nitrogen, by the Kjeldahl method, and for sulphur, by the Parr method. Details of the methods as applied to thiuram disulphides were described by Far Farquhar (2). The analytical data listed in Table III, identified the compound as diethanol thiuram disulphide.

Table III

Analysis

Sample (grams)	0.1145 N. acid CC.	% N found	% N theory
0.5194	32.07	9.902	10.28 %
0.5186	32.55	10.07	"
Average		9.99	10.28

Sample (grams	$BaSO_4$ (grams)	% S found	% S theory
0.5016	1.6816	46.06	47.08 %
0.5697	1.9020	45.86	"
Average		45.96	47.08 %

The previous preparation, properties, and analysis of diethanol thiuram disulphide have not been recorded in the literature.

<u>Determination of sulphur formed by decomposition of diethanol thiuram disulphide</u>:

According to theory previously explained, a molecule of any thiuram disulphide may be decomposed by heat, forming one atom of free sulphur in two distinct ways.

When the thiuram disulphide of ethanolamine was boiled with distilled water, sulphur was precipitated, but shortly afterward a yellow tar also separated from the solution, making it impossible to determine the yield of free sulphur. Several variations of this method failed to give check results in duplicate trials. But when 0.02 moles of the thiuram disulphide was mixed with 25 cc. distilled water and allowed to stand at room temperature for 14 days, a slow evolution of hydrogen sulphide was evident, and the white thiuram disulphide was gradually converted into a layer of yellow sulphur. Occasional shaking aided the evolution of hydrogen sulphide. The sulphur was filtered off in a fritted glass crucible, dried, and weighed. The results, Run I in Table IV, indicated that with larger quantities of thiuram disulphide, a closer approximation to theoretical results might be obtained. Accordingly, the same experiment was repeated in duplicate runs, with tripled quantities of thiuram disulphide and water. After standing for 17 days at room temperature, the quantity of free sulphur obtained was very nearly the theoretical one gram-atom, as shown in runs IIa and IIb of Table IV.

Table IV

Determination of Sulphur Formed by Decomposition of Diethanol Thiuram Disulphide

Run	$(HOCH_2CH_2NHCS_2-)_2$		Sulphur	found	Atoms sulphur recovered from 1 mole thiuram
	grams	moles	grams	atoms	
I	5.448	0.0200	0.536	0.0167	0.836
II(a)	16.34	0.0600	2.114	0.0659	1.099
II(b)	16.34	0.0600	2.088	0.0651	1.086

Determination of hydrogen sulphide formed by decomposition of diethanol thiuram disulphide:

According to the theory already outlined, when a thiuram disulphide is decomposed by heat to yield the mustard oil, then one mole of thiuram disulphide also produces one mole of hydrogen sulphide. Several methods were attempted to determine the yield of hydrogen sulphide evolved. Those not successful were:

absorption of dry H_2S in ascarite;
absorption of H_2S in $CuSO_4$ solution; and
decomposition of the thiuram disulphide in a solution of $CuSO_4$.

In the method finally developed, the thiuram disulphide was decomposed by refluxing with water. The vapors from the decomposition flask, after passing through a short reflux condenser, were led into a 250 cc. Erlenmeyer flask, which was immersed in ice and acted as a trap for any mustard oil or carbon disulphide which may have distilled over. From the trap, the evolved gas was bubbled in turn through two 250 cc. wash bottles, containing a known excess of standard iodine - potassium iodide solution. Throughout the course of the reaction, a slow current of air was drawn through the train of apparatus, to carry all of the hydrogen sulphide through the iodine solutions. The air was introduced into the system at the base of the reflux condenser, by means of a long glass tube open at one end to the atmosphere. A few grams of sodium carbonate were dissolved in each absorption bottle to increase the solubility of the hydrogen sulphide.

When decomposition was complete, the iodine solutions were transferred to a large beaker, rinsing the bottles thoroughly. An excess of 6 normal acetic acid was added and the excess iodine was titrated with standard thiosulphate solution, using starch as indicator. One mole of hydrogen sulphide was equivalent to each mole of iodine which had been consumed during the reaction. Subtracting the amount of iodine equivalent to the thiosulphate used, from the total amount of iodine used, gave as result the number of moles of iodine equivalent to the hydrogen sulphide produced:

$$H_2S + I_2 \longrightarrow 2\,HI + S\ .$$

An accurately weighed sample, usually 1/50 mole, of the thiuram disulphide, was decomposed by boiling with about 125 cc. of water. At completion of decomposition, any thiourea left in the flask was filtered off and recrystallized. This method was applied throughout this research. The results obtained with diethanol thiuram disulphide are listed in Table V.

Table V

Yield of Hydrogen Sulphide from Diethanol Thiuram Disulphide in Terms of Equation:

$$(HOCH_2CH_2NH\text{-}CS\text{-}S\text{-})_2 \longrightarrow H_2S + S + 2\ HOCH_2CH_2N{=}C{=}S$$

Run	$(HOCH_2CH_2NHCS_2)_2$ used (moles)	0.8490 N. I_2 used (cc.)	H_2S found (moles)	H_2S yield % theory
I	0.0200	44.5	0.0189	94.5
II	0.0200	44.63	0.01894	94.7

The data in the preceding Table IV indicates that one gram-mole of diethanol thiuram disulphide yields one gram-atom of sulphur. In addition, the percent theory yield of hydrogen sulphide, based upon that type of decomposition which yields sulphur, hydrogen sulphide, and a mustard oil, is practically 95 %.

<u>Isolation and identification of mercapto-oxazoline</u>:

On long or vigorous heating of the thiuram disulphide alone or with various solvents, the product was a tar of varying density and color. The polymerization which caused the tar was avoided to a large extent by following the procedure described below. A quantity of the thiuram disulphide not exceeding 5 to 7 grams was treated with 2 to 3 times its volume of normal butyl alcohol. The mixture was gently heated on a hot plate to near the boiling point of the alcohol, whereupon a clear yellow solution was obtained, accompanied by a voluminous evolution of hydrogen sulphide. When the frothing due to the gas ceased and a clear solution remained, the vessel was cooled rapidly in an ice bath, or preferably, a freezing mixture. The yellow precipitate formed was filtered off, pressed very dry, and recrystallized from boiling alcohol. On cooling the alcohol solution, a small amount of sulphur was precipitated, which was filtered from the cold solution. The alcoholic filtrate was then evaporated in the cold, giving white needle-shaped crystals, later identified as mercapto-oxazoline. The product was recrystallized twice from alcohol in the same way, using Darco for the first recrystallization. Because of the incomplete decomposition of the thiuram disulphide and the large proportion of product lost in the recrystallizations necessary for this procedure, no yield of mercapto-oxazoline was determined. The melting point of the pure product is 96-97°. Prolonged heating causes it to polymerize.

Duplicate samples were analyzed for nitrogen and sulphur in the same way as previously stated for the thiuram disulphide of ethanolamine. The results are listed in Table VI.

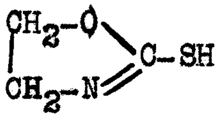
Table VI

Analysis

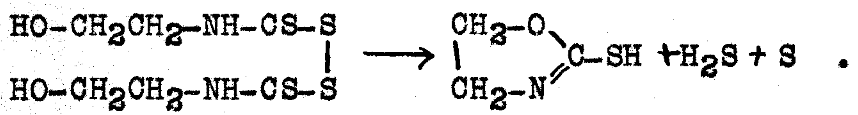
Sample (grams)	0.1145 N. acid (cc.)	% N found	% N theory
0.4773	40.25	13.52	13.59
0.4982	41.94	13.50	"
Average		13.51	13.59

Sample (grams)	$BaSO_4$ (grams)	% S found	% S theory
0.3270	0.7082	29.75	31.10
0.3333	0.7341	30.26	"
Average		30.01	31.10

The analyses conclusively identify the product as mercapto-oxazoline. It is very soluble in alcohol and water. Its solution in water gives a white precipitate with mercuric chloride or silver nitrate, soluble in dilute acids. This is a characteristic reaction of the mercapto- group, supporting the formula:



The equation for the decomposition of diethanol thiuram disulphide thus has been shown to be:



<u>Reaction of Diethanol Thiuram Disulphide with Ethanolamine:</u>

When 8 grams of diethanol thiuram disulphide were refluxed in 100 cc. of methyl alcohol with the theoretical quantity of ethanolamine (3.5 grams), hydrogen sulphide was evolved, and brown tarry resins were obtained, from which it was impossible to recover the expected thiourea.

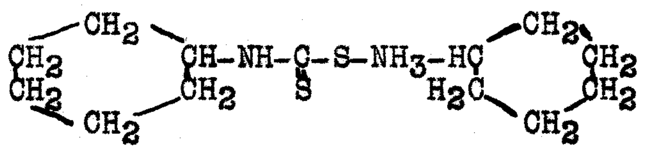
II. Cyclohexylamine

Earlier work on cyclohexylamine:

Von Baeyer, in 1894, prepared cyclohexylamine, and reacted it with phenyl mustard oil (52). He showed that the addition of carbon disulphide to a solution of the amine in ether gives an instantaneous precipitation of the dithio carbamic salt. Skita and Rolfes (53) reacted cyclohexylamine to form the dithio carbamate, thiourea, and mustard oil. The dithio carbamate, from cold amine and carbon disulphide, melted at 160° when recrystallized. The barium salt of the dithio carbamic acid has also been prepared (50). The thiourea was obtained by heating the amine and carbon disulphide in alcoholic potassium hydroxide. Its melting point, when recrystallized, was 180-181°. The mustard oil was obtained from the thiourea by heating with phosphoric acid or with mercuric chloride. A better method for preparing the mustard oil, but of which no record of its application to cyclohexylamine exists, consists of treating the thiuram disulphide first with sodium ethylate, then with iodine (54). Another synthesis of the di-cyclohexyl thiourea was accomplished by heating N-methylene cyclohexylamine with melted sulphur (55). The melting point of the thiourea obtained was 179-180°. The thiuram disulphide derived from cyclohexylamine has not been recorded in the literature.

Cyclohexylamine salt of cyclohexyl dithio carbamic acid:

The dithio carbamate of cyclohexylamine is also called cyclohexylammonium cyclohexyl dithio carbamate. Its formula is:



Cyclohexylamine, 8 cc., was dissolved in 100 cc. of absolute methyl alcohol, cooled to 0°. Then 20 cc. of carbon disulphide was added rapidly, with noticeable evolution of heat. The mixture was kept ice-cold for about 15 minutes, whereupon precipitation of the dithio carbamate commenced. When precipitation was complete, the mass of white crystals was filtered off, washed with methanol, pressed free of solvent, and air-dried.

The melting point, taken in a capillary tube, varied with the manner in which it was taken. When the sample was immersed in a bath at 100° and heated gradually, it softened at 160°, gas was evolved, then it turned into a solid which melted sharply at 181°. A mixture of the dithio carbamate with the thiourea gave the same melting point values, when heated gradually from 100°. But it was shown that the two compounds were not identical, since the same mixture melted instantly when plunged into a bath at about 170°, below the melting point of the thiourea. It was evident that the compound believed to be the dithio carbamate decomposed repidly, with evolution of gas (hydrogen sulphide) to yield the pure thiourea. A pure sample of the dithio carbamate was plunged into a bath at 158° and heated rapidly. It melted sharply at 160° (the correct melting point), evolved hydrogen sulphide, then solidified. A portion of the dithio carbamate was recrystallized from hot alcohol. A copious evolution of hydrogen sulphide occurred when the solution was heated, and the dithio carbamate was precipitated by cooling the alcoholic solution. The pure dithio carbamic salt gave a melting point of 159-160°, when it was inserted into a bath at 156° and heated rapidly. When the melting point reading was taken slowly, the melting point of the thiourea, 180-181°, was observed. These results establish conclusively the identity of the cyclohexylamine salt of cyclohexyl dithio carbamic acid, and prove that it is decomposed rapidly and quantitatively by heat to the corresponding thiourea.

$$C_6H_{11}NH\text{-}CS\text{-}S\text{-}H \cdot H_2N\text{-}C_6H_{11} \longrightarrow (C_6H_{11}NH)_2CS + H_2S$$

Preparation of di-cyclohexyl thiuram disulphide and determination of ratio, amine : iodine :

In a preliminary experiment, it was found that cyclohexylamine can also be converted into the thiuram disulphide in the same way as ethanolamine. The procedure was varied to allow for differences in solubility, since the di-cyclohexyl thiuram disulphide is quite soluble in carbon disulphide, methyl alcohol, and most other organic solvents.

Duplicate runs were made in which an accurately measured quantity of cyclohexylamine, about 10 grams, was reacted with a mixture of 75 cc. of methanol and 25 cc. of carbon disulphide. The ratio of amine to iodine was determined by titrating the cold suspension of the dithio carbamate with a 0.7980 N. solution of iodine in methanol. At the end point, the solvent was evaporated off and the thiuram disulphide isolated in the manner described under <u>general procedure</u>. Both gross and pure yields (ground and washed with methanol) were measured. The gross yield, which is the correct measure of the extent of the reaction, ran better than 95 % theoretical. The results are shown in Table VII.

Table VII

Molar ratio, $C_6H_{11}NH_2:I_2$, and yield of Di-cyclohexyl Thiuram Disulphide

	I	II	Average
Moles amine used	0.1080	0.1058	
Moles iodine used	0.03103	0.03052	
Ratio, $\frac{\text{moles amine}}{\text{moles iodine}}$	3.481	3.466	3.478
Gross yield (grams)	8.7 g.	9.2 g.	
Gross yield (%)	92.5 %	99.8 %	96.2 %
Pure yield (grams)	7.5 g.	7.9 g.	
Pure yield (%)	79.8 %	85.7 %	82.7 %

Complete interaction of cyclohexylamine and iodine according to the theoretical equation,

$$4\ C_6H_{11}NH_2 + 2\ CS_2 + I_2 \longrightarrow (C_6H_{11}NH\text{-}CS\text{-}S\text{-})_2 + 2\ C_6H_{11}NH_2 \cdot HI,$$

requires the ratio of amine to iodine to be 4 : 1 . The best ratio obtainable in these experiments is an average of 3.478 : 1 . The di-cyclohexyl thiuram disulphide, purified by grinding and washing with absolute methanol, melted at 79.5-80°, with decomposition.

Identification of di-cyclohexyl thiuram disulphide:

Since di-cyclohexyl thiuram disulphide has not been reported previously in the literature, it was identified by duplicate sulphur and nitrogen determinations on purified samples melting at 80°. The analyses established the formula as

$$C_6H_{11}NH\text{-}CS\text{-}S\text{-}S\text{-}CS\text{-}NHC_6H_{11}\ ,$$

with results as listed in Table VIII.

Table VIII

Analysis

Sample (grams)	0.2541 N. acid (cc.)	% N found	% N theory
0.8594	18.88	7.82	8.04
0.8912	19.78	7.90	"
Average		7.86	8.04

Sample (grams)	$BaSO_4$ (grams)	% S found	% S theory
0.4345	1.1568	36.56	36.81
0.5192	1.3790	36.48	"
Average		36.52	36.81

More precise data is difficult to secure since most of the thiuram disulphides decompose spontaneously. This renders their purification by recrystallization very difficult.

Determination of hydrogen sulphide and thiourea formed by decomposition of di-cyclohexyl thiuram disulphide:

Duplicate samples of di-cyclohexyl thiuram disulphide were decomposed by refluxing with water. The hydrogen sulphide evolved and the thiourea produced (by the second sample) were determined, using the same procedure and apparatus described for the corresponding compound of ethanolamine. It was found that of the two possible courses of decomposition, that leading to mustard oil and hydrogen sulphide occurred to the extent of about 28 %, while a 64 % yield of the thiourea was obtained. The results are listed in Table IX.

Table IX

Yield of Hydrogen Sulphide and Thiourea Formed by Decomposition of Di-cyclohexyl thiuram Disulphide

Run	Sample (moles)	H_2S found (moles)	Yield H_2S, % theory	Thiourea (moles)	yield, % theory
I	0.0200	0.005393	26.96	------	------
II.	0.0200	0.005765	28.82	0.01290	64.5
Average			27.89		

Free sulphur was observed in the residue in the decomposition flask, while carbon disulphide was collected in the trap. **The thiourea was** recrystallized, melting at 179.5-180°, thus identifying it. In run II, the quantity of hydrogen sulphide and thiourea determined corresponded to 93.3 % of the amount of thiuram disulphide originally used.

Reaction of di-cyclohexyl thiuram disulphide with cyclohexylamine:

In accordance with the equations stated in the theoretical section, the thiuram disulphide of cyclohexylamine can be expected to react with the amine, to produce di-cyclohexyl thiourea, hydrogen sulphide, and sulphur, according to the following equation:

$$(C_6H_{11}NH-CS-S-)_2+2\ C_6H_{11}NH_2 \longrightarrow 2(C_6H_{11}NH)_2CS+H_2S+S.$$

A known weight of the thiuram disulphide was mixed with a small excess of cyclohexylamine in a 250 cc. Erlenmeyer flask. The flask was attached to a reflux condenser, then heated gradually on an oil bath. Much foaming due to the evolution of hydrogen sulphide occurred, while the temperature was gradually raised to 145° at the end of an hour. The temperature was then kept at 120-130° for five more hours. About 150 cc. of distilled water was added to the cooled contents of the flask, and the solid was crushed to insure disintegration of the residue. The water was heated to 90° to extract the excess amine from the solid residue, then the suspension of thiourea and sulphur in water was cooled in an ice bath, filtered, and washed thoroughly with distilled water. The dried product, containing free sulphur, was weighed as the crude yield. It was separated from sulphur by recrystallization, thereafter being considered as the pure yield.

The observed yield of crude product, consisting of the thiourea and sulphur, was 100 % theoretical, while that of the pure product was 95 %. These results are tabulated in Table X. The pure product was recrystallized once more from alcohol, using Darco, and then was identified by its melting point, 180-181°.

Table X

Reaction of Di-cyclohexyl Thiuram Disulphide with Cyclohexylamine

Run	Thiuram used (grams)	Crude product (gms.)	Crude product %	Pure Product (gms.)	Pure Product %	Melting point
I.	12.7	18.6	99.5	16.5	94.2	179.5-181°
II.	13.2	19.4	100.0	17.4	95.6	180-181°

III. Benzylamine

Earlier work on benzylamine:

Symmetrical dibenzyl thiourea was first prepared by Strakosch (56), in 1872, by refluxing an alcoholic solution of benzylamine and carbon disulphide until no more hydrogen sulphide was produced. He gave the erroneous melting point of 114°. In 1891, Salkowski (57) repeated the same work and showed that the true melting point of the thiourea is 148°. In the same paper, he described the preparation of the benzylamine salt of benzyl dithio carbamic acid,

$$C_6H_5CH_2NH\text{-}CS\text{-}S\text{-}H\cdot H_2NCH_2C_6H_5\ ,$$

obtained by adding carbon disulphide to a cold solution of benzylamine in alcohol. The compound precipitated as white crystals, showing a melting point of about 119°, with decomposition. As the compound decomposes, hydrogen sulphide is developed, and the melting point gradually rises. By heating the dithio carbamate at 100° for an hour in a stream of air, it was converted almost quantitatively into the thiourea. This behavior is similar to that already described for the corresponding cyclohexyl compound. Salkowski found that the thiourea was stable to the usual reaction for conversion into the corresponding mustard oil, i. e., heating with concentrated phosphoric or hydrochloric acid.

The benzylamine salt of dithio carbamic acid, $H_2N\text{-}CS\text{-}S\text{-}H\cdot H_2NCH_2C_6H_5$, has also been prepared (58), but not by the addition of carbon disulphide to the amine. Von Braun (37) synthesized the thiourea by treating a mixture of the amine and carbon disulphide with 3 % hydrogen peroxide. He recorded a melting point of 146°.

At the same time, in 1902, Von Braun prepared the dibenzyl thiuram disulphide, following the procedure described for his work in the theoretical section, and found the melting point to be 71°. When heated to 100°, the thiuram disulphide decomposed in both possible ways, forming the mustard oil and the thiourea, to approximately equal extents. The thiourea thus obtained was identical in melting point with that prepared by the use of hydrogen peroxide. Benzyl mustard oil has been prepared in good yield by a method also developed by Von Braun (59), which consists of treating the thiuram disulphide successively with sodium ethylate and iodine.

The thiourea, melting at 147-8°, has also been synthesized by the interaction of benzylamine and thiophosgene, $CSCl_2$ (20). Two years later, in 1926, it was again prepared, this time using neither condensing agent nor solvent (19). The recorded melting point was 145-6°. The most recent synthesis of dibenzyl thiourea is by Underwood and Dains (60) in 1935, with the reaction of benzylamine and perthiocyanic acid, $H_2C_2N_2S_3$, to yield dibenzyl thiourea, melting at 147-8°, which appears to be the most accurate melting point.

Benzylamine salt of benzyl dithio carbamic acid:

The dithio carbamate of benzylamine is also known as benzylammonium benzyl dithio carbamate, $C_6H_5CH_2NH{-}CS{-}S{-}H \cdot H_2NCH_2C_6H_5$. Benzylamine, 10 cc., was dissolved in 40 cc. of ice-cold methanol, then 15 cc. of carbon disulphide was gradually added, while the mixture was cooled in an ice-bath to absorb the large quantity of heat liberated. A voluminous precipitate of the white dithio carbamate was formed, which was filtered off, washed several times with methyl alcohol, then air-dried. When a melting point reading was taken in the usual way, i.e., by gradually heating a sample in a capillary tube, the melting point was 120-124°, which compared satisfactorily with that of Salkowski, about 119°. But when the sample in a capillary tube was plunged into a bath at 125°, and heated rapidly, it melted fairly sharply at 134°. Both melting points are accompanied by decomposition to the thiourea, but the more probable melting point is 134°, since the procedure used minimizes the extent of decomposition before melting.

Preparation of dibenzyl thiuram disulphide and determination of molecular ratio, amine : iodine :

The same procedure used with cyclohexylamine was applied to benzylamine, using a 0.7628 N. solution of iodine in methyl alcohol for the titration. The results, listed in Table XI, show a ratio of amine to iodine which is very nearly the theoretical 4 : 1, and a gross yield amounting to 96 % of the theory.

Table XI

Molar ratio, $C_6H_5CH_2NH_2:I_2$, and Yield of Dibenzyl Thiuram Disulphide

	I	II	Average
Moles amine used	0.09432	0.09523	
Moles iodine used	0.02291	0.02351	
Ratio, $\frac{\text{moles amine}}{\text{moles iodine}}$	4.117	4.052	4.084
Gross yield (grams)	8.5	8.1	
Gross yield (%)	98.9	93.3	96.1

The combined yields of the thiuram disulphide were ground to a paste with carbon disulphide, filtered, washed twice with carbon disulphide, then twice with methyl alcohol. The dried product consisted of snow-white crystals, melting at 80-81°.

Identification of dibenzyl thiuram disulphide:

Although the observed melting point did not agree with that recorded by Von Braun, 71°, the identity of the product was evident from the method of preparation. However, as a further check, duplicate samples were analyzed for sulphur, with the results shown in Table XII. The formula of the thiuram disulphide is

$C_6H_5CH_2NH-CS-S-S-CS-NH-CH_2C_6H_5$.

Table XII

Table XII

Analysis

Sample (grams)	$BaSO_4$ (grams)	% S found	% S theory
0.6097	1.5352	34.57	35.2
0.5320	1.3400	34.59	"
Average		34.6	35.2

Having thus established the identity of the thiuram disulphide, its correct melting point is set at 80-81°, not 71°. The compound is insoluble in water, moderately soluble in methyl alcohol, and very soluble in carbon disulphide. It has an anise-like odor, which may be due to traces of impurities.

Determination of hydrogen sulphide and thiourea formed by decomposition of dibenzyl thiuram disulphide:

The procedure used for determining the hydrogen sulphide and thiourea formed by decomposition of a thiuram disulphide has already been described. This method was applied to duplicate 0.0200 mole samples of dibenzyl thiuram disulphide. The results were only moderately precise, corresponding to a total of 106 % of the thiuram disulphide used. That is, from the two possible decompositions, the hydrogen sulphide yield corresponded to 10 %, while the dibenzyl thiourea was equivalent to 96 % of the original amount of thiuram disulphide. These results are listed in Table XIII.

Table XIII

Yield of Hydrogen Sulphide and Thiourea Formed by Decomposition of Dibenzyl Thiuram Disulphide

Run	Sample	H_2S found	Yield H_2S,	Thiourea yield,	
	(moles)	(moles)	% theory	(moles)	% theory
I.	0.0200	0.00219	10.95	0.0191	95.5
II.	0.0200	0.00177	8.87	0.0195	97.5
Average			9.91	0.0193	96.5

Free sulphur and carbon disulphide were observed among the products, as is to be expected from the theory. The recrystallized thiourea melted at 145.5-146°, which agrees with the melting point recorded in the literature.

<u>Reaction of dibenzyl thiuram disulphide with benzylamine</u>:

Dibenzyl thiuram disulphide was reacted with benzylamine in exactly the same manner as has been described for the corresponding cyclohexyl compounds, yielding the thiourea and sulphur according to the equation -

$$(C_6H_5CH_2NH-CS-S-)_2 + 2\ C_6H_5CH_2NH_2 \longrightarrow 2(C_6H_5CH_2NH)_2CS + H_2S + S.$$

The yield of crude product, consisting of thiourea and sulphur, was about 107 % of the theoretical value, while that of the recrystallized product, the thiourea, was almost 100 %. The results obtained with the benzyl compounds are listed in Table XIV.

Table XIV

Reaction of Dibenzyl Thiuram Disulphide with Benzylamine

Run	Thiuram used (grams)	Crude Product (gms.)	Crude Product %	Pure Product (gms.)	Pure Product %	Melting point
I.	12.35	19.2	104	17.2	99.1	146.5°
II.	12.80	21.1	110	18.1	100.6	147°
Average			107 %		99.8 %	147°

The pure product was recrystallized again to check the tabulated melting point with the recorded values. The observed melting point of the pure thiourea is 147°, agreeing with the most probable values in the literature.

IV. Isopropylamine

The amines which have been studied so far were representatives of these three classes of primary amines - hydroxy-aliphatic, cyclo-aliphatic, and aromatic-aliphatic. Von Braun was not able to obtain a thiuram disulphide from any primary aromatic amine. His experience was repeated in this research with aniline, using basically the same procedure already described in this section for the other amines. The product was an indeterminate mixture, smelling strongly of triphenyl guanidine and phenyl mustard oil. Since the instability of disubstituted thiuram disulphides prevents their purification by recrystallization, this trial was discarded. There remained the application of the reactions considered in this research to a typical unsubstituted primary aliphatic amine. For this purpose, isopropylamine was chosen. The quantity available was just sufficient to prepare the thiuram disulphide and the thiourea.

Earlier work on isopropylamine:

In 1882, Jahn (61) synthesized isopropylamine and prepared the thiourea by shaking a solution of the amine with carbon disulphide, then steam distilling the mixture over mercuric chloride. The mustard oil was observed, but the main product was di-isopropyl thiourea, melting at 161°. In this reaction, the intermediate formation of the dithio carbamate was observed. The salt was not isolated. Von Braun (37) used isopropylamine as one of the primary amines in his research on thiuram disulphides. He obtained di-isopropyl thiuram disulphide, melting at 69°.

Preparation of di-isopropyl thiuram disulphide:

About 2 grams of isopropylamine were dissolved in 15 cc. of ice-cold methanol, then 5 cc. of carbon disulphide was added gradually, with pronounced evolution of heat in the solution. A solution of iodine in methanol and carbon disulphide was added to an end point, then the solution was evaporated to a very small volume by blowing air over it. A small amount of distilled water was added to precipitate the thiuram disulphide and to dissolve the amine hydriodide. The precipitated thiuram disulphide was filtered and pressed dry, then washed three times with cold methanol. It was light yellow at this point, smelling of mustard oil, and melting at 64-67°. The thiuram disulphide melts with decomposition, giving off hydrogen sulphide. It is very soluble in organic solvents, decomposing partially. The impure thiuram disulphide was washed repeatedly with cold ether. It dried as pure white crystals, melting at 69.5°. Von Braun recorded 69°. Mustard oil was found in the ether filtrate. No determination of yield was made.

Reaction of di-isopropyl thiuram disulphide with isopropylamine:

About 0.3 gram of di-isopropyl thiuram disulphide was placed in a small glass-stoppered bottle, immersed in a freezing mixture, then about 1 cc. of cold isopropylamine was added. The mixture became quite warm, darkened, and hydrogen sulphide was evolved.It was allowed to stand for one day at 0°- 5° , then warmed gently on a water bath to remove the excess of low-boiling amine. Then 10 cc. of distilled water was added, being heated until the precipitated thiourea dissolved. It was precipitated by cooling the solution and recrystallized again from distilled water. The dry product consisted of silvery-white plates melting at 140.0°. Jahn recorded the melting point as 161°.

Synthesis of di-isopropyl thiourea:

Since the melting point observed for the expected thiourea did not agree with that reported by Jahn, the thiourea was again prepared, but in another way, in order to redetermine and ascertain its correct melting point.

About 5 cc. of isopropylamine was added to a mixture of 50 cc. of carbon disulphide and 7 cc. of pyridine. The addition of the amine produced a vigorous reaction with evolution of heat, accompanied by the precipitation of a white crystalline dithio carbamate. The mixture was refluxed for 6 hours, at the end of which time no more hydrogen sulphide was eliminated and the dithio carbamate had gone into solution. The carbon disulphide was then steam-distilled off; enough water was added to bring the volume to 100 cc., then it was heated to dissolve the thiourea. The hot solution was filtered, then cooled to 0° to precipitate the di-isopropyl thiourea. The thiourea thus obtained was recrystallized from hot water containing Darco. It melted at 139.5°. It was thus evident that the same thiourea was obtained by both procedures, and that the melting point of di-isopropyl thiourea is 140°, not 161° as recorded in the literature.

Identification of Di-isopropyl thiourea:

Although the thiourea was identified by the manner of its synthesis from the amine and carbon disulphide according to a procedure which could yield no other product, a sample was analyzed for sulphur, as a further check. By the Parr method, 0.2710 gram of thiourea gave 0.3996 gram of barium sulphate, corresponding to 20.25 % sulphur. This value is in agreement with the theoretical for di-isopropyl thiourea, which is 20.01 % sulphur.

SUMMARY AND CONCLUSIONS

In this thesis, a reaction mechanism scheme for the synthesis of symmetrical disubstituted thioureas from primary amines and carbon disulphide has been proposed, which applies to those methods involving the use of oxidizing agents to effect the elimination of hydrogen sulphide. The mechanism proposes the following consecutive reactions:

(1) the usual addition of two molecules of amine and one molecule of carbon disulphide to form the corresponding dithio carbamate:

$$2\ RNH_2 + CS_2 \longrightarrow RNH\text{-}CS\text{-}S\text{-}H\cdot H_2NR \tag{1}$$

(2) the interaction of the dithio carbamate with oxidizing agents, notably iodine, to form the corresponding disubstituted thiuram disulphide:

$$2\ RNH\text{-}CS\text{-}S\text{-}H\cdot H_2NR + I_2 \longrightarrow (RNH\text{-}CS\text{-}S\text{-})_2 + 2\ RNH_2\cdot HI \tag{2}$$

(3) the decomposition by heat of the thiuram disulphide in either or both of two possible ways, to yield (a) the corresponding mustard oil, hydrogen sulphide, and sulphur –

$$(RNH\text{-}CS\text{-}S\text{-})_2 \longrightarrow 2\ R\text{-}N{=}C{=}S + H_2S + S\ \text{–} \tag{3a}$$

or (b) the corresponding thiourea, carbon disulphide, and sulphur –

$$(RNH\text{-}CS\text{-}S\text{-})_2 \longrightarrow (RNH)_2CS + CS_2 + S \tag{3b}$$

(4) the condensation of the mustard oil of equation (3a) with more of the primary amine, if present, to yield the corresponding thiourea:

$$R\text{-}N{=}C{=}S + RNH_2 \longrightarrow RNH\text{-}CS\text{-}NHR \tag{4}$$

(5) the combination of the carbon disulphide of equation (3b) with more of the primary amine, if present, to yield the corresponding thiourea:

$$2\ RNH_2 + CS_2 \longrightarrow RNH\text{-}CS\text{-}NHR + H_2S \qquad (5)$$

In the synthesis of thioureas, all of these reactions may occur during the course of the synthesis, giving in summation the equation:

$$4\ RNH_2 + CS_2 + I_2 \longrightarrow (RNH)_2CS + 2\ RNH_2{\cdot}HI.$$

This mechanism explains the fact that tetrasubstituted thioureas can not be prepared from secondary amines and carbon disulphide, since the intermediate tetrasubstituted thiuram disulphides formed by the reaction parallel to equation (2) is stable under the reaction conditions, as shown by Von Braun. It is thereby isolated without decomposition.

In substantiation of this mechanism scheme, the reactions of four classes of primary amines were studied - (I) hydroxy-aliphatic (ethanolamine), (II) cyclo-aliphatic (cyclohexylamine), (III) aromatic-aliphatic (benzylamine), and (IV) unsubstituted aliphatic (isopropylamine).

In the cases of cyclohexylamine and benzylamine, the first intermediate noted in the reaction mechanism scheme - the dithio carbamate - was isolated and identified.

The thiuram disulphides of all four of these amines - the next intermediates - were prepared and identified. The molar ratio of amine to iodine in equation (2) and the percent theoretical yield of thiuram disulphide were determined for each amine, with the exception of isopropylamine.

In studying the two types (equations 3a and 3b) of decomposition of the thiuram disulphides, the yields of the following products of decomposition were determined: (1) from diethanol thiuram disulphide - sulphur and hydrogen sulphide; (2) from di-cyclohexyl thiuram disulphide - hydrogen sulphide and thiourea; (3) from dibenzyl thiuram disulphide - hydrogen sulphide and thiourea.

The relative extents of these decompositions varied widely, as noted in the following summary tabulation.

Thiuram Disulphide from:	Yield H_2S by equation (3a) % theoretical	Yield Thiourea by equation (3b) % theoretical
Ethanolamine	94.6 %	------------
Cyclohexylamine	27.9 %	64.5 %
Benzylamine	9.9 %	96.5 %

With the increasing molecular weight of the amine, the percent extent of the decomposition yielding hydrogen sulphide and mustard oil (equation 3a) decreased, while the extent of the decomposition yielding thiourea (equation 3b) increased.

Each of the thiuram disulphides combined with the corresponding primary amine to give practically a theoretical yield of the corresponding thiourea, with the exception of ethanolamine, which yielded an unresolvable tar.

The following new compounds, not recorded in the literature, were prepared and identified:

(1) diethanol thiuram disulphide, M.P. 98°;

(2) di-cyclohexyl thiuram disulphide, M.P. 80°; and

(3) mercapto-oxazoline, M.P. 96-97°.

Marked differences in the melting points of the following compounds from the melting points recorded in the literature were determined and repeatedly checked. They are as follows:

(1) ethanolamine hydriodide, M.P. 84°;

(2) benzylammonium benzyl dithio carbamate, M.P. 134°;

(3) dibenzyl thiuram disulphide, M.P. 80-81°; and

(4) di-isopropyl thiourea, M.P. 140°.

The experimental results and data secured in this investigation of the reactions of the four primary amines of widely different classes lend support to an alternative reaction mechanism scheme for the synthesis of thioureas, wherein the intermediate formation of a thiuram disulphide precedes the formation of a thiourea.

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