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I hereby recommend that the thesis prepared under my supervision by BRUCE S. FARQUHAR

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The Interaction of Primary and Secondary Aryl Amines with Carbon Disulfide in the Presence of Pyridine and Iodine

A dissertation submitted to the
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by

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INTRODUCTION: HISTORICAL

Nearly one hundred years ago, A. W. Hofmann(1) discovered that a reaction occurred between carbon disulfide and the various amines. His first method of procedure was to heat the amine (aniline) with carbon disulfide until a product was precipitated. These substances reacted to give a thiourea (thio-carbanilide) and hydrogen sulfide:

$$CS_2 + 2C_6H_5NH_2 \longrightarrow C_6H_5\text{-}N(H)\text{-}C(=S)\text{-}N(H)\text{-}C_6H_5 + H_2S.$$

The volatile hydrogen sulfide was expelled during the heating. Even today this method by which Hofmann prepared sym. diphenyl thiourea is still employed and the equation for the reaction expresses satisfactorily the change which takes place.

Since the essential reaction for the formation of thioureas effects elimination of hydrogen sulfide in conformity with a general type equation,

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

most of the subsequently used methods have been designed to promote the elimination of hydrogen sulfide through its reaction with some suitable reagent, thereby effecting more complete reaction. These new methods will be discussed in their chronological order.

Hofmann's investigations were not further studied until 1870 when Claus(2) proposed a modification. His method

was analogous to that of Hofmann in that he used aniline and carbon disulfide, but incorporated sulfur monochloride into the reaction mixture to react with the hydrogen sulfide. On interaction of equivalent molar quantities of aniline and carbon disulfide, in the presence of sulfur monochloride, the hydrogen sulfide reacted to form hydrogen chloride and free sulfur. The hydrogen chloride combined with the excess of the amine. The reactions occurring may be represented by the following equations:

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

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

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

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

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

Claus and Krull(3) further investigated this method and obtained nearly quantitative yields of the thioureas.

Perhaps the most frequently used method for preparation of these thioureas, originally proposed by Hofmann(1), is that of Weith(4), who, in 1873, interacted carbon disulfide and aniline in an alcoholic potassium hydroxide solution. The hydrogen sulfide which was liberated reacted with the potassium hydroxide to give potassium sulfide, or the hydrosulfide,

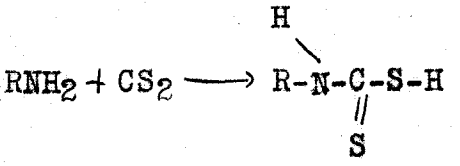
$$H_2S + 2KOH \longrightarrow K_2S + 2H_2O$$

$$H_2S + KOH \longrightarrow KHS + H_2O$$

and in this way the reaction proceeded nearly to completion.

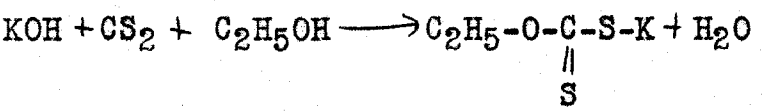
Rathke(5), in 1878 suggested that the Hofmann reaction likely involved the intermediate formation of a substituted di-

thio carbamic acid,

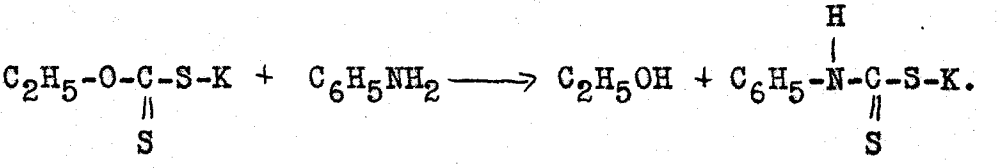


His procedure was as follows:

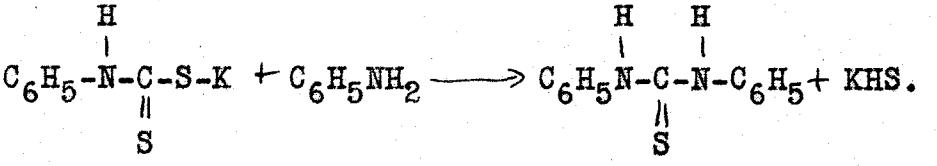
Ethyl alcohol and potassium hydroxide were dissolved in a large excess of carbon disulfide, and a yellow precipitate was formed. Analysis of the precipitate showed it to be potassium ethyl xanthate formed according to the equation:



When this potassium ethyl xanthate was allowed to react with an amine the ethoxy group was replaced by an amine residue to yield the potassium salt of the corresponding di-thio carbamic acid, thus



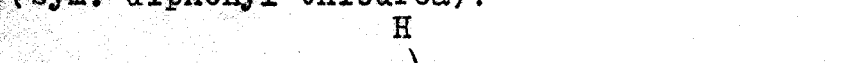
Then upon further reaction of the amine (aniline) in the absence of carbon disulfide Rathke found he had as his product Hofmann's thiocarbanilide:



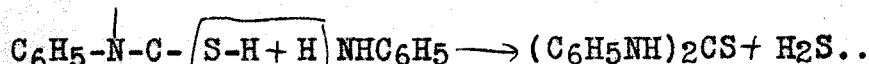
Thus these three reactions were shown to be involved in the method for preparation of thioureas of Weith(4).

To Rathke this was proof of the existence of intermediate products in the formation of thioureas. He reasoned that in the direct interaction of carbon disulfide with aniline the first product must be the phenyl di-thio carbamic acid, which, with another molecule of aniline, will form thiocarbanilide

(sym. diphenyl thiourea):



(1)



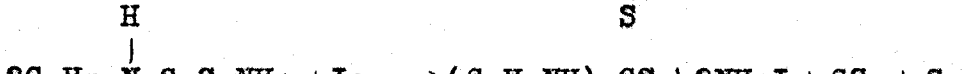
(2)

$\sum$ (1), (2)

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

The last equation, of course, is the one proposed by Hofmann(1). Rathke proceeded to investigate the assumption of an intermediate compound by first preparing and identifying the di-thio carbamic acid, as first carried out by Debus(6). This was then further reacted with aniline, whereupon the thiourea was immediately formed, with the elimination of hydrogen sulfide as he had assumed.

Losanitsch(7), in 1892, further verified Rathke's assumption of the existence of an intermediate compound. He obtained the ammonium salt of phenyl di-thio carbamic acid. This salt, when reacted with iodine, gave the thiourea accompanied by precipitation of ammonium iodide, sulfur, and formation of carbon disulfide in half of the amount initially used, as noted in the equations:



Losanitsch proved the existence of the intermediate compound by still another series of reactions. From the ammonium salt of di-thio carbamic acid he prepared the corresponding mustard oil (phenyl isothiocyanate). By interacting this oil with another molecule of aniline he obtained an addition product, which analysis proved to be thiocarbanilide:

$$C_6H_5NHCSSNH_4 \longrightarrow C_6H_5\text{-}N{=}C{=}S + NH_4HS$$

$$C_6H_5\text{-}N{=}C{=}S + C_6H_5NH_2 \longrightarrow (C_6H_5NH)_2CS.$$

Hugerschoff(8) immediately followed Losanitsch in the similar assumption of an intermediate product. He, however, did not attempt to further the proof of the existence of the di-thio carbamic acids. He was more interested in their derivatives. His scheme of preparation was analogous to those of Hofmann and Weith in that he used an alcoholic solution of the amine and carbon disulfide. Hugerschoff, however, used sulfur as a catalyst and by this method was able to obtain nearly quantitative results, in conformity with the accepted equation,

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

Prior to 1887, all of the thioureas prepared were symmetrical di-substituted products. Billetier(9) in this same year, was the first to prepare both the unsymmetrical, the tri-, and the tetra-substituted thioureas. His method of preparation was different from any previously employed. He used thiophosgene in place of carbon disulfide and obtained phenyl thio carbamyl chloride,

$$2C_6H_5NH_2 + CSCl_2 \longrightarrow C_6H_5\text{-}N(H)\text{-}C(=S)\text{-}Cl + C_6H_5NH_2 \cdot HCl,$$

which upon further reaction with aniline yielded the symmetrically substituted diphenyl thiourea:

$$C_6H_5NH\text{-}C(=S)\text{-}Cl + 2C_6H_5NH_2 \longrightarrow (C_6H_5NH)_2CS + C_6H_5NH_2\cdot HCL.$$

However, when he interacted the thio carbamyl chloride with some other amine he obtained an unsymmetrical derivative:

$$RNHC(=S)\text{-}Cl + 2R'NH_2 \longrightarrow RNH\text{-}C(=S)\text{-}NHR' + R'NH_2\cdot HCl.$$

It is readily seen that it was possible to obtain also the tri- and tetra-substituted product by use of an analogous series of reactions:

$$2\,\mathrm{HN}(R')(R) + CSCl_2 \longrightarrow \mathrm{ClC(=S)N}(R')(R) + \mathrm{H_2N}(R')(R)\cdot HCl$$

$$\mathrm{ClC(=S)N}(R')(R) + 2\,\mathrm{HN}(R'')(H) \longrightarrow \mathrm{N}(R')(R)\mathrm{C(=S)N}(R'')(H) + \mathrm{H_2N}(R'')(H)\cdot HCl$$

or

$$\mathrm{ClC(=S)N}(R)(R') + 2\,\mathrm{HN}(R''')(R'') \longrightarrow \mathrm{N}(R')(R)\mathrm{C(=S)N}(R''')(R'') + \mathrm{H_2N}(R''')(R'')\cdot HCl.$$

Billetier prepared the following tetra-substituted thioureas by this method; sym. di-ethyl diphenyl thiourea, sym. dimethyl diphenyl thiourea, and methyl ethyl diphenyl thiourea.

In 1902, Delepine(10) synthesized esters of the di-thio carbamic acids. The amine salt of the di-thio carbamic acid was prepared by interaction of two molecules of the amine with one of carbon disulfide,

$$RNH_2 + CS_2 \longrightarrow R\text{-}N(H)\text{-}C(=S)\text{-}S\text{-}H$$

$$R\text{-}N(H)\text{-}C(=S)\text{-}S\text{-}H + RNH_2 \longrightarrow R\text{-}N(H)\text{-}C(=S)\text{-}S\text{-}NH_3R$$

which, when treated with an alkyl halide, formed the ester of the di-thio carbamic acid,

$$R\text{-}N(H)\text{-}C(=S)\text{-}S\text{-}NH_3R + RX \longrightarrow R\text{-}N(H)\text{-}C(=S)\text{-}S\text{-}R + NH_3R\cdot X$$

and an alkyl substituted ammonium salt. This work further substantiates the mechanism of the reaction for the formation of thioureas as formulated by Rathke and Losanitsch.

Delepine produced mixed thioureas from the corresponding mustard oils in the same way that Losanitsch produced the symmetrically substituted thioureas:

$$RNH_2 + CS_2 \longrightarrow RNHCSSH$$

$$RNHCSSH + AgNO_3 \longrightarrow RNHCSSAg + HNO_3$$

$$2RNHCSSAg \longrightarrow 2RNCS + Ag_2S + H_2S$$

$$RNCS + R'NH_2 \longrightarrow RNHC(=S)\text{-}NHR'$$

or

$$RNCS + R'R''NH \longrightarrow RNH\text{-}C(=S)\text{-}NR'R''.$$

The tetra-substituted products could not be synthesized in this way as no mustard oils could be formed from secondary amines.

Jacobson and Hugerschoff(11), in 1903, interacted carbon disulfide and hydrazobenzene to obtain thiocarbanilide.

The first product was assumed to be the enol (aci- or mercapto) form of the thiourea,

$$C_6H_5NH\text{-}NHC_6H_5 + CS_2 \longrightarrow C_6H_5\text{-}N{=}C(SH)\text{-}NHC_6H_5 + S$$

$$C_6H_5\text{-}N{=}C(SH)\text{-}NHC_6H_5 \longrightarrow (C_6H_5NH)_2CS$$

which rearranges, as shown above, to the keto thiourea. As can readily be seen, a tri-substituted thiourea was easily obtained by use of a substituted hydrazobenzene,

$$R\text{-}N(R')\text{-}N(H)\text{-}R + CS_2 \longrightarrow R\text{-}N(R')\text{-}C(SH){=}NR + S,$$

but no tetra-substituted products were possible, which fact provides evidence of the actual existence of an enol form of the thiourea. A tetra-substituted hydrazobenzene, of course, provides no hydrogen atom for the formation of the enol modification.

In 1904, Pawlewski(12) interacted the mustard oils with the aldoximes and ketoximes to obtain the symmetrical and unsymmetrical thioureas. He did not obtain very satisfactory results, as the reactions are complicated and are accompanied by the formation of various by-products.

Krulla(13), in 1913, was very much interested in a way to eliminate the hydrogen sulfide from the sphere of reaction. He attempted the oxidation of the hydrogen sulfide by the use of hydrogen peroxide,

$$H_2S + H_2O_2 \longrightarrow 2H_2O + S$$

but the method was very unsatisfactory.

Krulla next interacted the amines and carbon disulfide in the presence of the corresponding nitro compound; for instance, aniline and nitrobenzene. The latter was reduced to the amine by the liberated hydrogen sulfide, with the formation of aniline, water, and sulfur;

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

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

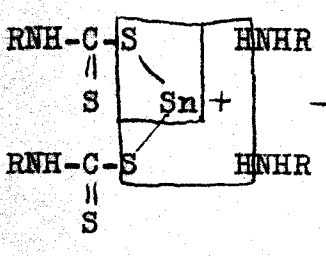
$\sum$ (1), (2)

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

The aniline formed by the reduction of the nitrobenzene was in turn reacted upon by the carbon disulfide to form the thiourea. By this method Krulla was able to obtain very satisfactory results.

Krulla then attempted to use freshly prepared lead oxide (PbO) and stannous oxide (SnO) to remove the hydrogen sulfide; but the former proved unsatisfactory, the latter very satisfactory. To explain the reaction he assumed the formation of the stannous salt of the di-thio carbamic acid:

$$2RNH_2 + SnO + 2CS_2 \longrightarrow (RNHCSS)_2Sn + H_2O \quad \ldots\ldots(1)$$



$$\longrightarrow 2(RNH)_2CS + SnS + H_2S \quad \ldots\ldots(2)$$

$$SnO + H_2S \longrightarrow SnS + H_2O \quad \ldots\ldots(3)$$

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

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

The most recent development in the procedure for the elimination of hydrogen sulfide is the use of the tertiary amine, pyridine. This method was developed by Fry(14), embodying two independent methods for its use.

The first method consisted in promoting the elimination of hydrogen sulfide by adding the base pyridine, which catalytically removed the hydrogen sulfide in conformity with the reversible reaction:

$$H_2S + C_5H_5N \rightleftharpoons C_5H_5N\begin{matrix}SH\\H\end{matrix}.$$

The amine was refluxed with carbon disulfide and a slight excess of pyridine in a flask provided with an upright water-cooled condenser. After completion of the reaction, the contents of the flask were subjected to steam distillation, until the excess carbon disulfide and volatile pyridine were removed. The residue in the flask was freely washed with water, then dilute hydrochloric acid, and then water again. The product was crystallized from a suitable solvent. By use of this method Fry was able to obtain purer products in nearly quantitative yields.

Fry's second method for effecting complete removal of hydrogen sulfide consisted in adding a carbon disulfide solution of iodine to the reaction mixture containing pyridine. The hydrogen sulfide immediately reacted with the iodine, thus

$$H_2S + I_2 \rightleftharpoons 2HI + S,$$

forming sulfur and hydrogen iodide. The hydrogen iodide thus formed simultaneously reacted with pyridine to form pyridonium iodide, which, being but very sparingly soluble in the large excess

of carbon disulfide precipitated out and thus displaced the above equilibrium virtually to completion. The amine and pyridine were dissolved in a large excess of carbon disulfide, and a calculated amount of iodine, dissolved in carbon disulfide, was added to the reaction mixture, which was allowed to stand or gently refluxed until the typical iodine color vanished. The mixture was then distilled with steam and the product purified. Nearly quantitative results were obtained in conformity with the equations:

$2RNH_2 + CS_2 \longrightarrow (RNH)_2CS + H_2S$ .....(1)

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

$2HI + 2C_5H_5N \longrightarrow 2C_5H_5N \cdot HI$ .....(3)

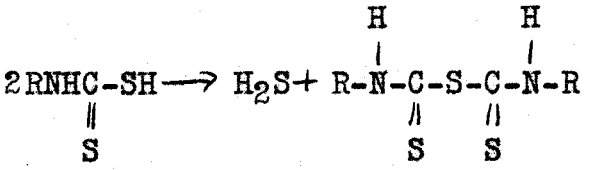
$\sum$ (1), (2), (3)

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

Raiford and McNulty(15) have made a study of the efficiency of different methods for synthesis of thioureas. The methods studied were those of Weith(4), Hugerschoff(8), Snedker(16) and Fry(14). Fry's method was modified to the extent that the mixture was mechanically stirred until the reaction was completed in order to prevent the carrying down of iodine as the pyridonium iodide precipitated. Of the large number of compounds studied, Fry's method gave the highest yields, with only one exception.

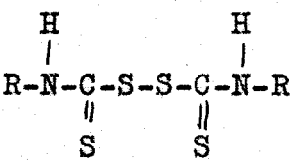
To date, it is the consensus of opinion that the intermediately formed di-thio carbamic acid actually exists in the reaction mixture and by subsequent reaction with another

molecule of the amine is converted into the thiourea. Hlasiwetz and Kachler(17) analyzed a decomposition product of the di-thio carbamic acid and thus obtained a compound which they termed a substituted thiuram sulfide,

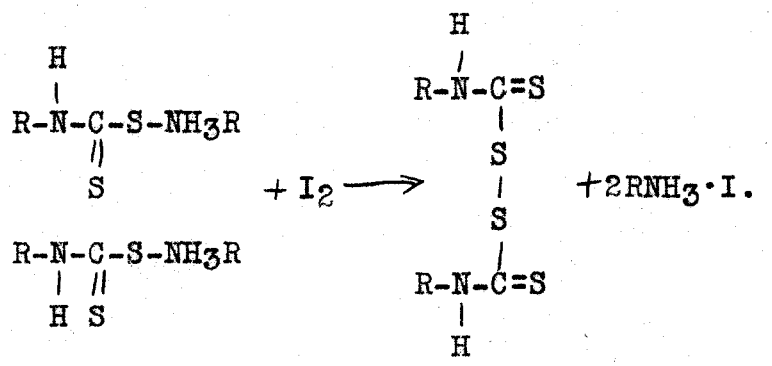


the thiuram grouping being  . A glance at the above equation will show that the thiuram monosulfide may be considered the thio-anhydride of the corresponding di-thio carbamic acid.

J. von Braun(18) was the first to use iodine in any attempt to prepare the substituted thioureas from the direct interaction of the amines with carbon disulfide. In this work von Braun used two mols of amine and one mol of carbon disulfide to form the amine salt of the di-thio carbamic acid. Iodine, dissolved in alcohol, was added to the ice-cold solution of the amine. However, he was not successful in obtaining the desired compounds. Instead he obtained a compound of the thiuram disulfide type,

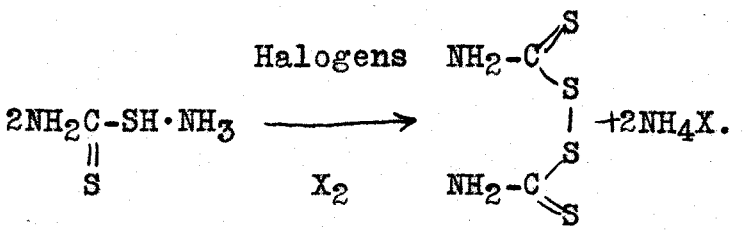


by the interaction (oxidation) of two molecules of the salts of the di-thio carbamic acid by one molecule of iodine:

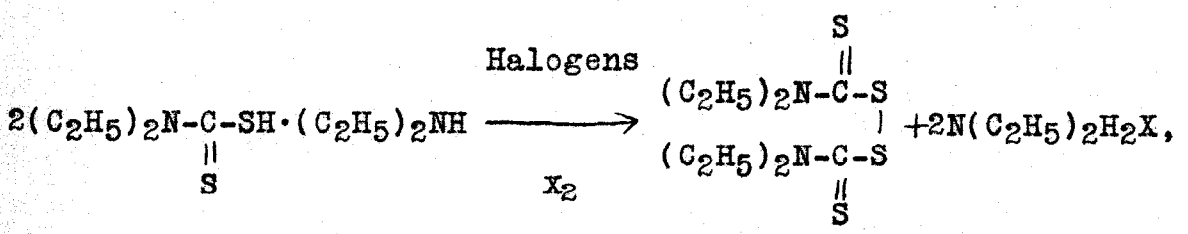


It can readily be seen that both the primary and the secondary amines will react in this manner to form the corresponding di-thio carbamic acid.

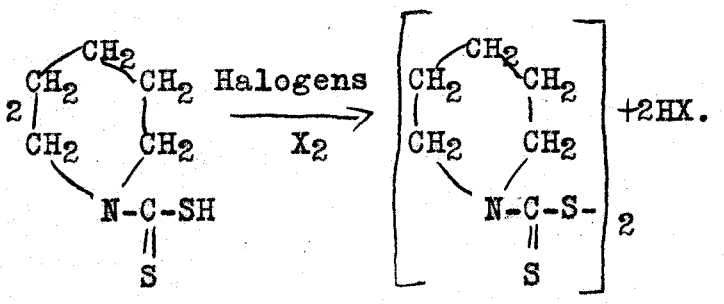
Prior to the time of von Braun's work, Debus(6), Grodzki(19), Ehrenberg(20), and Freund(21) obtained the thiuram disulfide derivatives by treatment of the di-thio carbamic salts with halogens. Debus prepared thiuram disulfide itself by oxidation of ammonium di-thio carbamate:



Similarly, Grodzki prepared tetra-ethyl thiuram disulfide from the diethylamine salt of diethyl di-thio carbamic acid:



and Ehrenberg synthesized dipiperidyl thiuram disulfide from piperidyl di-thio carbamic acid:



Freund also found that the methyl and ethyl amine salts of methyl and ethyl di-thio carbamic acids respectively, were converted by bromine into the corresponding thiuram disulfides.

The work of von Braun and others with secondary amines yielded no thioureas. Thiuram disulfides were always formed. It may be noted here that primary amines yield thioureas when an excess of carbon disulfide is employed and the di-thio carbamic acid (or salt) is not isolated. If two molecules of the amine and one molecule of carbon disulfide react, the amine salt of the di-thio carbamic acid is formed and may in turn be converted into the thiuram disulfide compound by a separate oxidation reaction. But only in this way are thiuram disulfides produced from primary amines. Fry's and the other methods all yield thioureas from primary amines.

An explanation for this marked difference in behavior of primary and secondary amines, namely that a primary amine may yield either a thiourea or a thiuram disulfide, while a secondary amine yields only a thiuram disulfide, will be offered in the next section entitled "Theoretical."

THEORETICAL

Thiourea and its analogues are generally thought of as existing in two tautomeric forms:

$$HN{=}C(SH){-}NH_2 \rightleftharpoons NH_2{-}C(=S){-}NH_2.$$

The enol form is generally called the thio-carbimide and the keto form the thio-carbamide. The chemical behavior of thiourea depends upon the conditions prevalent in the particular experiment to be conducted, and offers evidence of the existence of both tautomeric forms.

The fact, as noted by Jacobson and Hugerschoff(11), that no thioureas can be prepared from tetra-substituted hydrazobenzenes offers evidence that a thiourea which is produced from a mono-, di-, or tri-substituted hydrazobenzene must have been formed in the enol modification. This is shown by the following equations as applied to a tri-substituted hydrazobenzene:

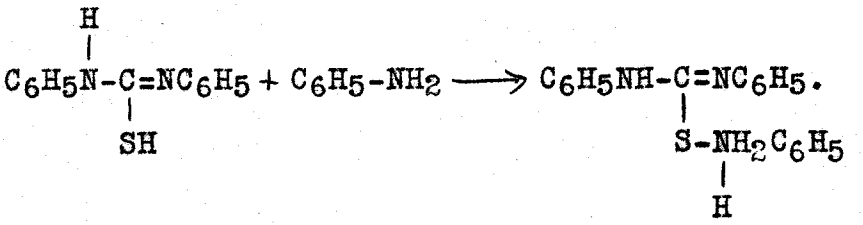
$$R{-}N(R){-}N(H){-}R + CS_2 \longrightarrow R{-}N(R){-}C(SH){=}N{-}R + S$$

$$R{-}N(R){-}C(SH){=}N{-}R \longrightarrow R_2N{-}C(=S){-}NHR.$$

It is at once quite obvious that no more than three hydrogen atoms of the hydrazobenzene can be substituted, in order that the fourth hydrogen atom may be available for formation of the enol modification of the thiourea.

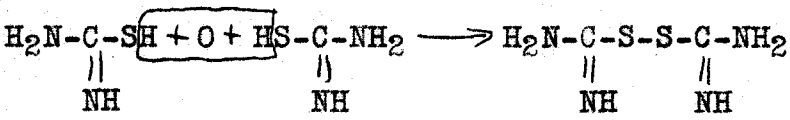
Bedford and Sebrell(22) obtained a crystalline compound from a solution of thiocarbanilide in aniline. Analysis showed that it consisted of one molecule of thiocarbanilide and

one of aniline. Bedford and Sebrell then concluded that the thiourea must have reacted in the enol form with aniline to form a salt, viz.:



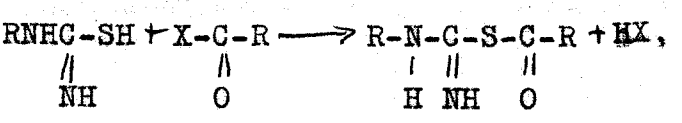
Moreover, Bedford and Sebrell have actually prepared metallic salts of the mercapto (enol) form of thiocarbanilide, namely zinc mercaptide and lead mercaptide(23).

Storch(24) has shown that nitrous acid, and other reagents in acid solution, oxidize thiourea to a feeble base, named formamidine disulfide by Fichter and Wenk(25) who obtained it electrolytically. This indicates that the reactant was in the enol form in order to eliminate water and bring about coupling of the residues:



E. A. Werner(26) has obtained this compound as the dihydriodide, by oxidation with iodine. With alkaline permanganate Werner(27) obtained the free base which immediately decomposed. From the decomposition products Werner isolated 65% of the cyanamide thus produced.

Werner agrees that treatment of a thiourea with an alkyl haloid yields a <u>thio</u> ester and not a nitrogen substituted thiourea:



It is obvious that the only way in which this thio-ester could be produced is by acylation of the enol sulfur atom. Dixon and Taylor(28) seem to disagree partially with this evidence.

It is to be concluded from the above experimental facts that mercapto (enol) thiourea actually exists when conditions favorable to its formation are imposed.

One of the methods of preparation of mixed thioureas is the treatment of mustard oils with amines, e.g., methyl ethyl thiourea is prepared from methyl isothiocyanate and ethylamine,

$$CH_3NCS + C_2H_5NH_2 \longrightarrow CH_3NH\text{-}\underset{\underset{S}{\|}}{C}\text{-}NHC_2H_5,$$

assuming formation of the keto modification. Similarly, if ethyl isothiocyanate is reacted with methylamine the same compound should be obtained:

$$C_2H_5NCS + CH_3NH_2 \longrightarrow C_2H_5NHC(=S)NHCH_3.$$

But, if the enol form is assumed two entirely different compounds should be formed, depending on the mustard oil and amine used. With methyl isothiocyanate we should expect:

$$CH_3\text{-}N{=}C{=}S + C_2H_5NH_2 \longrightarrow CH_3\text{-}N{=}\underset{\underset{H\text{-}N\text{-}C_2H_5}{|}}{C}\text{-}SH,$$

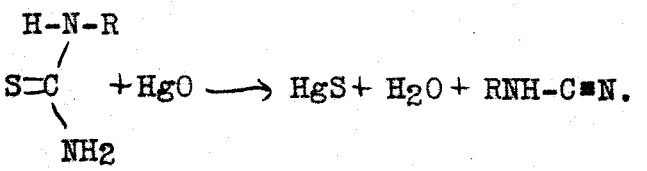
whereas with ethyl isothiocyanate we should have the other compound formed:

$$C_2H_5\text{-}N{=}C{=}S + CH_3NH_2 \longrightarrow C_2H_5\text{-}N{=}\underset{\underset{H\text{-}N\text{-}CH_3}{|}}{C}\text{-}SH.$$

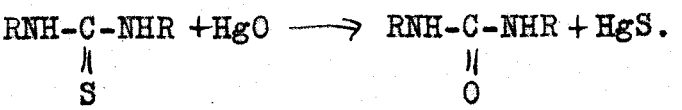
Experiments have shown that, irrespective of the mode of

reaction, the same product is obtained. Thus under these conditions the thiourea exists in the keto form.

When a mono-substituted thiourea is desulfurized by mercuric oxide a substituted cyanamide is formed(29):



This fact per se offers no direct evidence for the existence of either the enol or keto modifications as both forms could react as shown by the above equation. But if the thiourea is of the N, N' di-substituted type, desulfurization yields the keto form of the thiourea:



Capps and Dehn(30) have carried out the desulfurization of thioureas of the above type by use of bromate and iodate solutions, obtaining good yields of the corresponding substituted ureas. Needless to say, the enol form could not react as above.

From the above experimental facts it is to be concluded that either the enol or the keto form of thiourea actually exists when favorable conditions are imposed.

- - - - - - - - - - - -

It has been noted in the historical review that primary amines yield thioureas while secondary amines yield thiuram disulfides. According to the ideas of Rathke and Losanitsch primary amines form thioureas in conformity with the following equations:

$$RNH_2 + CS_2 \longrightarrow RNHCSSH$$

$$RNHCSSH + HNHR \longrightarrow (RNH)_2CS + H_2S.$$

Moreover, secondary amines <u>should</u> react in the same manner:

$$R_2NH + CS_2 \longrightarrow R_2NCSSH$$

$$R_2NCSSH \quad HNR_2 \longrightarrow (R_2N)_2CS + H_2S.$$

This, however, is not the case.

Snedker(31) attempted to explain this phenomenon, namely <u>that secondary amines do not yield thioureas</u>, by stating that the secondary amine exhibits a lack of acidic hydrogen. But, since the di-thio carbamic acids of secondary amines are also known to exist, thioureas from secondary amines should be formed in conformity with the equations given above.

Fry and Culp(32) have shown that if the two tautomeric modifications of thiourea are accepted, an explanation may be provided whereby the marked difference in behavior of primary and secondary amines with carbon disulfide is at once clarified. Thus, primary and secondary amines would both react first to form the corresponding di-thio carbamic acids:

$$RNH_2 + CS_2 \longrightarrow RNHCSSH$$

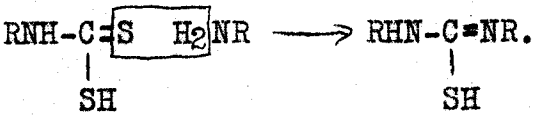
$$R_2NH + CS_2 \longrightarrow R_2NCSSH.$$

An additional molecule of a <u>primary</u> amine would split out hydrogen sulfide, <u>not</u> by the interaction of a hydrogen atom of the amine and the thio-hydroxyl group of the carbamic acid,

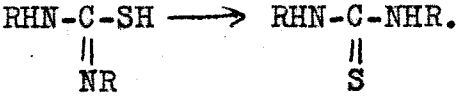
$$RHN\text{-}C(=S)\text{-}SH \quad HNHR \longrightarrow RNHC(=S)NHR,$$

<u>but</u> by the interaction of <u>two</u> hydrogen atoms of the amine and

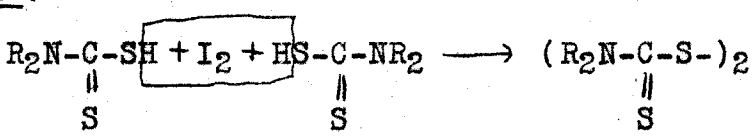
the thione sulfur atom of the corresponding di-thio carbamic acid to yield the enol modification of the thiourea, thus:



The enol form, being less stable than the keto, would rearrange to the latter, presumably under the influence of heat:



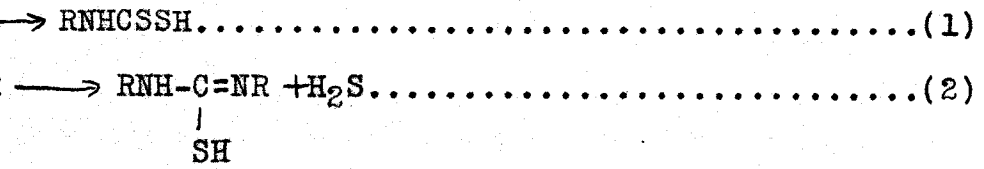
It is at once obvious that a <u>secondary amine</u> lacks sufficient hydrogen for a similar transformation into a thiourea, and, under the conditions of the experiment, the corresponding di-thio carbamic acid would be oxidized by iodine to a <u>thiuram disulfide</u>.



Fry and Culp have supported this hypothesis by the synthesis of sym. dimethyl diphenyl, sym. diethyl diphenyl, sym. diethyl di alpha naphthyl, and sym. diethyl di beta naphthyl thiuram disulfides in the presence of iodine and pyridine. In no instance was a thiourea formed from any of the <u>secondary</u> amines.

The reactions involved in the methods of Fry and Culp for the preparation of thioureas and thiuram disulfides may be represented by the following equations.

For primary amines:



$$RNH\text{-}C(=NR)\text{-}SH \longrightarrow RNH\text{-}C(=S)\text{-}NHR \quad \ldots\ldots (3)$$

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

$$2C_5H_5N + 2HI \longrightarrow 2C_5H_5NHI \quad \ldots\ldots (5)$$

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

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

For secondary amines:

$$2CS_2 + 2R_2NH \longrightarrow 2R_2NCSSH \quad \ldots\ldots (1)$$

$$2R_2NCSSH + I_2 \longrightarrow (R_2NCSS\text{-})_2 + 2HI \quad \ldots\ldots (2)$$

$$2C_5H_5N + 2HI \longrightarrow 2C_5H_5NHI \quad \ldots\ldots (3)$$

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

$$2CS_2 + 2R_2NH + I_2 + 2C_5H_5N \longrightarrow (R_2NCSS\text{-})_2 + 2C_5H_5N\cdot HI.$$

It may be noted here again that primary amines yield thiuram disulfides only when, as shown by other investigators, the intermediately formed di-thio carbamic acid, or salt, is isolated and then subsequently subjected to oxidation. Otherwise primary amines, under the conditions of Fry's method, yield thioureas, while secondary amines yield thiuram disulfides. An extension of this method to secondary amines other than those employed by Fry and Culp, will be given in the experimental part of this thesis.

OBJECTS OF THE INVESTIGATION

This thesis is concerned with the use of Fry's method for the production of thioureas and thiuram disulfides from primary and secondary amines respectively in the presence of pyridine and iodine, in carbon disulfide solution. A detailed description of the method will be given in the next section entitled "Experimental."

Since Fry(14) also showed that the reaction between aniline and carbon disulfide, in the presence of iodine and pyridine, could yield the corresponding mustard oil, thus,

$$RNH_2 + CS_2 + I_2 + 2C_5H_5N \longrightarrow RNCS + 2C_5H_5NHI + S,$$

it was thought advisable, in the first experiments conducted, to investigate this reaction and to extend its application to the other amines for the synthesis of mustard oils. Inasmuch as these preliminary experiments resulted in formation of thiocarbanilides and sym. triphenyl guanidines as well as the mustard oils, they were abandoned in favor of experiments designed to yield solely thioureas and thiuram disulfides.

Since Fry and Culp(32) employed a 100% excess of pyridine in the reaction mixture, it was thought advisable to determine the optimum concentration of pyridine and to study its effect upon (1) the time necessary for reaction, (2) yields of thioureas, and (3) yields of thiuram disulfides.

After the optimum concentration of pyridine had been determined, a study of the inhibitory effects of substituents on the formation of thioureas and thiuram disulfides was also

undertaken. Since no thiuram disulfides had been prepared which contained substituents in the benzene nucleus this study lead to the synthesis of several new compounds of this type.

The thesis was also undertaken with the additional endeavor of further experimentally supporting the hypothesis of Fry and Culp, wherein an explanation is offered for the marked difference in behavior of primary and secondary amines with carbon disulfide, in the presence of iodine and pyridine. The reactions of the following amines were studied.

Primary amines:

ortho, meta, and para chlor anilines

ortho, meta, and para brom amilines

para iodo aniline

2-6 di-brom aniline

Secondary amines:

diphenylamine

methylaniline

ethyl aniline

methyl ortho toluidine

methyl meta toluidine

methyl para toluidine

meta nitro methylaniline

para nitro methylaniline

In addition, new asymmetric tri-substituted thioureas were prepared from phenyl isothiocyanate and methyl o-, m-, and p-toluidine.

EXPERIMENTAL

I. General Procedure for Synthesis of Thioureas and Thiuram Disulfides.

A one-liter, round-bottom, three-neck flask is attached by a side arm to an upright water-cooled Liebig condenser and fitted with a mechanical stirrer running through a glass mercury seal. The third neck of the flask is fitted with a 250 cc. dropping funnel containing iodine dissolved in carbon disulfide. The amine, pyridine, and carbon disulfide are placed in the flask. Rubber stoppers are used throughout. The stirrer is started and the contents are heated to gentle refluxing by use of a hot-water bath. When the amine is completely dissolved, the iodine solution is run rapidly into the flask. If the reaction becomes too violent the hot-water bath is removed and replaced by a cold one until ebullition abates. The heating is continued until the typical iodine color vanishes. At this point the flask containing a copious precipitate of pyridonium iodide is removed from the apparatus and cooled under the tap. The precipitate is filtered by suction onto a Büchner funnel and washed with carbon disulfide. All washings are combined with the filtrate. The solution is then subjected to steam distillation until all carbon disulfide has been removed. The material in the reaction flask, after cooling under the tap, is filtered off on a Büchner funnel, freely washed with water, and air-dried by suction. The filtrate, containing pyri-

dine and pyridonium iodide is discarded. The reaction mixture, after being finely ground in a porcelain mortar, is placed in a 500 cc. Erlenmeyer flask, and 200 cc. of 3N hydrochloric acid are added to remove the final traces of pyridine and unreacted amine. The mixture is heated for 15-20 minutes at a temperature of 75° C. From time to time, the flask is removed from the heat, stoppered, and vigorously shaken. Then the material is filtered on a Büchner funnel, washed freely with water, and air-dried by suction. The crude product is dried completely in a desiccator and weighed. If the product is a thiourea, sulfur will be present. The latter is removed by extraction of the thiourea with a suitable solvent such as benzene, methyl, or ethyl alcohol, from which the thiourea can be obtained by crystallization. If the product is a thiuram disulfide, no sulfur is formed. The thiuram disulfide may be purified by grinding in a mortar under ether or alcohol in which it is very sparingly soluble. The filtered suspension is washed until the runnings are colorless. The thiuram disulfides may be finally purified by crystallization from mixtures of benzene and ethyl alcohol, benzene and carbon disulfide, or carbon disulfide and ethyl alcohol.

Several points in this procedure will bear discussion. In some cases the amine may be fairly insoluble in carbon disulfide and an additional amount of pyridine must be added to effect complete solution.

A special stop-cock grease, impervious to carbon

disulfide, was used in the cock of the dropping funnel. This was prepared from glycerol, dextrin, and mannitol according to the directions of Meloche and Frederick(33).

Raiford and McNulty(15) have observed that, in some cases, iodine is carried down by the pyridonium iodide. Trowbridge and his co-workers(34) have shown that iodine actually combines with pyridonium iodide to form pyridonium periodides of the following molecular formulas:

$C_5H_5N \cdot HI \cdot I$	dark brown short needles	m. p. 188-92° C
$C_5H_5N \cdot HI \cdot I_4$	brown-black	m. p. 78-82° C
$C_5H_5N \cdot HI \cdot I_6$	glistening green scales	m. p. 63-64° C.

Raiford and McNulty have modified Fry's original procedure to the extent that the reacting mixtures are mechanically stirred, in an attempt to prevent the formation of these compounds. The writer has observed that continued refluxing and stirring tend to break up the periodides. Their formation may be largely prevented by allowing the iodine solution to fall drop-wise on the surface of the liquid in the reaction flask, rather than by complete addition at once.

In some cases the product formed may be sparingly soluble in the carbon disulfide solution. Then it is best to add water directly to the reaction flask without filtering off the pyridonium iodide.

Occasionally the product in the reaction flask, after removal of carbon disulfide, is present as an oil. This oil, however, usually solidifies on cooling the flask under the

water tap. The solid is then removed by filtration.

Fry has prolonged the steam distillation until the soluble but volatile pyridine has been removed as well as the carbon disulfide. It has been observed that when this is done, the products, due to the lengthy distillation, become darker in color and are not obtained in as good yields with as high degrees of purity, as is the case when the steam distillation is maintained only long enough for complete removal of the carbon disulfide. Furthermore, excessive steam distillation may sometimes volatilize the thioureas. The treatment of the product with successive portions of water, dilute hydrochloric acid, and water is sufficient to remove all traces of pyridine and unused amine.

II. Synthesis of Mustard Oils from Primary Amines.

In an attempt to verify quantitatively the following general type reaction:

$$RNH_2 + CS_2 + I_2 + 2C_5H_5N \longrightarrow RNCS + S + 2C_5H_5NHI,$$

it was discovered that sym. triphenyl guanidines and thioureas were formed in addition to the mustard oils. The formation of these two by-products would suggest that the thiourea was formed initially:

$$2RNH_2 + CS_2 + I_2 + 2C_5H_5N \longrightarrow (RNH)_2CS + S + 2C_5H_5NHI,$$

and then subsequently was transformed into the mustard oil and guanidine:

$$(RNH)_2CS \longrightarrow RNH_2 + RNCS$$

$$(RNH)_2CS + RNH_2 \longrightarrow (RNH)_2C{=}NR + H_2S.$$

Of the reactions studied in connection with the mechanism involved none save the following approached quantitative verification:

$$2(C_6H_5NH)_2CS + I_2 + 2C_5H_5N \longrightarrow (C_6H_5NH)_2C{=}NC_6H_5 + C_6H_5NCS + S + C_5H_5N\cdot NI.$$

Since a primary amine, when treated with an excess of iodine over that amount theoretically required for formation of a thiourea:

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

is accompanied by formation of substituted guanidines and thioureas as well as the mustard oil, it was deemed advisable to abandon these experiments and to carry out those designed to yield solely thioureas and thiuram disulfides, as previously noted.

III. Reactions of Primary Amines.

IIa. Reaction of Ortho Chloraniline: Synthesis of sym. di-(ortho chlor phenyl) thiourea and the determination of the optimum concentration of pyridine in the formation of thioureas.

In the above description of the experimental procedure, no mention was made of the molecular proportions of the reactants employed. Since pyridine was used in excess to promote the extent of the occurrence of the reaction, a brief description of the experiments employed to arrive at the optimum concentration of pyridine should be included. Further objectives relate to the effect of the excess pyridine upon the time necessary for reaction and the yield of sym. di-(ortho chlor phenyl) thiourea.

Separate experiments were conducted with ortho chloraniline using the following quantities of amine, iodine, pyridine, and carbon disulfide, based upon the type equation:

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

Reagents Used (equivalent quantities of amine and iodine):

Ortho chloraniline, 0.2 mole, 25.5 grams, purified by distillation in vacuo.

Carbon disulfide, 100 cc.

Pyridine (a) 0.4 mole, 31.6 grams, 100% excess

(b) 0.3 mole, 23.7 grams, 50% excess

(c) 0.2 mole, 15.8 grams, 0% excess

Iodine Solution: iodine, 0.1 mole, 25.4 grams

carbon disulfide, 200 cc.

The crude product (thiourea and sulfur) was dissolved in 250 cc. methyl alcohol, quickly filtered from the sulfur by

use of a platinum cone and suction, placed in a crystallizing dish, allowed to crystallize, filtered with suction, washed with a little methyl alcohol, dried and weighed as the pure product.

If the pyridine salt of the di-thio carbamic acid was formed in this experiment:

$$RNHCSSH + C_5H_5N \longrightarrow RNHCSS\text{-}\underset{\underset{H}{|}}{N}{=}C_5H_5,$$

and if it were stable, subsequent condensation of the acid with additional amine would be inhibited, and the yields of the thiourea should be smaller the greater the concentration of pyridine.

A summary of the results obtained in employing 100%, 50%, and 0% excess pyridine is presented in the following table. A survey shows that when the concentration of pyridine is decreased, the time necessary for reacting is increased, and the yield of thiourea is decreased. The fact that the decreased concentration of pyridine caused no increase in yields of the thiourea indicates that no complex salt of the intermediate acid and pyridine is formed. The use of 100% excess pyridine produces the greatest yield of thiourea in a minimum of time and thus appears to be the optimum concentration.

TABLE I

Run	% Excess Pyridine	Time for Reaction	Theory Crude (Thiourea + S) Grams	% Theory Crude (Thiourea + S) Grams	%	% Theory Pure Thiourea Grams	%
1a	100	90 min.	32.9	32.1	97.6	23.6	79.5
1b	100	80 min.	32.9	30.6	93.0	23.3	78.4
2a	50	150 min.	32.9	30.8	93.6	23.2	78.1
2b	50	145 min.	32.9	30.8	93.6	23.1	77.8
3a	0	6-7 hrs.	32.9	28.7	87.2	21.3	71.7
3b	0	6-7 hrs.	32.9	28.7	87.2	20.7	69.8
av.1a,1b	100	85 min.	32.9	31.4	95.3	23.5	79.0
av.2a,2b	50	148 min.	32.9	30.8	93.6	23.1	78.0
av.3a,3b	0	6-7 hrs.	32.9	28.7	87.2	21.0	70.8

The melting point of sym. di-(ortho chlor phenyl) thiourea was given as 145°C by Hofmann(35). Fry(14) reports 130.5°C. Repeated crystallizations from methyl alcohol give a constant melting point of 131.5°C, using a short-stem calibrated thermometer (Peters and Rost).

IIIb. Reaction of Meta Chloraniline: Synthesis of sym. di-(meta chlor phenyl) thiourea.

The method employed here and with the following primary amines has been described under Experimental Part, section I.

Reagents used (equivalent quantities of amine and iodine)

Meta chloraniline, 0.2 mole, 25.5 grams, purified by distillation in vacuo

Carbon disulfide, 100 cc.

Pyridine, 0.4 mole, 31.6 grams, the optimum concentration, 100% excess.

Iodine solution: iodine, 0.1 mole, 25.4 grams
carbon disulfide, 200 cc.

The results obtained are represented in the following table.

TABLE 2

Run	Time for Reaction	Theory Crude (Thiourea + S) Grams	% Theory Crude (Thiourea + S) Grams	%	% Theory Pure Thiourea Grams	%
1a	11 min.	32.9	30.4	92.4	23.1	77.8
1b	11 min.	32.9	31.6	96.05	24.7	83.2
av.	11 min.	--	31.0	94.2	23.9	80.5

A small amount of pyridonium periodides were formed in this experiment.

Repeated crystallizations from methyl alcohol give a constant melting point of 121°C which checks that of Fry(14), 121°C.

IIIe. Reaction of para chloraniline: Synthesis of sym. di-(para chlor phenyl) thiourea.

Reagents Used (equivalent quantities of amine and iodine)

Para chloraniline, 0.2 mole, 25.5 grams.

Pyridine, 0.4 mole, 31.6 grams, 100% excess

Carbon disulfide, 100 cc.

Iodine Solution: iodine, 0.1 mole, 25.4 grams

carbon disulfide, 200 cc.

The results obtained are represented in the following table.

TABLE 3

Run	Time for Reaction	Theory Crude (Thiourea + S) Grams	% Theory Crude (Thiourea + S) Grams	%	% Theory Pure Thiourea Grams	%
1a	4 min.	32.9	30.8	93.6	27.4	92.3
1b	4 min.	32.9	32.0	97.3	27.3	91.9
av.	4 min.	--	31.4	95.4	27.35	92.1

In this experiment a small amount of pyridonium periodides were formed. The thiourea was not very soluble in carbon disulfide so the pyridonium iodide was not filtered off before the steam distillation.

The thiourea was purified by crystallization from a 50% mixture of benzene and methyl alcohol. It melted at 168.5°C, which fully agrees with that of Fry(14) and Losanitsch (36).

Dyson and his co-workers(37a,37b,37c,37d) have studied the inhibitory effect of substituents upon (1) the

reactivity of the amino group in the formation of mustard oils and thioureas from thio phosgene and various primary amines and (2) the reactivity of the isothio cyano group in substituted aryl thio carbimides (mustard oils).

The inhibitory effect of ortho, meta, and para substituents upon the reactivity of the amino group in the formation of substituted thioureas by the direct action of carbon disulfide upon the monochlor anilines may be observed from a survey of the following table.

TABLE 4

Run	Substituent (mono chloro)	Time for Reaction	% Theory Crude (Thiourea + S)	% Theory Pure Thiourea
1a	ortho	90 min.	97.6	79.5
1b	ortho	80 min.	93.0	78.4
1a	meta	11 min.	92.4	77.8
1b	meta	11 min.	96.05	83.2
1a	para	4 min.	93.6	92.3
1b	para	4 min.	97.3	91.9
av.	ortho	85 min.	95.3	79.0
av.	meta	11 min.	94.2	80.5
av.	para	4 min.	95.4	92.1

The crude yields are the best indication of the actual amount of material obtained, as some of the product is always lost in the mother liquor during crystallization. (The crude yield consists of only thiourea and sulfur. The traces of pyridine and unused amine have been removed by the acid treatment.) The table shows that the crude yields are about the same in each case. The ortho chlorine atom, in closest proximity to the amino group, inhibits the reaction

to the greatest extent since 85 minutes are required for reaction. The meta chlorine atom, further away from the amino group than the ortho, inhibits the reaction to a lesser degree, and the para chlorine atom being furthest removed from the amino group, manifests the least inhibition. In fact, the time required for aniline itself to react is of the same magnitude as that for para chloraniline, which fact indicates no inhibitory effect in the para position.

IIId. Reaction of ortho bromaniline: Synthesis of sym. di-(ortho brom phenyl) thiourea.

Reagents used (equivalent quantities of amine and iodine)

Ortho bromaniline, 0.2 mole, 34.4 grams, finely pulverized

Pyridine, 0.4 mole, 31.6 grams, 100% excess

Carbon disulfide, 100 cc.

Iodine Solution: iodine, 0.1 mole, 25.4 grams

carbon disulfide, 200 cc.

The results obtained are represented in the following table.

TABLE 5

Run	Time for Reaction	Theory Crude (Thiourea + S) Grams	% Theory Crude (Thiourea + S) Grams	%	% Theory Pure Thiourea Grams	%
1a	180 min.	41.8	36.0	86.1	29.2	75.7
1b	170 min.	41.8	35.8	85.6	29.6	76.7
av.	175 min.	--	35.9	85.85	29.4	76.2

The pure thiourea was obtained by crystallization from a 50% mixture of methyl alcohol and benzene. Dyson and his co-workers(37b) report 157°C for the melting point. The product was crystallized five times and the melting point was recorded after each crystallization. Following are the results obtained:

1. Crystallized from 50% mixture of methyl alcohol and benzene.....m.p. 150°C
2. Recrystallized from methyl alcohol.....m.p. 152°C
3. " " " " .....m.p. 154°C
4. " " " " .....m.p. 154°C
5. " " " " .....m.p. 154°C

All melting points were taken with a short-stem calibrated thermometer. The results indicate that 154° C is the correct melting point for sym. di-(ortho brom phenyl) thiourea.

IIa. Reaction of meta bromaniline: Synthesis of sym. di-(meta brom phenyl) thiourea.

Reagents used (equivalent quantities of amine and iodine)

Meta bromaniline, 0.2 mole, 34.4 grams, purified by distillation in vacuo.

Pyridine, 0.4 mole, 31.0 grams, 100% excess.

Carbon disulfide, 100 cc.

Iodine Solution: iodine, 0.1 mole, 25.4 grams
carbon disulfide, 200 cc.

The results obtained are represented in the following table.

TABLE 6

Run	Time for Reaction	Theory Crude (Thiourea+S) Grams	% Theory Crude (Thiourea+S) Grams	%	% Theory Pure Thiourea Grams	%
1a	9 min.	41.8	41.3	98.5	33.7	87.3
1b	9 min.	41.8	41.3	98.5	32.4	84.0
av.	9 min.	--	41.3	98.5	33.1	85.65

Since the thiourea was not very soluble in the carbon disulfide the pyridonium iodide was not filtered off before steam distillation.

Periodides, in small amount, were formed which seemed to be broken up on further stirring and refluxing.

The product was crystallized from methyl alcohol. Kjellin(38) reports a melting point of 135°C. Von Braun and Beschke(39) report 128°C. The product was recrystallized three times from methyl alcohol and the melting point was recorded,

with the use of a short stem calibrated thermometer, after each crystallization. The results obtained are as follows:

1. Recrystallized from methyl alcohol.....m.p. 132°C
2. " " " " .....m.p. 132°C
3. " " " " .....m.p. 132°C

Therefore, the correct melting point for sym. di-(meta brom phenyl) thiourea is 132°C.

III. Reaction of para bromaniline: Synthesis of sym. di-(para brom phenyl) thiourea.

Reagents used (equivalent quantities of amine and iodine)

Para brom aniline, 0.2 mole, 34.4 grams

Pyridine, 0.4 mole, 31.6 grams, 100% excess.

Carbon disulfide, 100 cc.

Iodine Solution: iodine, 0.1 mole, 25.4 grams

carbon disulfide, 200 cc.

The results obtained are represented in the following table.

TABLE 7

Run	Time for Reaction	Theory Crude (Thiourea + S) Grams	% Theory Crude (Thiourea + S) Grams	%	% Theory Pure Thiourea Grams	%
1a	2 min.	41.8	41.5	99.25	29.8	77.2
1b	2 min.	41.8	41.5	99.25	30.1	78.0
av.	2 min.	--	41.5	99.25	29.95	77.6

Since the thiourea was not very soluble in carbon disulfide the pyridonium iodide was not filtered off before the steam distillation.

Periodides were formed in small amount, which seemed to be broken up on further stirring and refluxing.

The product was crystallized from a 50% mixture of benzene and ethyl alcohol, in the form of fine, clear, small prisms.

Otto(40) reports a melting point of 178° C. Von Braun and Beschke(39) state that the melting point is about 180° C.

Repeated crystallizations from a 50% mixture of benzene and ethyl alcohol gave a constant melting point of 185° C, with the use of a short stem calibrated thermometer. Therefore, 185° C is the correct melting point of sym. di-(para brom phenyl) thiourea.

The inhibitory effect of ortho, meta, and para substituents with respect to monobromanilines may be observed from the following table.

TABLE 8

Run	Substituent (mono brom)	Time for Reaction	% Theory Crude (Thiourea + S)	% Theory Pure Thiourea
1a	ortho	180 min.	86.1	75.7
1b	ortho	170 min.	85.6	76.7
1a	meta	9 min.	98.5	87.3
1b	meta	9 min.	98.5	84.0
1a	para	2 min.	99.25	77.2
1b	para	2 min.	99.25	78.0
av.	ortho	175 min.	85.4	76.2
av.	meta	9 min.	98.5	85.65
av.	para	2 min.	99.25	77.6

Again as with Table 4, the crude yields may be taken as the best indication of the actual amount of material obtained. It has been observed with the chloranilines (Table 4) that the ortho substituent did not affect the yield of the crude product, but required the greatest length of time for reaction, namely 85 minutes. With ortho bromaniline the yield was actually decreased in addition to requiring the greatest length of time for reaction, namely 175 minutes, which is double that for ortho chloraniline. Thus, it may be seen that the ortho bromine atom manifests at least twice the inhibitory effect of the ortho chlorine atom. The meta bromine atom, being further

removed from the amino group, shows considerably less inhibitory effect since only 9 minutes are required for reaction, and a greater yield is obtained. The para bromine atom is so far removed from the amino group that no inhibitory effect is observed.

It is of interest to note here that a di-ortho substituted aniline, such as 2-6 dibromaniline, scarcely reacts at all to form a thiourea.

Raiford and McNulty(41) have shown that a bromine atom in the ortho position to an amino group of a primary amine hinders the reaction more than a chlorine atom similarly placed. This fact is in agreement with the results obtained from the experiments.

IIg. Reaction of para iodo-aniline: Synthesis of sym. di-(para iodo phenyl) thiourea.

Reagents used (equivalent quantities of amine and iodine)

Para iodo-aniline, 0.2 mole, 43.8 grams

Pyridine, 0.4 mole, 31.6 grams, 100% excess

Carbon disulfide, 100 cc.

Iodine Solution: iodine, 0.1 mole, 25.4 grams

carbon disulfide, 200 cc.

The results obtained are recorded in the following table.

TABLE 9

Run	Time for Reaction Minutes	Theory Crude (Thiourea + S) Grams	% Theory Crude (Thiourea + S) Grams	%	% Theory Pure Thiourea Grams	%
1a	about 2	51.2	50.5	98.5	41.6	86.5
1b	about 2	51.2	51.1	99.7	40.6	84.7
av.	about 2	--	50.8	99.1	41.1	85.6

The carbon disulfide solution of the amine was so dark in color that the termination of the reaction could be approximated only by noting the amount of material (pyridonium iodide and the thiourea) precipitated in the flask. Because of the insolubility of the thiourea, the pyridonium iodide was not filtered off before the steam distillation.

The product was but very sparingly soluble in the common organic solvents. It was purified by extraction of the sulfur with carbon disulfide in a Soxhlet extractor.

Losanitsch(36), in 1872, prepared an iodinated thiourea, apparently the para compound, and reported a melting point of

173°C. Repeated extractions of the product with carbon disulfide gave an average melting point of 188.4°C (short-stem calibrated thermometer*), which really is a decomposition temperature, as the material in the capillary darkened appreciably. The different decomposition temperatures are as follows:

1. m.p. 188.8°C
2. m.p. 188.2°
3. m.p. 187.8°
4. m.p. 188.8°
5. m.p. 188.2°

av. m.p. 188.4°

The compound, metallic gray in color, is readily soluble in pyridine, very slightly soluble in carbon disulfide (about 0.25 gram in 100 cc. CS_2 at room temperature), and only sparingly soluble in alcohol and ether. Gray crystalline plates or needles are obtained on treating the material with hot alcohol and adding just enough pyridine to effect solution at the boiling temperature, or by dissolving the material in pyridine and precipitating it by the addition of ether. The crystals from the alcohol-pyridine solution melted at 189°C (with decomposition).

The percentage of nitrogen in the compound was determined by use of the Kjeldahl-Gunning method(42).

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* The melting points of all the compounds to be described in the next Experimental Parts (IV and V) were taken with a short-stem calibrated thermometer.

Sample g.	N/10 Acid c.c.	N Found %	N Theory %
0.3614	15.09	5.85	5.84
0.6160	25.66	5.84	
0.4811	19.99	5.82	

The percentage of sulfur was determined by fusing the compound with 10-15 grams sodium peroxide in a Parr bomb. Half of the peroxide was placed in the bomb, the sample weighed in, and then the remainder of the peroxide was added. The bomb was sealed and shaken vigorously for about four minutes to provide uniform mixing of the contents. To this end it is best that the material be in a finely divided form. A piece of asbestos was placed over a triangle on a tripod. The bomb was inserted through a hole in the asbestos. The small depression in the top of the bomb was filled with water. In this way the rubber gasket between the lid and the cup was protected against heat. The bomb was ignited with a sharp pointed flame for a period of three minutes. After the ignition the bomb was cooled under the tap, opened, and the lid was washed off into a 400 cc. beaker. The cup was removed from the outside jacket and placed in the beaker. A stirring rod was inserted and the beaker was covered with a watch glass. Then the cup was tipped over and the contents were leached out by the action of the water. After all action ceased the cup was removed and adhering liquid rinsed into the beaker. The contents were then neutralized with conc. hydrochloric acid with 1-2 cc. in

excess. The liquid was boiled for 10-15 minutes to expel hydrogen peroxide. From this point on the procedure was the same as that of Allen and Bishop(43).

Sample g.	$BaSO_4$ g.	S Found %	S Theory %
0.8822	0.4350	6.77	6.68
0.3102	0.1539	6.81	

The results obtained in the analyses of sulfur and nitrogen establish conclusively the identity of the compound as sym. di-(para iodo phenyl) thiourea, m.p. 188.4°C.

A summary of the results obtained in the synthesis of thioureas from para chlor, brom, and iodo-anilines is presented in the following table.

TABLE 10

Run	Substituent	Time for Reaction, Minutes	% Theory Crude (Theory S)	% Theory Pure Thiourea
1a	p. chlor	4	93.6	92.3
1b	p. chlor	4	97.3	91.9
1a	p. brom	2	99.25	77.2
1b	p. brom	2	99.25	78.0
1a	p. iodo	about 2	98.5	86.5
1b	p. iodo	about 2	99.7	84.7
av.	p. chlor	4	95.4	92.1
av.	p. brom	2	99.25	77.6
av.	p. iodo	about 2	99.1	85.6

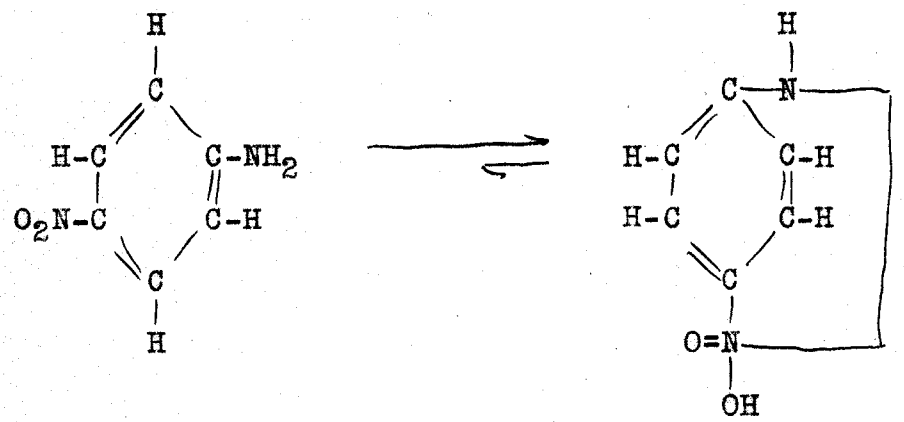
Again, as with preceding tables, the crude product (thiourea plus sulfur) is the best indication of the actual yield obtained. The results indicate that the para chlorine atom exerts very slight inhibitory effect, since four minutes

were required for reaction and a 95% yield was obtained. The para bromine and iodine atoms show no inhibitory effect as the time for aniline itself to react, about two minutes, is identical with that needed for the brom- and iodo-anilines. And as can be seen, the yield is nearly quantitative. It is to be concluded, then, that the para chlorine atom shows only slight inhibitory effect, and the para bromine and iodine atoms none whatever, in the synthesis of thioureas by use of the method previously described.

IIIh. Reaction of ortho, meta, and para nitranilines.

Fry(14) and other investigators were not successful in synthesizing thioureas from ortho and para nitranilines. Raiford and McNulty(41) have shown that larger groups, such as phenyl or other alkyl radicals, in the same positions, produce but little hindrance. This fact seems to show that the inhibitory effect is not dependent alone upon the weight and position of the substituent (steric effect), but that its chemical character plays a role.

To account for the non-reactivity of ortho and para nitranilines the following equilibrium may afford an explanation:



Because of such possible tautomerism, a ring is produced containing a secondary nitrogen atom, that is, a secondary amine results, and its configuration shows no reactivity with carbon disulfide (i.e. formation of a di-thio carbamic acid).

Since no thiourea can be produced from ortho or para nitranilines it is to be concluded that, under the con-

ditions of the experiment, the amine possibly exists in the peculiar enolic modification noted above. The non-reactivity of ortho nitraniline may be explained in the same manner.

On the other hand, a thiourea is easily obtained from meta nitraniline, which fact would indicate that the tautomerism only exists with respect to the ortho and para nitro groups.

IV. Reactions of Secondary Amines.

IVa. Reaction of mono-methylaniline: Synthesis of sym. dimethyl diphenyl thiuram disulfide, and the determination of the optimum concentration of pyridine.

The method employed here and for the following secondary amines in the synthesis of thiuram disulfides has been described under Experimental, Part I. In this description of the experimental procedure no mention was made of the molecular proportions of the reactants employed. Since pyridine was used in excess to promote the extent of the occurrence of the reactions studied, a brief description of the experiments employed to arrive at the optimum concentration of pyridine in the reactions with secondary amines, should be included. Further objectives relate to the effect of the excess pyridine upon the time necessary for reaction and the yield of sym. dimethyl diphenyl thiuram disulfide.

Separate experiments were conducted with mono methyl and mono ethyl aniline, using quantities of amine, iodine, pyridine, and carbon disulfide, based upon the general type equation:

$$2R_1R_2NH + CS_2 + I_2 + 2C_5H_5N \longrightarrow (R_1R_2NCSS)_2 + 2C_5H_5N\cdot HI.$$

Here it may be noted that the iodine only effects oxidation of the intermediate di-thio carbamic acid, since it is not possible for hydrogen sulfide to be evolved as is the case in the reaction of a primary amine (see Theoretical).

Reagents used (equivalent quantities of amine and iodine)

Mono-methylaniline: 0.2 mole, 21.4 grams, purified by distillation. B.P. 195-197°C.

Carbon Disulfide: 100 cc.

Iodine Solution: iodine, 0.1 mole, 25.4 grams carbon disulfide, 200 cc.

Pyridine: (a) 0.4 mole, 31.6 grams, 100% excess

(b) 0.3 mole, 23.7 grams, 50% excess

(c) 0.2 mole, 15.8 grams, 0% excess

The results obtained are recorded in the following table.

TABLE 11

Run	% Excess Pyridine	Time for Reaction (hrs.)	Theory for Thiuram Disulfide g.	% Theory Crude Product g.	%	% Theory Pure Product g.	%
1a	100	0.33	36.4	34.8	95.6	33.6	92.3
1b	100	0.33	36.4	34.5	94.8	33.2	91.2
2a	50	1.00	36.4	34.6	95.0	32.3	89.2
2b	50	1.00	36.4	34.0	93.4	31.0	85.2
3a	0	4.00	36.4	33.3	91.5	32.0	87.9
3b	0	4.00	36.4	33.1	91.0	31.4	86.3
av.1a,1b	100	0.33	----	34.7	95.2	33.4	91.8
av.2a,2b	50	1.00	----	34.3	94.2	31.7	87.2
av.3a,3b	0	4.00	----	33.2	91.3	31.7	87.1

The material after the treatment with acid (to remove unused amine and small amounts of pyridine) followed by free washing with water is designated as the crude product. The material after grinding under ether or alcohol and washing until all runnings are colorless is the pure product, as

evidenced by the fact that the melting point of the material (186°C) at this point corresponds to the value reported by Fry and Culp(32), 186°C. Von Braun reported 198°C(18). The pure product when recrystallized twice from ethyl alcohol gives a constant melting point of 186°C. The analyses of Culp for nitrogen and sulfur were 7.75 and 35.02 respectively, which agree with the actual percentages, 7.65 and 35.00 respectively, for sym. dimethyl diphenyl thiuram disulfide.

The crystals produced from alcohol are fine, colorless plates or leaves when viewed through the microscope.

A survey of Table 11 shows that when the concentration of pyridine is decreased only a slight decrease in yield is noted, but however, the time necessary for reaction increases markedly. It might be expected that the pyridine would react with the intermediate di-thio carbamic acid to form a salt, viz:

$$R_1R_2NH + CS_2 \longrightarrow R_1R_2NCSSH$$

$$R_1R_2NCSSH + C_5H_5N \longrightarrow R_1R_2NCSSNHC_5H_5,$$

which, if stable, would give smaller yields of product the greater the concentration of pyridine, since less di-thio carbamic acid would be available for oxidation to the thiuram. The fact that decreased concentrations of pyridine produced no increase in yield shows that the complex salt was either not formed, or if formed, it was easily decomposed. On the other hand, if one considers that all non-polar compounds in chemical reaction must suffer actual molecular collision,

greater yields and more rapid reaction would be expected when the concentration of one of the reactants is increased. This hypothesis, particularly with respect to the time element, is supported by the results obtained, namely that increased concentrations of pyridine bring about a marked decrease in the time necessary for reaction.

The optimum concentration of pyridine is a 100% excess over that amount theoretically needed to react with the hydrogen iodide formed, since the greatest yield of thiuram disulfide is produced in a minimum of time when this concentration is employed. It should be noted also that when the concentration is less than 100% excess of pyridine the formation of pyridonium periodides seems to be promoted. This would cause a lower yield because less iodine would be available for oxidation of the di-thio carbamic acid.

IVb. Reactions of mono-ethylaniline: Synthesis of sym. diethyl diphenyl thiuram disulfide and the effect of the concentration of pyridine upon the time necessary for reaction and yield of the disulfide.

Reagents used (equivalent quantities of amine and iodine)

Mono-ethylaniline: 0.2 mole, 24.2 grams, purified by distillation. B.P. 204-205°C.

Carbon Disulfide: 100 cc.

Iodine Solution: iodine, 0.1 mole, 25.4 grams
carbon disulfide, 200 cc.

Pyridine: (a) 0.4 mole, 31.6 grams, 100% excess
(b) 0.3 mole, 23.7 grams, 50% excess
(c) 0.2 mole, 15.8 grams, 0% excess

The results obtained are recorded in the following table.

TABLE 12

Run	% Excess Pyridine	Time for Reaction (hrs.)	Theory for Thiuram Disulfide g.	% Theory Crude Product g.	%	% Theory Pure Product g.	%
1a	100	11-12	39.2	38.6	98.5	37.9	96.8
1b	100	11-12	39.2	38.8	98.9	38.0	96.9
2a	50	20-25	39.2	38.5	98.2	37.9	96.7
2b	50	20-25	39.2	38.5	98.2	37.5	95.7
3a	0	75-85	39.2	34.1	87.0	31.6	80.7
3b	0	75-85	39.2	35.0	89.2	32.6	83.1
av.1a,1b	100	11-12	----	38.7	98.7	38.0	96.9
av.2a,2b	50	20-25	----	38.5	98.2	37.7	96.2
av.3a,3b	0	75-85	----	34.6	88.1	32.1	81.9

Here also, as in the experiment with mono-methylaniline, decreasing the concentration of pyridine caused a large increase in the time necessary for reaction, promoted the formation of pyridonium periodides, and decreased the yield of product.

Culp(32) obtained a yield of 44.7%. Stirring the mixture mechanically and adding the iodine solution slowly made possible a percentage yield more than double that of Culp, namely 96.85%. From this it is to be concluded that stirring has a profound effect upon the extent of occurrence of the reaction. In order that all experiments previously described and those which follow might be conducted under conditions as nearly alike as possible, it was attempted to maintain the same speed of stirring in all runs. The melting point of the compound (after treatment with alcohol) was 168°C. This checks Culp's value of 167.5°C. Von Braun reported 169-170°C(18).

Experiments conducted with mono-methyl and mono-ethylaniline indicate that 100% excess of pyridine over that theoretically required for formation of thiuram disulfides is the optimum concentration since the greatest yield is obtained in a minimum of time, with the formation of a minimum amount of periodides of pyridine when this concentration is employed.

IVc. Reaction of diphenylamine: Synthesis of tetra phenyl thiuram disulfide.

Reagents used (equivalent quantities of amine and iodine)

Diphenylamine: 0.2 mole, 33.8 grams, m.p. 54°C, purified by crystallization from ligroin.

Carbon Disulfide: 100 cc.

Iodine solution: iodine, 0.1 mole, 25.4 grams
carbon disulfide, 200 cc.

Pyridine: 0.4 mole, 31.6 grams, 100% excess.

The reaction mixtures were refluxed continuously for a month or more (mixtures allowed to stand over night and on next day refluxing continued). A copious precipitate of periodides of pyridine was formed. At the end of this period the mixtures were steam distilled until all carbon disulfide had been removed. The flasks containing the material as an oil were cooled under the tap until the oil solidified. The solid material was filtered out on a Buchner and then treated with hot alcohol to dissolve the large quantity of unused amine and iodine. A yellow solid material remained undissolved. This was filtered off and washed with alcohol until the runnings were colorless. This material is the desired product. The results obtained are recorded in the following table.

TABLE 13

Run	Time for Refluxing (weeks)	Theory for Thiuram Disulfide g.	% Theory Pure Product g.	%
1a	4	48.8	5.1	10.45
1b	4	48.8	5.6	11.46
2a	6	48.8	7.8	15.97
2b	6	48.8	7.2	14.75
3a	10	48.8	9.5	19.45
3b	10	48.8	10.0	20.45
av.1a,1b	4	----	5.35	10.95
av.2a,2b	6	----	7.50	15.36
av.3a,3b	10	----	9.75	19.95

The yellow fluffy material from the alcohol treatment appears in the form of spiny needles when viewed through the microscope. It melts at 217.5°C (with decomposition). The compound is insoluble in water, slightly soluble in carbon disulfide, sparingly soluble in alcohol and ether, and readily soluble in pyridine and chloroform.

Since a survey of the literature yielded no data on the preparation and identification of tetra phenyl thiuram disulfide, the percentages of nitrogen and sulfur were determined by methods previously employed(42) and (43).

Fifteen grams of sodium peroxide and one gram of potassium perchlorate were incorporated into the Parr bomb to effect complete oxidation of the sulfur. The results of the analyses are recorded in the following tables.

Sample g.	0.08568 N Acid c.c.	N Found %	N Theory %
0.5613	26.81	5.73	5.74
0.4038	19.31	5.74	

Sample g.	$BaSO_4$ g.	S Found %	S Theory %
0.1678	0.3211	26.28	26.26
0.1948	0.3701	26.09	

The results of the analyses conclusively establish the identity of the compound as tetra-phenyl thiuram disulfide, m.p. 217.6°C (with decomposition).

The following table serves to show the inhibitory effect of the methyl ethyl and phenyl groups when secondary amines are converted into their corresponding thiuram disulfide derivatives. Results from experiments with mono-methyl, mono-ethyl, and diphenylamine are recorded. Consideration of the formulas of the amines shows that the group, C_6H_5NH-, is common to all three. Hence any differences in time necessary for reaction may be attributed to the steric hindrance effect of the groups, methyl, ethyl, or phenyl.

TABLE 14

Run	R in C_6H_5NHR	Time for Reaction	Theory for Thiuram Disulfide g.	% Theory Pure Product g.	%
1a	methyl	20 min.	36.4	33.6	92.3
1b	methyl	20 min.	36.4	33.2	91.2
1a	ethyl	11-12 hrs.	39.2	37.9	96.8
1b	ethyl	11-12 hrs.	39.2	38.0	96.9
3a	phenyl	10 weeks	48.8	9.5	19.45
3b	phenyl	10 weeks	48.8	10.0	20.45
r.1a,1b	methyl	20 min.	36.4	33.4	91.8
r.1a,1b	ethyl	11-12 hrs.	39.2	37.95	96.85
r.3a,3b	phenyl	6-10 weeks	48.8	9.75	19.95

The results indicate that increase in weight of the substituent causes a very marked increase in the time necessary for reaction. It may be noted that about ten weeks are necessary for diphenylamine to give a yield of only 20%, while the reactions of mono-methylaniline and mono-ethylaniline are approximately complete in the times indicated. The results obtained with diphenylamine are not surprising in view of the fact that its chemical properties may be considered as intermediate between the strong salt forming compound, phenylamine (aniline) and the non-salt forming compound, triphenylamine. With triphenylamine the nitrogen is so protected by the three phenyl groups that it becomes non-reactive to mineral acids. The same is true of diphenylamine to a lesser degree since only two phenyl groups are present to hinder the reaction of salt formation. It may be concluded, then, that the same steric hindrance of the phenyl groups in diphenylamine accounts for the slight reactivity with carbon disulfide in the formation of a thiuram disulfide. With mono-methyl and mono-ethyl anilines the steric effect is not so pronounced as smaller groups are present. Hence greater yields of thiuram disulfides are obtained in shorter periods of time.

IVd. Reaction of methyl ortho-toluidine: Synthesis of sym. dimethyl di-(ortho-tolyl) thiuram disulfide.

Reagents used (equivalent quantities of amine and iodine)

Methyl ortho-toluidine: 0.2 mole, 24.2 grams

Carbon disulfide: 100 cc.

Pyridine: 0.4 mole, 31.6 grams, 100% excess

Iodine solution: iodine, 0.1 mole, 25.4 grams

carbon disulfide, 200 cc.

The results obtained are recorded in the following table.

TABLE 15

Run	Time for Reaction hrs.	Theory Thiuram Disulfide g.	% Theory Crude Product g.	%	% Theory Pure Product g.	%
1a	12-13	39.2	38.3	97.7	36.0	91.9
1b	12-13	39.2	38.7	98.7	36.8	93.9
av.	12-13	--	38.5	98.2	36.4	92.9

The compound was crystallized four times from a 50% mixture of benzene and ethyl alcohol. A constant melting point of 200.2°C was obtained. The compound (small, white prisms) is practically insoluble in water, sparingly soluble in methyl and ethyl alcohols and ether, and quite soluble in benzene, carbon disulfide, and pyridine.

No previous account of the preparation and identification of this compound has been found in the literature.

The percentages of nitrogen and sulfur were determined by methods previously noted.

Sample g.	0.1040 N Acid c.c.	N Found %	N Theory %
0.1015	5.01	7.19	7.14
0.2196	10.77	7.15	

Sample g.	$BaSO_4$ g.	S Found %	S Theory %
0.2054	0.4879	32.62	32.70
0.1875	0.4450	32.60	

The results of the analyses conclusively establish the identity of the compound as sym. dimethyl di-(ortho-tolyl) thiuram disulfide (m.p. 200.2° C).

IVe. Reaction of methyl meta-toluidine: Synthesis of sym. dimethyl di-(meta-tolyl) thiuram disulfide.

Reagents used (equivalent quantities of amine and iodine)

Methyl meta toluidine: 0.2 mole, 24.2 grams, purified by distillation in vacuo. B.P. 100-104° at 16 mm.

Carbon disulfide: 100 cc.

Pyridine: 0.4 mole, 31.6 grams, 100% excess.

Iodine Solution: iodine 0.1 mole, 25.4 grams carbon disulfide, 200 cc.

The results obtained are recorded in the following table.

TABLE 16

Run	Time for Reaction hrs.	Theory Thiuram Disulfide g.	% Theory Crude Product g.	%	% Theory Pure Product g.	%
1a	2	39.2	37.5	95.8	24.3	62.0
1b	2	39.2	36.5	93.2	23.5	60.0
av.	2	--	37.0	94.5	23.9	61.0

This compound was crystallized twice from carbon disulfide and once from a 50% mixture of benzene and methyl alcohol, giving very small white crystals. A constant melting point of 170-171° C was obtained. The compound is very soluble in carbon disulfide, pyridine, and benzene, fairly soluble in methyl and ethyl alcohol, very slightly soluble in ether, and practically insoluble in water.

No previous account of the preparation and identifi-

cation of this compound has been found in the literature.

The results of the analyses for nitrogen and sulfur are recorded in the following tables.

Sample g.	N/10 Acid c.c.	N Found %	N Theory %
0.1513	7.73	7.16	7.14
0.2909	14.83	7.14	

Sample g.	$BaSO_4$ g.	S Found %	S Theory %
0.1793	0.4281	32.77	32.70
0.2207	0.5267	32.78	

The results of the analyses conclusively establish the identity of the compound as sym. dimethyl di-(meta-tolyl) thiuram disulfide (m.P. 170-171° C).

IVf. Reaction of methyl para-toluidine: Synthesis of sym. dimethyl di-(para-tolyl) thiuram disulfide.

Reagents used (equivalent quantities of amine and iodine)

Methyl para-toluidine: 0.2 mole, 24.2 grams, purified by distillation in vacuo. B.P. 69-70° at 10 mm.

Carbon disulfide: 100 cc.

Pyridine: 0.4 mole, 31.6 grams, 100% excess

Iodine Solution: iodine, 0.1 mole, 25.4 grams carbon disulfide, 200 cc.

The results obtained are recorded in the following table.

TABLE 17

Run	Time for Reaction hrs.	Theory Thiuram Disulfide g.	% Theory Crude Product g.	%	% Theory Pure Product g.	%
1a	1.5	39.2	36.8	93.9	34.0	86.8
1b	1.5	39.2	36.3	92.7	33.3	85.0
av.	1.5	--	36.55	93.3	33.65	85.9

The compound was crystallized twice from carbon disulfide and once from ethyl alcohol. A constant melting point of 183°C was obtained. The compound darkened on melting, which may be evidence of decomposition. The compound was found to be insoluble in water, slightly soluble in ether, fairly soluble in methyl and ethyl alcohols, and very soluble in carbon disulfide, pyridine, and benzene.

The compound crystallized in fine long needles from

ethyl alcohol. When crystallization was carried out in a test-tube (slow cooling in the air) some of the needles were found to be over an inch in length. Crystals from carbon disulfide were small rectangular prisms, an aggregate having a yellowish tinge. Crystals from alcohol were perfectly white in aggregate.

The previous preparation and identification of this compound was <u>not</u> found in a survey of the literature.

The percentages of nitrogen and sulfur were determined and the results are recorded below.

Sample g.	0.0987 N Acid c.c.	N Found %	N Theory %
0.3883	20.15	7.18	7.14
0.7446	38.27	7.11	

Sample g.	$BaSO_4$ g.	S Found %	S Theory %
0.1869	0.4456	32.75	32.70
0.2410	0.5716	32.58	

The results of the analyses conclusively establish the identity of the compound as sym. dimethyl di-(para-tolyl) thiuram disulfide, (m.p. 183°C with decomposition).

The effects of the methyl substituent in the ortho, meta, and para positions to the methylamino group are summarized in the following table. Results from experiments with mono-methyl aniline, methyl ortho-, methyl meta-, and methyl para-toluidine are recorded.

TABLE 18

Run	R in $C_6H_4RNHCH_3$	Time for Reaction hrs.	% Theory Crude Product	% Theory Pure Product
1a	H	0.33	95.6	92.3
1b	H	0.33	94.8	91.2
1a	para CH_3	1.5	93.9	86.8
1b	para CH_3	1.5	92.7	85.0
1a	meta CH_3	2.0	95.8	62.0
1b	meta CH_3	2.0	93.2	60.0
1a	ortho CH_3	12.0	97.7	91.9
1b	ortho CH_3	12.0	98.7	93.9
av.	H	0.33	95.2	91.8
av.	para CH_3	1.5	93.3	85.9
av.	meta CH_3	2.0	94.5	61.0
av.	ortho CH_3	12-13	98.2	92.9

Here, as in preceding tables, the crude yield is the best indication of the actual amount of material obtained. The results indicate that when the methyl group is in the para position the reaction is inhibited to the least extent, since for the three compounds, methyl o-, m-, and p-toluidines, the time required for reaction is the smallest for the para compound. The para methyl group does show inhibition because the time required for methylaniline to react is only about 20 minutes. The greatest inhibition is manifested by the ortho methyl group since it is in closest proximity to the amino group. The inhibitory effect does not very appreciably alter the yields (crude products) as they are roughly the same in each case.

IVg. Reaction of meta-nitro methylaniline: Synthesis of sym. dimethyl di-(meta nitro phenyl) thiuram disulfide.

Reagents used (equivalent quantities of amine and iodine)

Meta nitro methylaniline: 0.2 mole, 30.4 grams, m.p. 64-65°C

Carbon disulfide: 100 cc.

Pyridine: 0.4 mole, 31.6 grams, 100% excess

Iodine solution: iodine, 0.1 mole, 25.4 grams

carbon disulfide, 200 cc.

The results obtained are recorded in the following table.

TABLE 19

Run	Time for Reaction hrs.	Theory Thiuram Disulfide g.	% Theory Crude Product g.	%	% Theory Pure Product g.	%
1a	3	45.4	45.3	99.9	38.0	83.8
1b	3	45.4	45.1	99.3	37.8	83.3
av.	3	--	45.2	99.6	37.9	83.55

Since the compound was not very soluble in carbon disulfide the pyridonium iodide was not filtered off before the steam distillation.

Periodides were found in small amount which seemed to be broken up on further stirring and refluxing.

The compound was obtained in the form of fine slightly yellow crystals on crystallization from benzene. On crystallization, twice from benzene and twice from a 50% mixture of benzene and carbon disulfide, a constant melting point of 172°C was obtained. The compound melted with decomposition.

The compound was found to be insoluble in water, slightly soluble in the ether and alcohol, fairly soluble in carbon disulfide and acetone, and very soluble in benzene, pyridine, and chloroform.

No previous account of the preparation and identification of this compound was found in the literature.

The determination of the nitrogen content of this compound called for a simple modification of the usual Kjeldahl-Gunning procedure because of the presence of the two nitro substituents. Their necessary reduction was effected by incorporation of two 12.5 cm. Sargent filter papers in the acid digestion mixtures. Blanks were run on the filter paper in order to apply a correction for its nitrogen content.

The percentage of sulfur was determined in the usual manner. The following tables show the results obtained in the analyses.

Sample g.	0.1040 N Acid c.c.	N Found %	N Theory %
0.1163	9.78	12.25	12.33
0.1347	11.43	12.36	

Sample g.	$BaSO_4$ g.	S Found %	S Theory %
0.1899	0.3887	28.10	28.23
0.2258	0.4630	28.16	

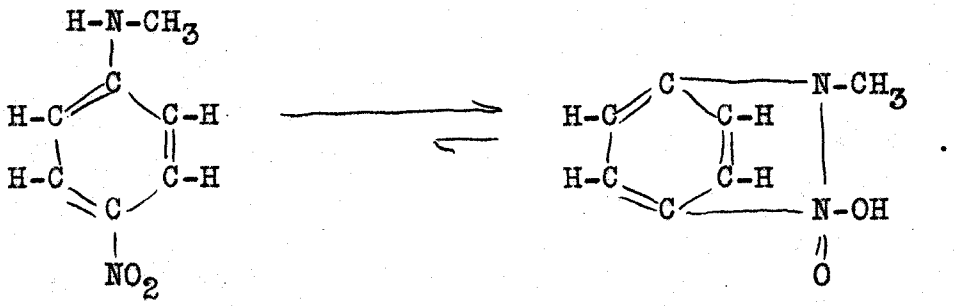
The results of the analyses conclusively establish the identity of the compound as sym. dimethyl di-(meta nitro phenyl) thiuram disulfide, m.p. 172°C (with decomposition).

IVh. Reaction of Para Nitro Methylaniline.

No thiuram disulfide could be obtained from this amine even though the reaction mixtures were stirred and refluxed for one and one-half months.

It will be recalled that meta nitraniline was readily converted into a thiourea while the ortho and para compounds were non-reactive. In the case of the secondary amines, meta nitro methylaniline may readily be converted into a thiuram disulfide (see Experimental, section IVg.).

To account for the non-reactivity of the para nitro methylaniline (and, presumably, also the ortho) the following type of molecular rearrangement, similar to that for ortho and para nitranilines, may be proposed:



containing a tertiary nitrogen atom, and such compounds cannot react with carbon disulfide to form di-thio carbamic acids. Apparently the meta compound does not suffer this rearrangement.

V. Synthesis of Tri-Substituted Thioureas from Mustard Oils and Secondary Amines.

a. Reaction of Phenyl Isothiocyanate and Methyl Ortho Toluidine. Synthesis of Alpha Phenyl, Beta Methyl, Beta Ortho Tolyl Thiourea.

Equivalent quantities of reagents in conformity with the following type equation were employed:

$$RNCS + R_1R_2NH \longrightarrow RNH\overset{\alpha}{-}\underset{\underset{S}{\|}}{C}\overset{\beta}{-}NR_1R_2$$

Phenyl isothiocyanate: 0.1 mole, 13.5 grams.
Methyl Ortho Toluidine: 0.1 mole, 12.1 grams.

The mustard oil was added to the amine in a 200 cc. long-neck, round-bottom flask fitted by cork to a reflux condenser. No perceptible evolution of heat was noticed on mixing reactants. The mixtures were heated with a small flame for about 30 minutes, and then allowed to stand for two days. At the end of this time the viscous oil had solidified to a crystalline mass. The products were dissolved in 25 cc. of hot ethyl alcohol, crystallized in an ice bath, filtered, washed with 15 cc. alcohol, dried, and weighed. The results obtained are indicated in the following table.

Run	Heat Evolution	Theory Thiourea g.	% Theory Pure Thiourea g.	%
1a	not perceptible	25.6	20.0	78.1
1b	not perceptible	25.6	20.7	80.8
av.	-----		20.35	79.45

The entire material was combined and recrystallized three times from alcohol. A constant melting point range of 89-90°C was obtained. On slow cooling, rectangular prismatic needles were obtained. On cooling in an ice bath, the crystals obtained appeared to be diamond shaped with ten facets when viewed through the microscope.

Since a survey of the literature yielded no data concerning the previous preparation and identification of this compound, its percentages of nitrogen and sulfur were determined by methods previously employed. The results of the analyses are recorded in the following tables.

Sample g.	0.1040 N Acid c.c.	N Found %	N Theory %
0.2788	21.00	10.97	10.94
0.4072	30.68	10.97	

Sample g.	$BaSO_4$ g.	S Found %	S Theory %
0.3223	0.2938	12.52	12.51
0.4207	0.3838	12.53	

The results of the analyses conclusively establish the identity of the compound as alpha phenyl, beta methyl, beta ortho tolyl thiourea, m.p. 89-90°C.

The material is readily soluble in ether, alcohol, benzene, carbon disulfide, pyridine, and chloroform.

Vb. Reaction of Phenyl Isothiocyanate and Methyl Meta Toluidine: Synthesis of Alpha Phenyl, Beta Methyl, Beta Meta-tolyl Thiourea.

Reagents used (equivalent quantities)

Phenyl isothiocyanate: 0.1 mole, 13.5 grams

Methyl meta toluidine: 0.1 mole, 12.1 grams

A decided heat effect was apparent on mixing reactants. After heating for 30 minutes and cooling, the contents of the flasks were very viscous oils, which did not crystallize on standing in an ice bath. One of the mixtures was steam distilled to remove unused amine and mustard oil. The distillate, after standing two days, slowly crystallized. Some of these crystals were removed to seed the material in the reaction flask which began to crystallize very slowly. After crystallization was complete, the solid material in the distillate and residue was combined and crystallized three times from the smallest possible quantity of ethyl alcohol by cooling in a $CaCl_2$-ice bath. The material was dried and weighed.

The material in the second flask was crystallized by seeding with a small quantity of the product from the first run. This was crystallized three times from alcohol and then combined with the first lot. The combined material was recrystallized once more from alcohol. A constant melting point range of 67.6-68°C was obtained. The low melting point accounts for the

volatility with steam. The crystals appear to be diamond shaped when viewed through the microscope.

The yields obtained are recorded in the following table.

Run	Heat Evolution	Theory Thiourea g.	% Theory Pure Thiourea g.	%
1a	decided	25.6	18.0	70.3
1b	decided	25.6	19.0	74.3
av.	---		18.5	72.3

A survey of the literature yielded no data on the previous preparation and identification of this compound. Accordingly, the percentages of nitrogen and sulfur were determined by methods previously employed. The results are shown in the following tables.

Sample g.	0.1040 N Acid c.c.	N Found %	N Theory %
0.3269	24.44	10.89	10.94
0.5272	39.62	10.95	

Sample g.	$BaSO_4$ g.	S Found %	S Theory %
0.2423	0.2213	12.54	12.51
0.2373	0.2165	12.53	

The results of the analyses conclusively establish the identity of the compound as alpha phenyl, beta methyl, beta meta tolyl thiourea, m.p. 67.6-68°C.

The material is readily soluble in ether, alcohol, benzene, carbon disulfide, pyridine, and chloroform.

Vc. Reaction of Phenyl Isothiocyanate and Methyl para Toluidine: Synthesis of Alpha Phenyl, Beta Methyl, Beta para Tolyl Thiourea.

Reagents used (equivalent quantities)

Phenyl isothiocyanate: 0.1 mole, 13.5 grams.

Methyl para toluidine: 0.1 mole, 12.1 grams.

A decidedly perceptible heat effect, greater than that in the experiments with methyl meta toluidine, was manifested upon mixing reactants. After heating for 30 minutes, crystals appeared on cooling. The products were crystallized from 25 cc. alcohol, filtered by suction, washed with a little alcohol, dried, and weighed. The entire material was combined and recrystallized three times from alcohol. A constant melting point of 89.4°C was obtained. The crystals from alcohol on cooling in an ice bath appeared as small colorless needles when viewed through the microscope. On slow cooling in air, the crystals were large, well defined and somewhat diamond shaped. The yields obtained are recorded in the following table.

Run	Heat Evolution	Theory Thiourea g.	% Theory Pure Thiourea g.	%
1a	very marked	25.6	20.0	78.2
1b	very marked	25.6	20.2	78.8
av.	---	--	20.1	78.5

Since a survey of the literature yielded no data on the previous preparation and identification of this compound,

its percentages of nitrogen and sulfur were determined by methods previously employed. The results of the analyses are recorded in the following tables.

Sample g.	0.1040 N Acid c.c.	N Found %	N Theory %
0.4745	35.63	10.93	10.94
0.3823	28.90	11.01	

Sample g.	$BaSO_4$ g.	S Found %	S Theory %
0.2723	0.2480	12.51	12.51
0.2051	0.1876	12.56	

The results of the analyses conclusively establish the identity of the compound as alpha phenyl, beta methyl, beta para tolyl thiourea, m.p. 89.4°C.

The compound is readily soluble in ether, alcohol, benzene, pyridine, carbon disulfide, and chloroform.

VI. Use of Quinoline and Iodine to effect removal of Hydrogen Sulfide in the Synthesis of Sym. Diphenyl Thiourea.

In the following final experiment it was desired to compare the action of quinoline as a substitute for pyridine in the synthesis of the simple sym. diphenyl thiourea.

Quantities of reagents in conformity with the following general type equation were employed:

$$2RNH_2 + I_2 + CS_2 + 2C_9H_7N \longrightarrow (RNH)_2CS + S + 2C_9H_7N \cdot HI$$

Reagents used (equivalent quantities of amine and iodine)

Aniline: 0.1 mole, 9.3 grams.

Quinoline: 0.2 mole, 25.8 grams purified by distillation, B.P. 234-238°C, 100% excess.

Carbon disulfide: 100 cc.

Iodine Solution: iodine, 0.05 mole, 12.7 grams
carbon disulfide, 200 cc.

The reaction mixtures containing copious precipitates of quinolonium iodide and the thiourea were filtered and washed with carbon disulfide. Filtrate and washings were combined. The residue of quinolonium iodide was extracted with carbon disulfide in a Soxhlet extractor to remove the thiourea. The carbon disulfide filtrate was concentrated by distillation and then evaporated to dryness. The residue of sulfur and thiourea was extracted with alcohol to remove the product. The sulfur residue was weighed. The quinolonium iodide, after the extraction, was removed from the thimble and weighed. The entire quantity of thiourea, from the carbon

disulfide filtrate and the extraction of the quinolonium iodide, was combined and weighed. The results obtained are recorded in the following table.

Run	Theory S g.	Theory QuHI g.	Theory Thiourea g.	% Theory S g.	%	% Theory QuHI g.	%	% Theory Thiourea g.	%
1a	1.6	25.7	11.4	1.3	81.3	25.0	97.3	10.3	90.4
1b	1.6	25.7	11.4	1.4	87.5	24.5	95.3	10.4	91.2
av.	---	----	----	1.35	84.1	24.75	96.0	10.35	90.8

The average yield of 91% is comparable to that obtained when pyridine is used. Therefore, it may be said that quinoline and iodine eliminate hydrogen sulfide with the same degree of efficiency as pyridine and iodine.

SUMMARY

1. The method previously developed in this laboratory (14) for preparation of sym. thioureas in conformity with the general type equation,

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

has been further investigated by extending the method of preparation to thioureas obtainable by the action of the following primary aryl amines: ortho-, meta-, and para-chloranilines; ortho-, meta-, and para-bromanilines; and para-iodo-aniline.

2. An analogous method(32) previously developed in this laboratory for the preparation of symmetrically substituted thiuram disulfides in conformity with the general type equation,

$$2R_1R_2NH + 2CS_2 + I_2 + 2C_5H_5N \longrightarrow (R_1R_2N\text{-}CSS\text{-})_2 + 2C_5H_5N\cdot HI,$$

has been reconfirmed with mono-methyl and mono-ethyl anilines. The method has also been extended to the interaction of diphenylamine, methyl ortho-, meta-, and para-toluidines, and meta-nitro methyl aniline. This led to the synthesis, identification by quantitative analysis, determination of the melting points, and description of properties of five new thiuram disulfides.

3. Preliminary to conducting the foregoing reactions, a study was made to determine the optimum concentration of pyridine to be used in the synthesis of the thioureas and thiuram disulfides noted in (1) and (2) above.

4. The inhibitory effects of substituents in the primary and secondary aryl amines used in the synthesis of res-

pective thioureas and thiuram disulfides have been studied.

a) The order of reactivities of the substituted primary aryl amines is as follows: para > meta > ortho.

b) The reactivities of the secondary aryl amines are of the same parallel order.

c) In relation to (b) the reactivities of methylaniline, ethylaniline, and diphenylamine decrease as the weight of the substituent increases, i.e., $CH_3 > C_2H_5 > C_6H_5$.

d) In the cases of the ortho and para nitranilines and the para nitro methyl aniline, from which no thioureas, or thiuram disulfides have ever been prepared, it is concluded that non-reactivity is caused by the chemical character of the substituent as well as its weight and position.

5. The general type reaction for the preparation of <u>unsymmetrical tri-substituted</u> thioureas,

$$RNCS + R_1R_2NH \longrightarrow RNHC(=S)NR_1R_2,$$

has been extended to the synthesis of three new compounds. Their identification by quantitative analysis, determination of melting point, and description of properties have been made.

6. The basic compound, quinoline, can be substituted for pyridine with the same efficiency in effecting the synthesis of the simple sym. diphenyl thiourea.

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