[Contribution from the W. A. Noyes Laboratory of Chemistry,
University of Illinois]

HYDRAZINE DERIVATIVES OF THE CARBONIC AND THIOCARBONIC ACIDS. II. DERIVATIVES OF THIOCARBOHYDRAZIDE

EARLE S. SCOTT[1,2] and L. F. AUDRIETH

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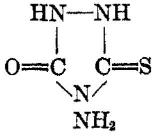
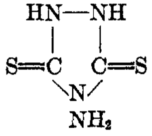
The study of the hydrazine derivatives of the carbonic and thiocarbonic acids was undertaken not only to elucidate the chemistry of this group of compounds but also to synthesize and furnish materials for use in a biological testing program.[3] In view of the antituberculin activity of certain thiosemicarbazones, it was felt that the preparation and study of structurally related compounds such as thiocarbohydrazide and the cyanate and thiocyanate condensation products of thiocarbohydrazide would be desirable. These monosubstituted derivatives of thiocarbohydrazide contain a free hydrazide function and are capable of forming aldehyde derivatives. Moreover, desolvation of these compounds could be expected to result in the formation of a number of interesting cyclic derivatives.

The preparation of the cyanate and thiocyanate addition products of thiocarbohydrazide, 1-carbamyl- and 1-thiocarbamyl-thiocarbohydrazide, respectively, had been reported by Guha in 1924 (1). The compound described as 1-carbamylthiocarbohydrazide (m.p. 230°) was prepared by adding potassium cyanate to an acidic solution of thiocarbohydrazide. It was said to cyclize to give monothiourazine (A) on treatment with hot, concentrated hydrochloric acid. The compound reported to be 1-thiocarbamylthiocarbohydrazide (m.p. 215°) was prepared by refluxing a solution containing thiocarbohydrazide, potassium thiocyanate, and hydrochloric acid, and was reported to give dithiourazine (B) on treatment with hot concentrated hydrochloric acid. Attempts to repeat the preparation of these compounds gave products whose melting points did not agree with those reported by Guha. The desired 1-carbamyl- and 1-thiocarbamyl-thiocarbohydrazides have now been synthesized, and their composition has been verified by elemental analysis and by the formation of a number of



(A) Monothiourazine



(B) Dithiourazine

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[1] Abstracted from the doctoral dissertation submitted to the Graduate College of the University of Illinois (1952). Present address: University of California, Berkeley 4, California.

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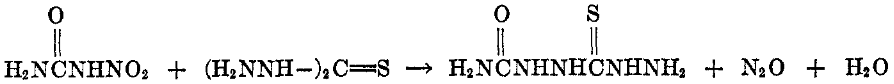
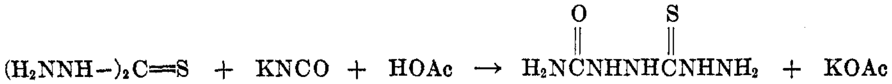
[3] Results are not given in this paper.

derivatives. In addition, each substance has been obtained by a completely different method of synthesis.

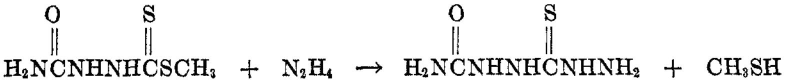
1-Carbamylthiocarbohydrazide was prepared by the reaction of thiocarbohydrazide with cyanic acid using both nitrourea (Equation 1) and a potassium cyanate-acetic acid solution (Equation 2) as sources of cyanic acid. It was also prepared by the hydrazinolysis of methyl semicarbazidodithiocarbonate (Equation 3) in alcohol in order to establish its structure.

1.


$$H_2N\overset{O}{\overset{\|}{C}}NHNO_2 + (H_2NNH-)_2C{=}S \rightarrow H_2N\overset{O}{\overset{\|}{C}}NHNH\overset{S}{\overset{\|}{C}}NHNH_2 + N_2O + H_2O$$

2.


$$(H_2NNH-)_2C{=}S + KNCO + HOAc \rightarrow H_2N\overset{O}{\overset{\|}{C}}NHNH\overset{S}{\overset{\|}{C}}NHNH_2 + KOAc$$

3.


$$H_2N\overset{O}{\overset{\|}{C}}NHNH\overset{S}{\overset{\|}{C}}SCH_3 + N_2H_4 \rightarrow H_2N\overset{O}{\overset{\|}{C}}NHNH\overset{S}{\overset{\|}{C}}NHNH_2 + CH_3SH$$

The products obtained from each of the three reactions were shown to be identical by mixture melting point determinations and by the preparation of the same benzaldehyde derivative.

1-Carbamylthiocarbohydrazide is a white powdery solid which melts with decomposition at 193–194°. It is very soluble in hot water and fairly soluble in cold water; it can be recrystallized from water although the recovery is frequently poor. It is insoluble in such organic solvents as alcohol, ether, and benzene. 1-Carbamylthiocarbohydrazide is stable toward air oxidation in the solid state and in acid solution; basic, aqueous solutions, however, turn red on exposure to air. That the desired compound contains both the hydrazide and the thio groups has been verified (a) by formation of 1-carbamylthiocarbohydrazones by reaction with aldehydes and (b) by methylation with methyl iodide, respectively. The methylated compound undergoes reaction with hydrazine to liberate methyl mercaptan and to form 1,2-diamino-3-ureido (2) showing clearly that the methyl group resides on the sulfur atom and further confirming the structure of 1-carbamylthiocarbohydrazide.

The preparation of 1-carbamylthiocarbohydrazide by the addition of cyanic acid to thiocarbohydrazide is the more attractive of the two available methods of synthesis, since thiocarbohydrazide is obtained easily from hydrazine and carbon disulfide, whereas methyl semicarbazidodithiocarbonate can be prepared only by a more involved procedure. Of the two methods of carrying out the cyanate addition reaction with thiocarbohydrazide, that in which nitrourea was used as the source of cyanic acid was the more successful. It has the advantage that the reaction is carried out in a hot solution, hence the amount of solvent may be limited. Moreover, no contaminating ions are left in the reaction mixture to complicate the isolation of the rather soluble product.

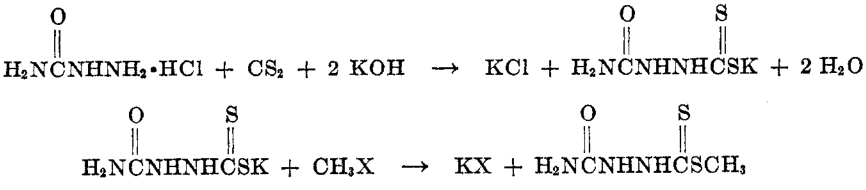
Moderately successful results were obtained using potassium cyanate as a source of cyanic acid when a slurry of thiocarbohydrazide was employed. As the cyanate addition reaction takes place, the solid thiocarbohydrazide dissolves. In all such cases, however, purification of the product was difficult.

Thiocarbohydrazide can react with two molecules of cyanic acid to produce 1,5-biscarbamylthiocarbohydrazide. The solid isolated from the reaction in which more than two moles of cyanic acid were added to thiocarbohydrazide was less soluble than 1-carbamylthiocarbohydrazide, melted at 215° as isolated from the reaction mixture, and did not react with benzaldehyde. When this material was recrystallized from water containing a small amount of hydrochloric acid, its melting point dropped with each recrystallization until it attained a value of 193–194° where it remained constant. The final product obtained was shown to be 1-carbamylthiocarbohydrazide. The melting point of the freshly prepared material agrees with that reported by Beckett and Dyson (3) for the product obtained from the reaction between thiophosgene and semicarbazide (m.p. 215°) to which they assigned the structure of 1,5-biscarbamylthiocarbohydrazide. This fact, coupled with the failure of the product obtained to react with benzaldehyde, supports the contention that both the hydrazide functions of thiocarbohydrazide reacted with cyanic acid to give 1,5-biscarbamylthiocarbohydrazide. The shifting melting point may be explained by the slow hydrolysis of this product during the recrystallization procedure.

At present, the hydrazinolysis of methyl semicarbazidodithiocarbonate is the best method of preparing appreciable quantities of pure 1-carbamylthiocarbohydrazide. In the presence of excess of hydrazine the solvolysis of the dithioester is fairly rapid. Preliminary experiments in which water was used as a solvent gave mixtures of solid products which could not be separted satisfactorily. In retrospect, this may be explained by assuming that at the temperature of the refluxing aqueous solution, both the methyl semicarbazidodithiocarbonate and the carbamylthiocarbohydrazide are subject to the base induced cyclization reactions characteristic of this group of compounds. It has been found (a) that absolute ethanol is a more satisfactory medium in which to carry out the hydrazinolysis reaction without incurring excessive side reactions and (b) that the use of anhydrous hydrazine rather than hydrazine hydrate speeds up the reaction and improves the yield.

The preparation of methyl semicarbazidodithiocarbonate may be accomplished using either semicarbazide hydrochloride or hydrazine as a starting material and using the reactions outlined in Equations 4 and 5, respectively.

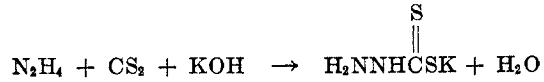
4.



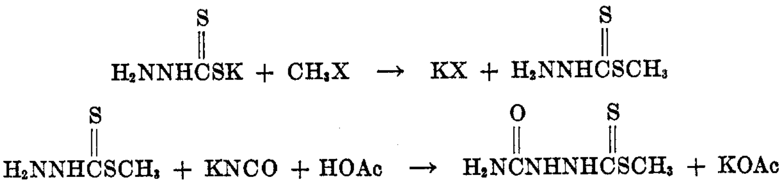
$$\mathrm{H_2N\overset{\overset{O}{\|}}{C}NHNH_2\cdot HCl + CS_2 + 2\,KOH \rightarrow KCl + H_2N\overset{\overset{O}{\|}}{C}NHNH\overset{\overset{S}{\|}}{C}SK + 2\,H_2O}$$

$$\mathrm{H_2N\overset{\overset{O}{\|}}{C}NHNH\overset{\overset{S}{\|}}{C}SK + CH_3X \rightarrow KX + H_2N\overset{\overset{O}{\|}}{C}NHNH\overset{\overset{S}{\|}}{C}SCH_3}$$

5.



$$\mathrm{N_2H_4 + CS_2 + KOH \rightarrow H_2NNH\overset{\overset{S}{\|}}{C}SK + H_2O}$$

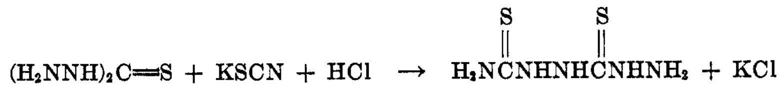


$$\mathrm{H_2NNH\overset{S}{\overset{\|}{C}}SK + CH_3X \rightarrow KX + H_2NNH\overset{S}{\overset{\|}{C}}SCH_3}$$

$$\mathrm{H_2NNH\overset{S}{\overset{\|}{C}}SCH_3 + KNCO + HOAc \rightarrow H_2N\overset{O}{\overset{\|}{C}}NHNH\overset{S}{\overset{\|}{C}}SCH_3 + KOAc}$$

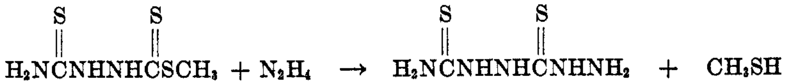
1-Thiocarbamylthiocarbohydrazide was prepared by the direct addition of thiocyanic acid to thiocarbohydrazide (Equation 6) and by the hydrazinolysis of methyl thiosemicarbazidodithiocarbonate (Equation 7).

6.



$$\mathrm{(H_2NNH)_2C{=}S + KSCN + HCl \rightarrow H_2N\overset{S}{\overset{\|}{C}}NHNH\overset{S}{\overset{\|}{C}}NHNH_2 + KCl}$$

7.



$$\mathrm{H_2N\overset{S}{\overset{\|}{C}}NHNH\overset{S}{\overset{\|}{C}}SCH_3 + N_2H_4 \rightarrow H_2N\overset{S}{\overset{\|}{C}}NHNH\overset{S}{\overset{\|}{C}}NHNH_2 + CH_3SH}$$

The identity of the products obtained by each procedure was established by a mixture melting point determination, by preparation of the benzaldehyde derivative, and by a comparison of the x-ray patterns of both the parent compounds and their benzaldehyde derivatives.

1-Thiocarbamylthiocarbohydrazide is a white solid melting with decomposition at 204–205°; it crystallizes from water in the form of fine needles. It is relatively insoluble in cold, moderately soluble in hot water, and insoluble in most organic solvents. The dry solid is relatively stable toward air oxidation, particularly if it has been recrystallized from a weakly acid solution. Some samples of this compound turned pink on long standing in a stoppered bottle and gave off hydrogen sulfide as a decomposition product. Basic, aqueous solutions of 1-thiocarbamylthiocarbohydrazide turn deep red on exposure to air, but acidic solutions apparently are stable. 1-Thiocarbamylthiocarbohydrazide reacts readily with carbonyl compounds in equal mole ratios demonstrating the presence of one free hydrazide function. The benzaldehyde and anisaldehyde derivatives were found to be insoluble in water and a variety of organic solvents, hence could not be purified for analysis or biological testing.

The addition of thiocyanic acid to thiocarbohydrazide requires more vigorous conditions than does the addition of cyanic acid. It might therefore be anticipated that a second thiocyanate addition would not complicate the synthesis of 1-thiocarbamylthiocarbohydrazide, and in fact, no evidence was obtained to indicate that such a reaction occurs. However, this direct synthesis is complicated by the tendency of both the starting material and the product to undergo desolvation cyclization under the experimental conditions required to effect their condensation. Two cyclic products have been isolated from such preparations, one of which (m.p. 240°) has been identified as 3-hydrazino-5-mercapto-1,2,4-triazole (C) (5), (a) by preparation of the benzaldehyde derivative and (b) by elemental analysis.

Anal. Calc'd for $C_2H_5N_5S$: C, 18.32; H, 3.84; N, 53.38.

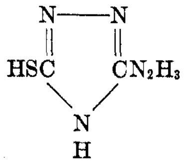
Found: C, 18.57; H, 3.75; N, 53.26.

The other product (m.p. 210–212°, when heated rapidly) may be 3,4-diamino-5-mercapto-1,2,4-triazole (D) (5), since it has the proper solubility characteristics and empirical composition.

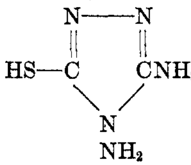
Anal. Calc'd for $C_2H_5N_5S$: C, 18.32; H, 3.93; N, 53.26.

Found: C, 18.71; H, 3.74; N, 53.02.

Both of these compounds could be expected to form from 1-thiocarbamylthiocarbohydrazide by a cyclization desolvation reaction involving the elimination of hydrogen sulfide. The presence of such cyclic derivatives may account for difficulties encountered in purifying the product by recrystallization and also for the low yield obtained using this synthesis.



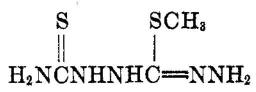
(C) 3-Hydrazino-5-mercapto-1,2,4-triazole



(D) 3,4-Diamino-5-mercapto-1,2,4-triazole

The hydrazinolysis of methyl thiosemicarbazidodithiocarbonate represents a more satisfactory method of preparing 1-thiocarbamylthiocarbohydrazide, if carried out in absolute ethanol using anhydrous hydrazine. If the hydrazinolysis is carried out in aqueous solutions, only cyclic products are obtained.

1-Thiocarbamylthiocarbohydrazide reacts with benzaldehyde to give a product which melts at 250°, but which cannot be recrystallized from the common organic solvents. It reacts with acetone to give a mono-acetone derivative having the expected composition. 1-Thiocarbamylthiocarbohydrazide reacts with the stoichiometric amount of methyl iodide in a basic solution to give an S-methyl derivative. This product reacts with carbonyl compounds indicating that the methyl group does not reside on one of the hydrazine nitrogen atoms. When a solution of the monomethyl derivative in 2 *N* sodium hydroxide is refluxed, methyl mercaptan is evolved and 3-hydrazino-5-mercapto-4,1,2-triazole (C) is obtained, indicating that the methyl group is on the sulfur atom adjacent to the free hydrazide group (E).



$$H_2N\overset{\overset{S}{\|}}{C}NHNH\overset{\overset{SCH_3}{|}}{C}{=}NNH_2$$

(E)

EXPERIMENTAL[4]

1-Carbamylthiocarbohydrazide. (a). From thiocarbohydrazide and nitrourea. Thiocarbohydrazide (21.2 g., 0.2 mole) suspended in 100 ml. of boiling water was treated with a total of 23 g. (0.2 mole) of nitrourea in small batches as fast as gas evolution would permit. The resulting solution was heated for about 3 minutes, filtered hot, and allowed to cool slowly. The product which precipitated was filtered off and the filtrate was evaporated to 25 ml.,

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[4] See Table I for a summary of the analytical data.

cooled in an ice-bath, and stirred vigorously to recover more of the product. The entire yield was recrystallized from the minimum amount of water to give 17.8 g. of 1-carbamylthiocarbohydrazide (60%) melting at 192–193°.

(*b*). *From thiocarbohydrazide and potassium cyanate.* Thiocarbohydrazide (21.2 g., 0.2 mole) was suspended in 150 ml. of water containing 26 ml. of glacial acetic acid. A solution of 18 g. of potassium cyanate in 50 ml. of water was added to this suspension at room temperature over a period of 75 minutes. The reaction mixture was stirred vigorously throughout the addition of potassium cyanate and for an additional 45 minutes. The resulting solution was boiled for 30 minutes to reduce the volume of water, then cooled to precipitate the product. The crude product so obtained weighed 18.0 g. (60%) but was impure, (m.p. 185–186°). After two recrystallizations from the minimum amount of water, the product weighed 14.3 g. (48.7%) and melted at 191–192°. The main contaminant in this product was shown to be thiocarbohydrazide which is difficult to remove by recrystallization.

(*c*). *By hydrazinolysis of methyl semicarbazidodithiocarbonate.* 1. Methyl semicarbazidodithiocarbonate was prepared according to the method of Arndt and Bielich (4). Potassium semicarbazidodithiocarbonate was not isolated in the pure state but was used directly in the preparation of the methyl ester. The over-all yield of crude methyl semicarbazidodithiocarbonate amounted to 80% based upon the quantity of semicarbazide hydrochloride employed. This product was used directly in the preparation of 1-carbamylthiocarbohydrazide.

2. Methyl semicarbazidodithiocarbonate was also prepared by a new method involving the reaction of methyl dithiocarbazinate with cyanic acid. Methyl dithiocarbazinate (12.2 g., 0.1 mole) was dissolved in 150 ml. of water containing 15 ml. of glacial acetic acid and sufficient alcohol to produce a clear solution at room temperature. Potassium cyanate (10 g., 0.12 mole) was dissolved in the minimum amount of water and was added dropwise over a period of one hour to the stirred solution. Stirring was continued for one hour after the addition of potassium cyanate was complete. Methyl semicarbazidodithiocarbonate precipitated during the course of the reaction and was collected and recrystallized from ethanol. A yield of 14 g. (89%) melting at 194° (lit. 193–194°) was obtained.

3. A solution of 12.8 g. (0.078 mole) of methyl semicarbazidodithiocarbonate and 4.0 ml. (0.12 mole) of 95% hydrazine in 200 ml. of absolute ethanol was refluxed for 90 minutes during which time methyl mercaptan was evolved and 1-carbamylthiocarbohydrazide precipitated on the walls of the reaction flask. The product was collected and recrystallized from water containing a few drops of hydrochloric acid. The product thus purified weighed 10.0 g. (86%) and melted at 191°.

1-Thiocarbamylthiocarbohydrazide. (*a*). *From thiocarbohydrazide and thiocyanic acid*

TABLE I

MELTING POINTS AND ANALYTICAL DATA

COMPOUND	M.P., °C.	ANALYTICAL DATA					
		Calc'd			Found		
		C	H	N	C	H	N
1-Carbamylthiocarbohydrazide	193–194	16.10	4.73	46.94	16.59	4.67	47.21
1-Thiocarbamylthiocarbohydrazide	204–205	14.54	4.27	42.39	14.74	4.15	42.63
Acetone thiocarbamylthiocarbohydrazone	188	29.25	5.40	34.12	29.31	5.51	34.27
1-Thiocarbamyl-S-methylisothiocarbohydrazide	149	20.10	5.06	39.07	20.29	5.07	39.09
Carbonyl derivatives of carbamylthiocarbohydrazide							
1. Benzaldehyde	213	45.55	4.68	29.51	45.66	4.90	29.35
2. Anisaldehyde	205	44.93	4.90	26.20	44.95	4.80	26.04
3. *p*-Hydroxybenzaldehyde	215	42.68	4.38	27.65	43.19	4.53	27.32

This procedure gives somewhat erratic yields, presumably because of the occurrence of side reactions. Thiocarbohydrazide (10.6 g., 0.1 mole) was dissolved in 150 ml. of water containing 10.0 g. of potassium thiocyanate and 8.4 ml. of concentrated hydrochloric acid. The solution was refluxed for two hours and then allowed to cool. The resulting product was filtered off and recrystallized from about 400 ml. of water containing a small amount of hydrochloric acid. The product so obtained was slightly impure (m.p. 203°) and weighed 5.3 g. (32%).

(*b*). *By the hydrazinolysis of methyl thiosemicarbazidodithiocarbonate.* Methyl thiosemicarbazidodithiocarbonate was prepared from potassium thiosemicarbazidodithiocarbonate following the procedure described by Arndt (4). Yields of 75–80% were obtained. A solution of 18.0 g. (0.1 mole) of methyl thiosemicarbazidodithiocarbonate and 5 ml. (0.13 mole) of 95% hydrazine in 250 ml. of absolute ethanol was stirred and refluxed for one hour. The solid which precipitated was removed by filtration and the filtrate was returned to the flask and refluxed for two more hours to give a second crop of the desired product. The entire yield was recrystallized from water after which it melted at 203–204° and weighed 9.3 g. (56%).

1-Thiocarbamyl-S-methylisothiocarbohydrazide. A solution of 2 g. of 1-thiocarbamylthiocarbohydrazide in 16 ml. of 1.0 *N* sodium hydroxide was treated with 1.8 g. of methyl iodide; the resulting mixture was cooled and shaken vigorously. The mixture assumed a deep red color as the reaction proceeded. Hydriodic acid was added to neutralize the reaction mixture which was then cooled in an ice-bath and stirred vigorously to induce crystallization. The pink solid was recrystallized from ethanol to separate it from some unreacted 1-thiocarbamylthiocarbohydrazide (0.5 g.). The recrystallized product melted at 149° and weighed 0.9 g. (55%). After two further recrystallizations, the product still melted at 149° and gave a satisfactory elemental analysis.

Carbonyl derivatives. The carbonyl derivatives were prepared by the addition of an alcoholic solution of the carbonyl compound to a slightly acidic aqueous solution of the hydrazide. Precipitation occurred rapidly in most instances. Recrystallization was effected using ethanol or water-ethanol mixtures. Melting points and analytical results for the benzaldehyde, anisaldehyde, and *p*-hydroxybenzaldehyde derivatives of 1-carbamylthiocarbohydrazide are given in Table I. The acetone derivative of 1-thiocarbamylthiocarbahydrazide was prepared by refluxing the parent compound in a 1:1 water-acetone mixture. The desired product crystallized from the solution on cooling.

SUMMARY

1-Carbamyl thiocarbohydrazide (I), $N_2H_3CSNHNHCONH_2$, has been prepared (a) by direct cyanate addition to thiocarbohydrazide and (b) by the hydrazinolysis of methyl semicarbazidodithiocarbonate. 1-Thiocarbamyl thiocarbohydrazide (II), $N_2H_3CSNHNHCSNH_2$, has in a similar fashion been obtained (a) from thiocarbohydrazide by thiocyanate addition and (b) by the hydrazinolysis of methyl thiosemicarbazidodithiocarbonate. 1-Thiocarbamyl-S-methylisothiocarbohydrazide, $H_2NNC(SCH_3)NHNHCSNH_2$, has been obtained by methylation of II in alkaline solution. Identity of products has been established by elemental analysis and by conversion of carbonyl derivatives.

URBANA, ILLINOIS

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