A mixture of 0.9 g. of II, 50 ml. of acetonitrile and 40 ml. of 0.17 *M* hypochlorous acid was adjusted to pH 8 with 7 ml. of 1 *N* sodium hydroxide. At the end of an hour the mixture was acidified to pH 4.7 and extracted with ether. About 32% of starting material was recovered after evaporating off the ether layer. When a similar amount of II was kept for an hour at pH 8 in a mixture of 50 ml. of acetonitrile plus 50 ml. of water, the starting material was almost completely recovered.

Interaction of 2-Chlorobenzothiazole with Aromatic Thiocarbamides. I. Formation of Guanylthiocarbamides and Sulfides

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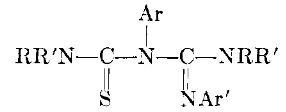
Interaction of 2-chlorobenzothiazole has been investigated with arylthiocarbamides. Hydrochlorides of the related substituted guanylthiocarbamides are obtained. 1,3-Diphenylthiocarbamide, however, gave bis(N,N'-diphenylguanyl) sulfide hydrochloride.

The interaction, mostly in alcoholic medium, of 2-chlorobenzothiazole with thiocarbamides has been investigated by Watt[1] and Scott and Watt.[2] Thiocarbamide and its monosubstituted derivatives were found to give mercaptobenzothiazole, benzothiazolyl sulfide and cyanamide corresponding to the thiocarbamide used, as the main products. Based on these facts a reaction mechanism which involved initial formation of S-2-benzothiazolylisothiouronium chloride as an intermediate stage was proposed, although this last could not be isolated in any of the cases studied. From disubstituted thiocarbamides even on prolonged action no products were obtained except in the case of N,N'-*o*-phenylenethiocarbamide (thiobenzimidazolone) where a gray solid believed to be an addition product was isolated. With trisubstituted thiocarbamides no reaction was observed.

In connection with our work[3] on 2-substituted benzothiazole derivatives the interaction of thiocarbamides and 2-chlorobenzothiazole was reinvestigated. In view of the extreme lability of the S-R link in isothiocarbamides where R was an acyl or an electronegative group in general, it was felt that the reaction conditions employed by the above workers were unconducive for the isolation of the addition or other more reactive products. In the present study, therefore, the reactions were carried out at the ordinary room temperature or at about 40–50° mostly without any solvent or with actone as solvent.

The reaction was investigated with (i) 1-phenyl-, (ii) 1-(*p*-tolyl)-, (iii) 1-(*o*-tolyl)-, (iv) 1-(2,6-dimethylphenyl)-, (v) 1-phenyl-3-methyl-, (vi) 1-phenyl-3-ethyl-, (vii) 1-(*p*-tolyl)-3-methyl-, (viii) 1-phenyl-3,3-dimethyl-, and (ix) 1,3-diphenylthiocarbamides.

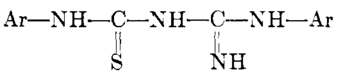
The products were colorless in all cases except the last one, *viz.*, (ix) where it had a lemon-yellow color. All were hydrochlorides, of unstable bases which could not be isolated in pure condition, except in the case of (v), (vi), (vii), and (viii) where they were found to be identical with the products obtained by the oxidation of the related thiocarbamides[4] with bromine in alcoholic medium and have been assigned structure Ia through Id, respectively.



$$\begin{matrix} & & \text{Ar} & & \\ & & | & & \\ \text{RR'N}- & \text{C}- & \text{N}- & \text{C}- & \text{NRR'} \\ & \| & & \| & \\ & \text{S} & & \text{NAr'} & \end{matrix}$$

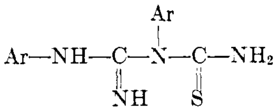
Ia from v, where R = H, R' = CH_3, Ar = Ar' = C_6H_5
Ib from vi, where R = H, R' = C_2H_5, Ar = Ar' = C_6H_5
Ic from vii, where R = H, R' = CH_3, Ar = Ar' = $CH_3C_6H_4$
Id from viii, where R = R' = CH_3, Ar = Ar' = C_6H_5

As judged from their decomposition products and other behavior there does not appear any doubt that the colorless products from other thiocarbamides also possessed similar structures. In the case of 1-phenyl- and 1-(*p*-tolyl)thiocarbamides, the products were found different from II, the 1-arylguanyl-3-arylthiocarbamides[5,6]



$$\begin{matrix} \text{Ar}-\text{NH}- & \text{C}- & \text{NH}- & \text{C}- & \text{NH}-\text{Ar} \\ & \| & & \| & \\ & \text{S} & & \text{NH} & \end{matrix}$$

II

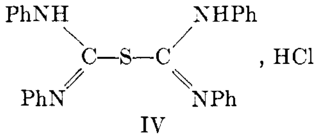


$$\begin{matrix} & & \text{Ar} & & \\ & & | & & \\ \text{Ar}-\text{NH}- & \text{C}- & \text{N}- & \text{C}- & \text{NH}_2 \\ & \| & & \| & \\ & \text{NH} & & \text{S} & \end{matrix}$$

III

where Ar = phenyl or *p*-(tolyl) group. That they were identical with III was confirmed by their almost quantitative and easy decomposition to diarylguanidine and thiocyanic acid, respectively.

The yellow product obtained from 1,3-diphenylthiocarbamide was proved by its identical behavior to be the hydrochloride (IV) corresponding to the hydrobromide of bis(N,N'-diphenylguanyl) sulfide described by Suresh.[7] The infrared absorption spectra of IV



IV

and of bis(N,N'-diphenylguanyl) sulfide hydrobromide prove unequivocally their identical sulfide structures.

There is evidence suggesting that in the case of the above reactions the initial product is an S-(2-benzothiazolyl)isothiouronium chloride[8] as envisaged by Watt[1] and as shown by Suresh and D'Souza[9] in the case of reaction with *p*-toluenesulfonyl chloride and by

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[1] G. Watt, *J. Org. Chem.*, **4**, 436 (1939).

[2] W. Scott and G. Watt, *ibid.*, **2**, 148 (1937).

[3] C. P. Joshua, *J. Indian Chem. Soc.*, **37**, 621 (1960); **38**, 155, 979 (1961).

[4] P. K. Srivastava, unpublished work.

[5] S. N. Dixit, *J. Indian Chem. Soc.*, **37**, 153 (1960).

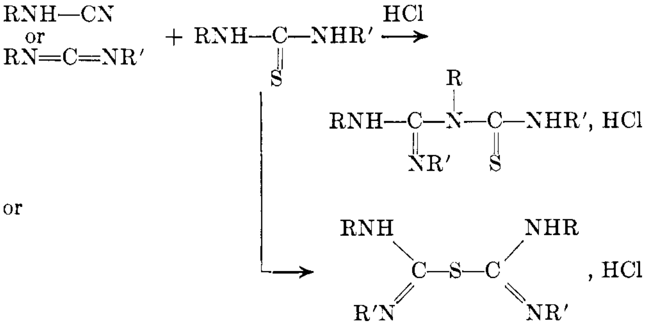
[6] K. S. Suresh, *J. Sci. Res. Banaras Hindu Univ.*, IX (**2**), 92 (1958–1959).

[7] K. S. Suresh, *J. Indian Chem. Soc.*, **37**, 483 (1960).

[8] R. H. Sahasrabudhey, C. P. Joshua, and S. N. Pandey, *Proc. Indian Sci. Congr.*, Part III, Abstracts, 102 (1961).

[9] K. S. Suresh and M. S. A. D'Souza, *J. Vikram Univ.*, 3 (**3**), 10 (1959).

Pandeya and Joshua[10] in the reaction of N-alkylthiocarbamides with 2-chlorobenzothiazole. This, being unstable, decomposes into mercaptobenzothiazole, hydrochloric acid and the related cyanamide. It is likely that one of the following reactions then takes place.



where R is an aryl group and R′ an alkyl or hydrogen.

The reaction affords a method for the preparation of guanylthiocarbamides carrying more than one substituent in the formamidino grouping and also with a substituent on the nitrogen to which the formamidino group was attached.

Experimental

The required aromatic thiocarbamides were obtained by the usual methods; *viz.*, (1) isomerization of the related amine thiocyanates obtained in solution by mixing aqueous solutions of amine hydrochloride and ammonium thiocyanate and (2) by the reaction of an aryl or alkyl isothiocyanate with an appropriate amine.

2-Chlorobenzothiazole was prepared by the reaction of 2-mercaptobenzothiazole with thionyl chloride.

Interaction of 2-Chlorobenzothiazole with 1-Arylthiocarbamides. Formation of 1-(Arylguanyl)-1-arylthiocarbamide Hydrochlorides.—The interaction of 2-chlorobenzothiazole with 1-arylthiocarbamides was carried out in acetone. A typical set of details pertaining to the reaction of 1-phenylthiocarbamide is as follows.

A clear solution of doubly crystallized 1-phenylthiocarbamide (10 g.) in acetone (50 ml.) was mixed with 2-chlorobenzothiazole (4.5 ml.) and kept aside for some time. Within 10 min. the reaction mixture warmed up and a clot-like precipitate was formed which on standing for some time granulated as a white microcrystalline powder. The solid was filtered, washed with warm acetone and then finally with ether (yield 9.5 g., m.p. 158°). The product was extremely soluble in water and ethanol and could not be crystallized from these solvents. From aqueous solution (which was acidic) a picrate (m.p. 142°) was obtained on addition of picric acid.

The 1-(*p*-tolyl)-, 1-(*o*-tolyl)-, and 1-(2,6-dimethylphenyl)thiocarbamides also reacted in a similar manner. The reaction can be facilitated by warming the mixture on a water bath at about 40–50° and by adding a drop of concentrated hydrochloric acid. The products obtained were slightly hygroscopic and decomposed gradually on keeping if moisture was not excluded.

Evaporation of the acetone mother liquors and washings left a sticky mass which, when treated with alkali, largely dissolved and was reprecipitated when acidified. On crystallization from ethanol, needle shaped crystals, m.p. 178°, identified as 2-mercaptobenzothiazole by undepressed mixture melting point with an authentic sample, were obtained.

(i) 1-(Phenylguanyl)-1-phenylthiocarbamide hydrochloride (product from 1-phenylthiocarbamide), m.p. 158°. Picrate m.p. 142°.

Anal. Calcd. for $C_{14}H_{14}N_4S \cdot HCl$: equiv. wt., 306.5; C, 54.81; H, 4.89; N, 18.27; S, 10.44; Cl, 11.58. Found: equiv. wt., 311.5; C, 54.98; H, 4.89; N, 18.83; S, 10.82; Cl, 11.82.

(ii) 1-(*p*-Tolylguanyl)-1-*p*-tolylthiocarbamide hydrochloride (product from 1-(*p*-tolyl)thiocarbamide), m.p. 146°. Picrate, m.p. 145°.

Anal. Calcd. for $C_{16}H_{18}N_4S \cdot HCl$: N, 16.7. Found: N, 16.82

(iii) 1-(*o*-Tolylguanyl)-1-*o*-tolylthiacarbamide hydrochloride (product from 1-(*o*-tolyl) (thiocarbamide), m.p. 156°. Picrate m.p. 152°

Anal. Calcd. for $C_{16}H_{20}N_4SO \cdot HCl$: equiv. wt., 352.5; C, 54.56; H, 5.67; N, 15.88. Found: equiv. wt., 349.2; C, 54.90; N, 15.82.

(iv) 1-(2,6-Dimethylphenylguanyl)-1-(2,6-dimethylphenyl)-thiocarbamide hydrochloride [product from 1-(2,6-dimethylphenyl)-thiocarbamide], m.p. 157°. Picrate, m.p. 136°.

Anal. Calcd. for $C_{18}H_{22}N_4S \cdot HCl$: equiv. wt., 362.5; C, 59.58; H, 6.34; N, 15.44. Found: equiv. wt., 365.8; C, 60.81; H, 6.74; N, 15.56.

Behavior of 1-(Phenylguanyl) 1-Phenylthiocarbamide Hydrochloride with Water, Acid, and Alkali.—Aqueous solutions of 1-(phenylguanyl)-1-phenylthiocarbamide hydrochloride decomposed gradually on standing; the decomposition was rapid when heated; phenylthiocarbamide (m.p. 154°), phenylcarbamide (m.p. 147°), and hydrochloric acid were formed. When heated under reflux with concentrated hydrochloric acid and steam distilled, a few drops of an oily substance smelling of mustard oil separated. (This was identified as phenyl isothiocyanate by its reaction with aniline, when 1,3-diphenylthiocarbamide was obtained.) The warm residual solution deposited needle-shaped crystals which were identified as phenylthiocarbamide (m.p. 154°); the filtrate, on cooling and standing, deposited more crystals. They were a mixture of phenylthiocarbamide and phenylcarbamide which could be separated by fractional crystallization from water.

Addition of a very dilute solution of alkali to an aqueous solution of 1-(phenylguanyl)-1-phenylthiocarbamide hydrochloride afforded a white fluffy precipitate which could be isolated without much decomposition when the solution was still slightly acidic. This was the free base (m.p. 85°). It decomposed gradually on keeping and could not be crystallized. When warmed with a moderately strong solution of alkali, 1-(phenylguanyl)-1-phenylthiocarbamide decomposed. The solid product and the filtrate were examined. Phenylcyanamide, phenylthiocarbamide, diphenylguanidine, and thiocyanic acid were identified as follows:

When the ice-cooled alkaline filtrate was made just acidic to litmus, phenylcyanamide hydrate[11] precipitated as a white creamy mass. It was found soluble in excess of acid and gave a silver salt. When boiled with dilute hydrochloric acid it formed phenylcarbamide, m.p. 147°, identified by comparison with an authentic sample. The alkaline filtrate, on acidification and treatment with a few drops of very dilute ferric chloride solution, gave a very deep red color which could be extracted with ether indicating the presence of thiocyanic acid. Extraction of the alkali-insoluble residue with cold, dilute acid and reprecipitation with alkali yielded diphenylguanidine, m.p. 147°. It did not show any depression in melting point when mixed with an authentic sample. The residue which was insoluble in both dilute acid as well as alkali could be crystallized from hot water and was found to be phenylthiocarbamide.

Decomposition of 1-(Phenylguanyl)-1-phenylthiocarbamide Hydrochloride with Ammonium Hydrogen Sulfide.—An ethanolic solution of ammonia saturated with hydrogen sulfide was mixed with a solution of 5 g. of the hydrochloride of 1-(phenylguanyl)-1-phenylthiocarbamide, and hydrogen sulfide gas passed through the solution for about 10 min. The resulting solution, after evaporation of alcohol, was treated with strong ammonia. Shining white crystals were collected and crystallized from boiling water (yield 3 g.). They were soluble in very dilute acid and were identified as diphenylguanidine (m.p. 147°). The ammoniacal sulfide mother liquors gave a deep red color, indicating thiocyanic acid, when acidified and treated with ferric chloride.

Interaction of 2-Chlorobenzothiazole with 1-Phenyl-3-methylthiocarbamide. Formation of 1-(N-Phenyl-N′-methylguanyl)-1-phenyl-3-methylthiocarbamide Hycrochloride.—1-Phenyl-3-methylthiocarbamide (10 g.) was triturated with 2-chlorobenzothiazole (4.2 ml.) in a china dish. The reaction mixture warmed up and became a pasty, pale yellow mass. On treatment with warm, dry acetone and ether a white crystalline solid (about 9 g.) was obtained, m.p. 162°. It was acidic to litmus.

Anal. Calcd. for $C_{16}H_{18}N_4S \cdot HCl$: equiv. wt., 334.5. Found: equiv. wt., 335.5.

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(10) S. N. Pandeya and C. P. Joshua, *J. Vikram Univ.*, 1962, in press.

(11) R. Sahasrabudhey and H. Krall, *J. Indian Chem. Soc.*, **19**, 343 (1942).

It formed a picrate, m.p. 155°, and on treatment with dilute alkali gave a free base, m.p. 83°, which was found identical with the base obtained by Srivastava[4] by the bromine oxidation of 1-phenyl-3-methylthiocarbamide.

Anal. Calcd. for $C_{16}H_{18}N_4S$: C, 64.20; H, 6.30; N, 18.72. Found: C, 64.18; H, 6.15; N, 18.84.

An aqueous solution of the hydrochloride decomposed when heated under reflux for about 1 hr. On steam distillation a few drops of an oily liquid smelling of mustard oil and identified as phenyl isothiocyanate were obtained. The residual solution on cooling gave a crystalline solid from which 1-methyl-3-phenylthiocarbamide, m.p. 114°, and 1-methyl-3-phenylcarbamide, m.p. 147°, were separated by fractional crystallization from water. Methylamine was evolved when the acidic filtrate was treated with strong alkali, and some unchanged base, m.p. 83°, precipitated.

Reaction with strong hydrochloric acid also afforded the same products. When the hydrochloride of the above guanylthiocarbamide or the free base was decomposed with ammoniacal hydrogen sulfide, N,N'-diphenyl-N''-methylguanidine, m.p. 109°, was obtained. These observations are in agreement with those made earlier.[4]

Interaction of 2-Chlorobenzothiazole with 1-(*p*-Tolyl)-3-methylthiocarbamide. Formation of 1-(N-*p*-Tolyl-N'-methylguanyl)-1-*p*-tolyl-3-methylthiocarbamide Hydrochloride.—The reaction was carried out as above using the reactants in the same proportion. A white, crystalline, acidic solid, m.p. 113° was obtained. With aqueous picric acid it afforded a picrate, m.p. 140°, and on treatment with dilute alkali precipitated the free base, m.p 72°.

Anal. Calcd. for $C_{18}H_{22}N_4S$: C, 66.25; H, 6.74; N, 17.17; equiv. wt. (hydrochloride), 362.5. Found: C, 66.31; H, 6.93; N, 16.90; equiv. wt. (hydrochloride), 365.3.

Analogous to the behavior of the above compounds on reaction with hydrochloric acid, it afforded 1-(*p*-tolyl)-3-methylthiocarbamide, m.p. 126°, 1-(*p*-tolyl)-3-methylcarbamide, m.p. 178°, *p*-tolylisothiocyanate and methylamine.

Interaction of 2-Chlorobenzothiazole with 1-Phenyl-3-ethylthiocarbamide. Formation of 1-(N-Phenyl-N'-ethylguanyl)-1-phenyl-3-ethylthiocarbamide Hydrochloride.—The reaction was carried out as above using the reactants in the same proportion. A white, crystalline, acidic solid, m.p. 158° was obtained. With aqueous picric acid it afforded a picrate, m.p. 136°, and on treatment with dilute alkali precipitated the free base, m.p. 85°, which decomposed gradually on keeping.

Anal. Calcd. for $C_{18}H_{22}N_4S \cdot HCl$: equiv. wt., 362.5. Found: equiv. wt., 370.3.

Anal. Calcd. for $C_{18}H_{22}N_4S$: N, 17.17; S, 9.81. Found: N, 17.21; S, 9.92.

Interaction of 1-Phenyl-3,3-dimethylthiocarbamide and 2-Chlorobenzothiazole. Formation of 1-(N,N-Dimethyl-N'-phenylguanyl)-1-phenyl-3,3-dimethylthiocarbamide Hydrochloride.—Finely powdered 1-phenyl-3,3-dimethylthiocarbamide (10 g.) and 2-chlorobenzothiazole (4.2 ml.) were triturated in a china dish and allowed to stand after adding a droplet of concentrated hydrochloric acid. The reaction mixture warmed up within a few minutes, and a yellowish sticky mass was obtained. Washing with warm, dry acetone and ether yielded a product, m.p. 105° (about 9 g.).

Anal. Calcd. for $C_{18}H_{22}N_4S \cdot HCl$: equiv. wt., 362.5. Found: equiv. wt., 364.5.

It afforded a picrate m.p. 139°. On treatment with alkali the free base, m.p. 118°, was obtained which was found identical with the product obtained by Srivastava[4] from the bromine oxidation of 1-phenyl-3,3-dimethyl-thiocarbamide.

Anal. Calcd. for $C_{18}H_{22}N_4S$: C, 66.25; H, 6.74; N, 17.17. Found: C, 65.78; H, 6.65; N, 17.46.

On prolonged heating with strong hydrochloric acid, like other derivatives of this type (*vide supra*), it decomposed into 1-phenyl-3,3-dimethylthiocarbamide, m.p. 134°, 1-phenyl-3,3-dimethylcarbamide, m.p. 131°, phenyl isothiocyanate, and dimethylamine.

Interaction of 2-Chlorobenzothiazole with 1,3-Diphenylthiocarbamide. Formation of bis(N,N'-Diphenylguanyl)sulfide Hydrochloride.—Finely powdered, doubly crystallized 1,3-diphenylthiocarbamide (10 g.) and 2-chlorobenzothiazole (4 ml.) were thoroughly mixed in a china dish, and a drop of concentrated hydrochloric acid was added to facilitate the reaction. Within a few minutes the reaction mixture warmed up, and a yellow sticky product was obtained. On washing with dry, warm, acetone a pale yellow microcrystalline powder (about 9 g.) separated, m.p. 155° (dec.). It was found to be acidic to litmus.

Anal. Calcd. for $C_{26}H_{22}N_4S \cdot HCL$: equiv. wt., 458.5; C, 68.04; H, 5.01; N, 12.21. Found: equiv. wt., 454.0; C, 68.14; H, 5.88; N, 12.27.

The product decomposed at once on contact with water giving phenyl isothiocyanate and triphenylguanidine hydrochloride, m.p. 248°, which on treatment with base gave free triphenylguanidine, m.p. 145°. Its identity with the free base of the hydrobromide formed by the oxidation of 1,3-diphenylthiocarbamide with bromine in ethanol[7] was established by a comparison of infrared spectra. The following absorption characteristics were noted.

Above derivative (hydrochloride): 3290 m, 2800 s, 2100 m, 1630 s, 1570 s, 1494 s, 1440 s, 1338 s, 1260 m, 1200 m, 1176 m, 1036 w, 1026 m, 908 s, 833 m, 745 s, 735 s, 690 s, 638 m.

Suresh's[7] compound (hydrobromide): 3320 m, 2800 s, 2090 m, 1630 s, 1570 s, 1494 s, 1440 s, 1336 s, 1260 m, 1200 m, 1176 m, 1036 w, 1025 m, 908 s, 835 m, 745 s, 735 s, 690 s, 638 m.

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