[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF CINCINNATI.]

NEW METHODS OF PREPARING THIOCARBANILIDES.

BY HARRY SHIPLEY FRY.

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The three most commonly recorded methods of preparing aromatic thiocarbanilides involve, respectively, the following reactions: first, the interaction of a primary amine (or substituted amines) and carbon bisulfide according to equation (I).

$$\text{I. } 2RNH_2 + CS_2 \longrightarrow (RNH)_2CS + H_2S;$$

second, the combination of primary amines and mustard oils, thus:

$$\text{II. } RNH_2 + RNCS \longrightarrow (RNH)_2CS;$$

third, the interaction of guanidines and carbon bisulfide, thus:

$$\text{III. } (RNH)_2 = C = NR + CS_2 \longrightarrow (RNH)_2CS + RNCS.$$

The second and third methods require, respectively, mustard oils and guanidines, compounds which are ordinarily prepared from thiocarbanilides. Hence the fundamental and most generally employed method of preparing thiocarbanilides is that represented by equation (I).

The purpose of the present paper is two-fold: first, to consider some of the advantages and disadvantages of the established methods of conducting the reaction represented by equation (I); and second, to describe some new methods which are quantitatively applied to the preparation of some known and some hitherto unknown thiocarbanilides.

The success of the interaction of an amine and carbon bisulfide in the preparation of a thiocarbanilide depends upon the method one employs for eliminating hydrogen sulfide. In some instances this has been successfully accomplished by adding a minute quantity of sulfur to an alcoholic solution of the amine and carbon bisulfide. Hugershoff[1] found that *o*- and *p*-toluidine, *p*-phenetidine, *p*-aminophenol, and naphthylamine when heated for one or two hours with carbon bisulfide, alcohol and sulfur, gave quantitative yields of the corresponding thiocarbanilides. The successful elimination of the hydrogen sulfide was here attributed to a catalytic action of the added sulfur.

Another method, and by far the most common, for the elimination of hydrogen sulfide involves the addition of potassium or sodium hydroxide to an alcoholic solution of the amine and carbon bisulfide.

The applicability of each of the above methods is limited because certain amines (especially the substituted amines) do not yield the corresponding thiocarbanilides. Thiourethanes or mixtures of thiourethanes and some thiocarbanilide are obtained. This is due to the presence of alcohol (as solvent) which in many cases reacts either with the amine or with some of the thiocarbanilide present according to the typical equations:

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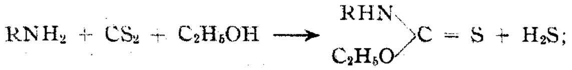
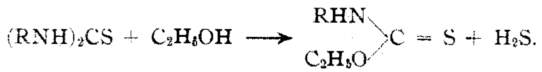
[1] *Ber.*, 32, 2245 (1899).



$$RNH_2 + CS_2 + C_2H_5OH \longrightarrow \begin{matrix} RHN \\ C_2H_5O \end{matrix}\!\!>C = S + H_2S;$$



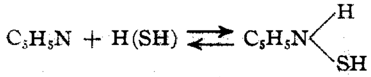
$$(RNH)_2CS + C_2H_5OH \longrightarrow \begin{matrix} RHN \\ C_2H_5O \end{matrix}\!\!>C = S + H_2S.$$

Thus, for instance, Losanitsch[1] obtained no thiocarbanilide but *m*-nitrophenylthiourethane by heating together *m*-nitraniline, carbon bisulfide and alcohol. When *p*-nitraniline[2] was heated for a long time with carbon bisulfide and alcohol no reaction took place. Potassium hydroxide was then added in order to eliminate hydrogen sulfide and thereby complete the reaction for the formation of di-*p*-nitrothiocarbanilide, but instead the product obtained was *p*-nitrophenylthiourethane. Furthermore, Losanitsch states that "the formation of thiourethanes along with thiocarbanilides always occurs when an aromatic amine, carbon bisulfide and alcoholic potash are heated together for some time." In this manner he obtained from aniline, *p*-chloraniline, and *p*-toluidine the corresponding thiourethanes.

The above and many similar reactions, which are ordinarily regarded as methods of preparing thiocarbanilides, either fail to yield the anticipated product or result in the formation of other unexpected derivatives. This is due chiefly to the presence in the reaction mixture of alcohol or alcoholic potash. Therefore, in endeavoring to find a general and more satisfactory method of preparing thiocarbanilides it was deemed advisable to avoid the use of alcohol as solvent and of the inorganic bases, potassium or sodium hydroxide, as reagents for effecting the elimination of hydrogen sulfide in the typical reaction:

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

The first method herewith proposed is to eliminate the hydrogen sulfide through interaction with the organic base pyridine. (Pyridine while analogous to ammonia possesses the advantage of not lending itself to the formation of substituted amines or amides by interaction with halogen substituted derivatives.) It was assumed that pyridine would promote the above reaction by forming an unstable addition compound with hydrogen sulfide (analogous to ammonium sulfide) namely, pyridonium sulfide, which in turn would decompose yielding free hydrogen sulfide and regenerate the original pyridine according to the reversible reaction:



$$C_5H_5N + H(SH) \rightleftarrows C_5H_5N\!<\begin{matrix} H \\ SH \end{matrix}$$

In order to test the practicability of this proposed method a quantitative comparison was made with the older method as described by Gattermann,

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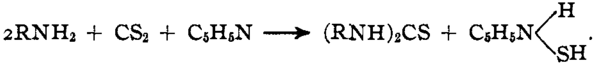
[1] *Ber.*, 16, 49 (1883).

[2] *Ibid.*, 15, 470 (1882).

"Practical Methods of Organic Chemistry," for the conversion of aniline to thiocarbanilide. Gattermann heats for three hours a mixture of aniline (40 grams), carbon bisulfide (50 cc.), and alcoholic potash (10 grams potassium hydroxide and 50 cc. alcohol). The yield is 30 to 35 grams, *i. e.*, from 61.2% to 71.3% of the theoretical amount. Recrystallization from alcohol is necessary if pure thiocarbanilide is desired.

In the proposed method the same quantities of aniline and carbon bisulfide were heated with 17 grams of pyridine for three hours in a flask provided with a reflux condenser. Hydrogen sulfide was evolved freely. The excess of carbon bisulfide and pyridine were driven off by steam distillation. The white crystallin residue was transferred to a filter, washed with dilute hydrochloric acid and then freely with water. When dry, a sample of the contents of the filter melted at 154° thus proving the product to be *pure* thiocarbanilide. The yield was 42 grams, or 85.6% of the theoretical. Thus in the conversion of aniline to thiocarbanilide the substitution of pyridine for alcoholic potash possesses the advantages of giving a purer product and a greater yield.

This method as applied to aniline was extended to the following substituted primary aromatic amines: *o*-, *m*-, and *p*-chloranilines; *o*-, *m*-, and *p*-nitranilines. In each experiment one-half mol of the amine, one-fourth mol of pyridine, and 50 cc. of carbon bisulfide were heated together for three hours in a flask equipped with a reflux condenser. The relative quantities noted, with the exception of carbon bisulfide, which was in excess, are required by the following equation:



$$2RNH_2 + CS_2 + C_5H_5N \longrightarrow (RNH)_2CS + C_5H_5N\begin{matrix}\diagup H \\ \diagdown SH\end{matrix}.$$

Briefly stated, the method of recovering the thiocarbanilide was as follows: first, steam distillation of the reaction mixture until all traces of carbon bisulfide and pyridine were driven off; then the residual unaffected amines were removed by treatment with dilute hydrochloric acid. The substances insoluble in dilute acid proved to be thiocarbanilides. They were purified by crystallization from benzene or alcohol and identified by an analysis (determination of the sulfur content) or by their melting points.

Amine.	Grams.	Thiocarbanilide.	Grams.	Per cent. of theory.	M. P. (°C).
$C_6H_5NH_2$	40.0	$(C_6H_5NH)_2CS$	42.0	85.60	154.0
o-$C_6H_4ClNH_2$	63.7	*o*-$(C_6H_4ClNH)_2CS$	2.3	3.09	130.5
m-$C_6H_4ClNH_2$	63.7	*m*-$(C_6H_4ClNH)_2CS$	22.1	29.76	121.0
p-$C_6H_4ClNH_2$	63.7	*p*-$(C_6H_4ClNH)_2CS$	23.0	30.97	168.0
o-$C_6H_4NO_2NH_2$	69.1	*o*-$C_6H_4NO_2NH)_2CS$	...	...	...
m-$C_6H_4NO_2NH_2$	69.1	*m*-$(C_6H_4NO_2NH)_2CS$	trace	...	160.0
p-$C_6H_4NO_2NH_2$	69.1	*p*-$(C_6H_4NO_2NH)_2CS$	...	...	...

The preceding table indicates the actual quantities of the amines employed in the several experiments, the quantities of the thiocarbanilides recovered, the percentages of the theoretical yields, and the melting points of the thiocarbanilides.

An inspection of the yields in the preceding table shows that aniline is most readily converted to a thiocarbanilide by the method under consideration. *o*-, *m*-, and *p*-nitranilines are practically unaffected. It should be mentioned that di-*o*- and di-*p*-nitrothiocarbanilides have never been prepared. A few observations on the melting point of di-orthochlorothiocarbanilide are noteworthy. Several anomalous statements regarding the preparation of this compound and its melting point are to be found in the literature. P. Meyer[1] states that by treatment of *o*-chloroaniline with carbon bisulfide a thiocarbanilide melting at 145°–146° is obtained. This statement is contradicted by E. Grosch[2] in these words: "When *o*-chloroaniline reacts with carbon bisulfide, with or without the addition of alcoholic potash, the expected formation of di-*o*-chlorothiocarbanilide does not take place. There is obtained an oil which, on treatment with hydrochloric acid, yields the *o*-chloroaniline salt of phenylthiocarbamic acid of the formula $C_6H_4Cl.NH.CS.SH.(NH_2C_6H_4Cl)$. The thiocarbanilide, however, can be prepared by treating ortho-chloraniline with thiophosgene, and melts at 141°, and not at 145° as recorded by P. Meyer." The compound which I obtained melted neither at 145° nor at 141°, but after repeated recrystallizations from various solvents melted at 130.5°. In order to establish positively its identity as di-*o*-chlorothiocarbanilide a sulfur determination was made with the following results:

Weight of substance.	$BaSO_4$.	Found S.	Theory S.
0.3241 g.	0.2550 g.	10.81%	10.79%

The low yield of di-*o*-chlorothiocarbanilide and the absence of reaction in the case of *o*-nitraniline is in accord with the commonly occurring inactivity of the *o*-substituted derivatives of benzene. The comparatively small yields of di-*m*- and di-*p*-thiocarbanilides may be attributed to the limiting of the time of the reaction to three hours, for when these reactions were discontinued the evolution of hydrogen sulfide was still very pronounced. More satisfactory yields were obtained by employing another method, now to be considered.

This other method, which also proposes to effect the elimination of hydrogen sulfide in the typical reaction (I):

$$\text{I. } 2RNH_2 + CS_2 \longrightarrow (RNH)_2CS + H_2S,$$

involves the addition of a calculated quantity of iodine dissolved in carbon bisulfide to a solution of the amine in carbon bisulfide and pyridine. The use of iodine to eliminate hydrogen sulfide, according to equation (II)

$$\text{II. } H_2S + I_2 \longrightarrow 2HI + S,$$

is not new, but the simultaneous use of pyridine to combine immediately

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[1] *Ber.*, **13**, 14 (1880).

[2] *Ibid.*, **32**, 1088 (1899).

with the liberated hydrogen iodide, forming pyridinium iodide according to equation

$$\text{III. } C_5H_5N + HI \longrightarrow C_5H_5N.HI,$$

constitutes an entirely new method for the completion of equation (I). The withdrawal of hydrogen iodide prevents the reversal of reaction (II), and the insolubility of the pyridinium iodide in carbon bisulfide prevents the occurrence of any reduction, which the presence of free hydrogen iodide might occasion. All of the above reactions may be embraced in one equation (A):

$$\text{A. } 2RNH_2 + CS_2 + I_2 + 2C_5H_5N \longrightarrow (RNH)_2CS + 2C_5H_5N.HI + S.$$

It should be noted that in this proposed reaction two molecular weights of the amine require one molecular weight of iodine and yield two of pyridinium iodide. It is equally probable that iodine, in greater quantity, might lead to the formation of a mustard oil according to the following equation (B):

$$\text{B. } RNH_2 + CS_2 + I_2 + 2C_5H_5N \longrightarrow RNCS + 2C_5H_5N.HI + S.$$

Here the ratio is $RNH_2:I_2:2C_5H_5N.HI$.

Quantitative determinations of the amount of iodine absorbed and the amount of pyridinium iodide precipitated would serve as a test of the value of the proposed reactions for effecting the elimination of hydrogen sulfide and as methods for the preparation of either thiocarbanilides or mustard oils. Aniline was selected for the following quantitative experiments:

5.091 grams of aniline and 13 grams of pyridine (an excess) were dissolved in 100 cc. of carbon bisulfide contained in a 250 cc. glass stoppered titration bottle, to which was added from a buret (about 5 cc. at a time) a standard solution of iodine in carbon bisulfide (1 cc. = 0.2 gram I_2). After each successive addition, the contents of the titration bottle were vigorously shaken, the iodine color vanished almost immediately, and a white, finely granular precipitate of pyridinium iodide was formed. After 69 cc. of the iodine solution had been added, the iodine color was permanent, thus denoting the end point of the reaction. The pyridinium iodide was filtered off, washed with carbon bisulfide, dried, and weighed 21.53 grams.

The theoretical quantities of iodine and pyridinium iodide corresponding to 5.091 grams of aniline in each of the above equations (A and B) and the quantities actually found are tabulated as follows:

	$C_6H_5NH_2$. Gram.	I_2. Gram.	$C_5H_5N.HI$. Gram.
Theory for equation (A)	5.091	6.94	11.32
Theory for equation (B)	5.091	13.89	22.64
Found	5.091	13.80	21.53

Thus it is evident that upon the addition of a sufficient quantity of iodine to aniline in the presence of carbon bisulfide and pyridine, a reaction represented by equation (B) takes place with the complete elimination of hydrogen sulfide and the consequent conversion of aniline to phenyl mustard oil.[1]

The possibility of obtaining thiocarbanilide by limiting the addition of iodine to the ratio $2RNH_2 : I_2$ of equation (A) now remains to be considered.

One-tenth mol aniline (9.30 grams) and $^1/_5$ mol pyridine (15.81 grams) were dissolved in 200 cc. of carbon bisulfide. To this solution was added $^1/_{20}$ mol iodine (12.7 grams) dissolved in 100 cc. of carbon bisulfide. As the iodine color vanished, pyridinium iodide was precipitated. The reaction-mixture was steam distilled until all traces of carbon bisulfide and pyridine had been driven over. The contents of the distilling flask consisted of thiocarbanilide, free sulfur, and pyridinium iodide. The latter being soluble in water is readily separated from the thiocarbanilide and sulfur by filtration. Treatment of the filter with dilute hydrochloric acid renders soluble any unaffected amine. The thiocarbanilide may be separated from the free sulfur by fractional crystallization from alcohol or benzene. The yield of thiocarbanilide was 9.15 grams or 81.7% of the theory. Thus it is possible to convert an amine to thiocarbanilide by limiting the quantity of iodine employed to the ratio $2RNH_2 : I_2$ according to equation (A) noted above.

This method as applied to aniline was extended to the following substituted primary aromatic amines: *o*-, *m*,- and *p*-chloroanilines; *o*-, *m*-, and *p*-nitranilines; *o*-, *m*-, and *p*-aminobenzoic acids.[2] The following table presents the quantities of the amines employed and of the thiocarbanilides obtained; the yields (per cent. of theory) and the melting points of the thiocarbanilides, and the approximate time required for the completion of the reaction in each experiment.

Amine.	Grams.	Thiocarbanilide.	Grams.	Per cent. of theory.	M. p.	Time.
$C_6H_5NH_2$	9.30	$(C_6H_5NH)_2CS$	9.15	81.70	154°	10 min.
o-$C_6H_4ClNH_2$	12.75	*o*-$(C_6H_4ClNH)_2CS$	11.40	76.67	130.5°	2 hrs.
m-$C_6H_4ClNH_2$	12.75	*m*-$(C_6H_4ClNH)_2CS$	13.40	90.23	121°	10 min.
p-$C_6H_4ClNH_2$	12.75	*p*-$(C_6H_4ClNH)_2CS$	14.70	98.99	168°	10 min.
o-$C_6H_4NO_2NH_2$	13.80	*o*-$(C_6H_4NO_2NH)_2CS$	...	...	....	....
m-$C_6H_4NO_2NH_2$	13.80	*m*-$(C_6H_4NO_2NH)_2CS$	14.10	88.40	160°	3 hrs.
p-$C_6H_4NO_2NH_2$	13.80	*p*-$(C_6H_4NO_2NH)_2CS$	...	...	....	....
o-$C_6H_4CO_2HNH_2$	13.70	*o*-$(C_6H_4CO_2HNH)_2CS$	...	...	....	....
m-$C_6H_4CO_2HNH_2$	13.70	*m*-$(C_6H_4CO_2HNH)_2CS$	13.40	84.78	300°+	5 min.
p-$C_6H_4CO_2HNH_2$	13.70	*p*-$(C_6H_4CO_2HNH)_2CS$	14.60	92.38	none	10 min.

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[1] This reaction may be used as a quantitative method for the determination of aniline by titration with a standard solution of iodine, the ratio for calculation being $RNH_2 : I_2$.

[2] In the experiments with the aminobenzoic acids the quantities of pyridine employed were increased from $^1/_5$ mol to $^3/_5$ mol in order to completely dissolve the difficultly soluble aminobenzoic acids.

In addition to the melting points, further proof of the identity of some of the thiocarbanilides was afforded by determining the percentage content of sulfur. This, of course, was necessary in the following cases: di-*o*-chlorothiocarbanilide, for which various melting points were recorded in the literature; di-*m*-carboxylthiocarbanilide, the melting point of which was too high for accurate determination with the facilities at hand; and the new compound, di-*p*-carboxylthiocarbanilide. The data are given in the following table:

Substance.	Gram.	$BaSO_4$. Gram.	Found. S. Per cent.	Theory. S. Per cent.
o-$(C_6H_4ClNH)_2CS$	0.3241	0.2550	10.81	10.79
m-$(C_6H_4ClNH)_2CS$	0.3945	0.3270	10.93	10.79
m-$(C_5H_4CO_2HNH)_2CS$	0.4398	0.3197	10.21	10.13
p-$(C_6H_4CO_2HNH)_2CS$	0.2668	0.2668	10.37	10.13

Some properties not recorded in the literature should be noted briefly. Di-*o*-chlorothiocarbanilide is fairly soluble in the common organic solvents. Spontaneous evaporation of a carbon disulfide solution yields small colorous rhombic crystals.

Di-*m*- and di-*p*-carboxylthiocarbanilides are very difficultly soluble in the usual organic solvents, but are readily dissolved in dilute solutions of sodium or potassium hydroxide from which they are reprecipitated by dilute acids in the form of fine chalky powders. The melting point of the meta compound lies above 300°. The para compound when heated decomposes without melting, yielding volatil products and a carbonaceous residue.

Summary.

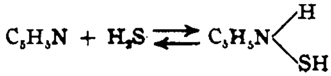
A review of the literature shows that the most commonly employed method of preparing thiocarbanilides involves a reaction represented by the equation:

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

The success of the method depends upon the means employed for effecting the elimination of hydrogen sulfide.

The presence of alcohol as solvent in the reaction-mixture, and the use of alcoholic potash or soda as reagents for eliminating hydrogen sulfide are disadvantageous since they lead to the formation of thiourethanes and thereby either prevent or limit the production of thiocarbanilides.

Two new methods of preparing thiocarbanilides, designed to obviate the above difficulties, are proposed. One method effects the elimination of hydrogen sulfide by employing pyridine, which presumably reacts according to the reversible equation:



$$C_5H_5N + H_2S \rightleftarrows C_5H_5N\begin{cases}H\\SH\end{cases}$$

The second method employs calculated quantities of iodine and pyridine in a carbon bisulfide solution of the amine. The reaction has been shown to proceed according to the equation:

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

This latter method is especially noteworthy since the yields of thiocarbanilides actually obtained run from 75 to 99% of the theoretical yields.

A quantitative method for the determination of aniline (dissolved in carbon bisulfide and pyridine) by titration with a standard solution of iodine is also described. The reaction proceeds according to the equation:

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

The failure to obtain thiocarbanilides from *o*-nitraniline, *p*-nitraniline and *o*-aminobenzoic acid, and an extension of the methods herein outlined to other amines, are subjects of investigation now in progress.

My grateful acknowledgments are due Mr. Edward M. James for the valuable assistance he has rendered in the experimental part of the present work.

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A MICRO-CHEMICAL METHOD FOR THE DETERMINATION OF α- AND β-AMINO ACIDS AND CERTAIN DERIVATIVES; IN PROTEOLYSIS, BLOOD AND URIN.

BY PHILIP ADOLPH KOBER AND KANEMATSU SUGIURA.

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TABLE OF CONTENTS.

1. Introduction.

As is well known, the copper compounds of amino acids and their derivatives, in certain cases, have been used for their isolation, but the amount of cupric hydroxide or oxide dissolved has not been used heretofore as an index to the amount of amino acid nitrogen in solution.

E. Fischer[1] and G. Zemplén, in 1909, suggested such a possibility; writing on the failure of γ-, δ- or ϵ-amino acids to dissolve cupric oxide they state: "Es liegt nahe diese Beobachtung in Zukunft als diagnostische Mittel für die stellung der Amino-gruppe zu benutzen." It is also of

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[1] *Ber.*, 42, 4883 (1909).