[CONTRIBUTION FROM THE W. A. NOYES LABORATORY OF CHEMISTRY, UNIVERSITY OF ILLINOIS]

HYDRAZINE DERIVATIVES OF THE CARBONIC AND THIOCARBONIC ACIDS. IV. PREPARATION OF SOME DI- AND TRI-AMINOGUANIDINES BY THE HYDRAZINOLYSIS OF THIOETHERS[1, 2]

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A formal relationship based upon the solvent system concept may be developed between carbonic acid and trithiocarbonic acid, the aquo and thio compounds on one hand, and guanidine (*A*) and triaminoguanidine (*D*) as the completely ammonated and completely hydrazinated analogs, respectively, on the other (1). This relationship can be extended to include mono- and di-amino-

$$\begin{bmatrix} CO(OH)_2 \\ [CS(SH)_2] \end{bmatrix} \rightarrow \begin{bmatrix} C(NH)(NH_2)_2 & (A) \\ C(NH)(NH_2)(N_2H_3) & (B) \\ C(NH)(N_2H_3)_2 & (C) \\ C(N_2H_2)(N_2H_3)_2 & (D) \end{bmatrix}$$

guanidine (*B* and *C*), both of which may be regarded as mixed ammono hydrazino derivatives of the aquo and thio acids. The preparation of the guanidines, and of the mono-, di- and tri-aminoguanidines (2) is usually accomplished by procedures which entail solvation or solvolysis involving reaction between a carbonic acid derivative and a nitrogen base.

Although solvation reactions are limited largely to the preparation of guanidines and aminoguanidines, all members of the series can be prepared by solvolytic methods. The carbonic acid derivatives available as starting materials may contain such functional groups as: $\rangle C{=}O$, $\rangle C{=}S$, $\gg C{-}OR$, $\gg C{-}SR$, $\gg C{-}NH_2$, $\rangle C{=}NH$, $\gg C{-}NHNH_2$, $\rangle C{=}NNH_2$; the choice of reagent for preparation of the guanidines or of the aminoguanidines will depend upon the relative ease with which these functional groups undergo solvolytic attack. The $\rangle C{=}O$ group is stable with respect to solvolysis in this series of compounds and may therefore be eliminated from consideration. It has been shown that both the $\gg CNH_2$ and $\rangle C{=}S$ groupings are subject to hydrazinolysis

[1] Presented at the 123rd meeting of the American Chemical Society at Los Angeles, California in March, 1953.

[2] For earlier articles in this series see Audrieth, Scott, and Kippur, *J. Org. Chem.*, **19,** 733 (1954); Scott and Audrieth, *J. Org. Chem.*, **19,** 742 (1954) and Scott, Zeller, and Audrieth, *J. Org. Chem.*, **19,** 749 (1954).

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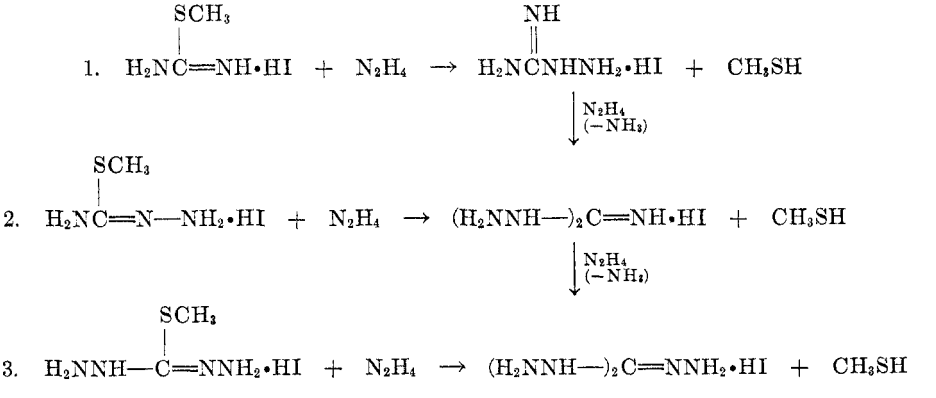
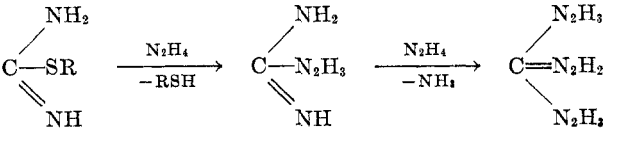
and such reactions have been used preparatively. However, the oxygen and thio-ether groups undergo such solvolytic reactions with even greater ease. These reactions occur so readily that they may be carried out without danger of solvolytic attack on other functional groups which may also be present. Since the direct alkylation of the oxygen atoms in the carbonic acid derivatives under consideration does not take place, it would appear that the method of choice for the preparation of the ammono and hydrazino carbonic acids entails the solvolysis of the appropriate thioethers.

It is evident from the number and variety of guanidine derivatives which have been prepared by aminolysis of the S-alkyl isothioureas that this procedure is rather generally applicable (3–5). It has also been shown that S-methylisothiosemicarbazides react with amines to give aminoguanidines (6). Since hydrazine is a relatively strong solvolytic agent it is not too surprising to note that both aminoguanidine (3, 4, 7) and diaminoguanidine (8) can be prepared in excellent yields by the hydrazinolysis of S-methylisothiourea (Equation 1) and of S-methylisothiosemicarbazide (Equation 2), respectively. The N-substituted derivatives of both have been synthesized using N-substituted isothioureas and isothiosemicarbazides as the starting materials (3, 4, 9). However, the preparation of triaminoguanidine[5] or of its derivatives using an S-methyl derivative of thiocarbohydrazide (an isothiocarbohydrazide) has not been reported previously.



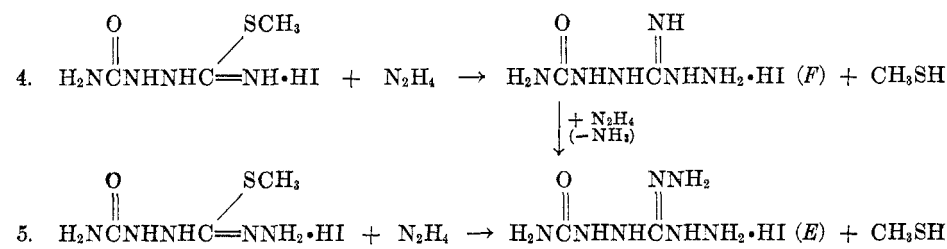
The S-methyl derivative of thiocarbohydrazide, S-methylisothiocarbohydrazide,[6] was prepared and isolated as the hydriodide by the reaction between methyl

[5] Reference is made to the Schotte (10) patent which discloses the preparation of triaminoguanidine from isothiourea ethers by treatment with an excess of hydrazine. This reaction is believed to involve initial solvolytic attack and elimination of the mercaptan to form aminoguanidine followed by further hydrazinolysis to triaminoguanidine with elimination of ammonia.



[6] Nomenclature of the compounds described in the present paper is developed along two

iodide and thiocarbohydrazide, and was characterized by elemental analysis of the hydriodide and picrate salts and by the preparation and analysis of the dibenzaldehyde derivative. Hydrazinolysis in ethanol was found to take place rapidly to give triaminoguanidine hydriodide which crystallized from the reaction mixture almost immediately (Equation 3). It has been further shown that S-methyl derivatives of N-substituted thiocarbohydrazides can also be subjected to hydrazinolysis. The cyanate condensation product of thiocarbohydrazide (11) was methylated using methyl iodide; the reaction product, 1-carbamyl-S-methylisothiocarbohydrazide hydriodide was allowed to react with hydrazine to give the triaminoguanidine derivative, 1,2-diamino-3-ureidoguanidine hydriodide (*E*) (Equation 5). This compound was also prepared by the hydrazinolysis of 1-amino-3-ureidoguanidine hydriodide (*F*) which in turn was obtained from 1-carbamyl-S-methylisothiosemicarbazide hydriodide and hydrazine (Equation 4).



It should be noted that (*E*) and (*F*) are the products to be expected from the condensation of cyanic acid with tri- and di-aminoguanidine, respectively. Earlier efforts in these laboratories to obtain these compounds by such a condensation reaction had failed to give the desired products.

It now became possible to compare the relative tendencies of the $\rangle C{=}S$ and $\rangle C{-}SCH_3$ groups to undergo solvolytic attack by studying the action of

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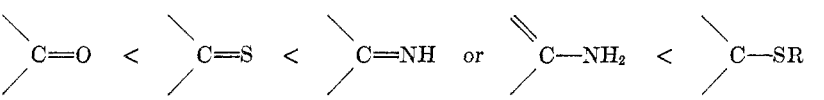
specific lines. The mixed ammono hydrazino carbonic acid derivatives, the aminoguanidines, are named as substituted guanidines, where positions are designated in accordance with the indexing system used by CHEMICAL ABSTRACTS. Thus, $NH_2{\cdot}\overset{1}{N}H\ C(:\overset{2}{N}NH_2)NHNHCONH_2$ is a triaminoguanidine derivative, 1,2-diamino-3-ureidoguanidine. Somewhat more difficult to name are the derivatives of thiocarbohydrazide, especially where alkylation on the sulfur atom has been achieved. It is obvious that thiocarbohydrazide, like thiourea and thiosemicarbazide, to both of which it is generically related, may be represented by an *iso* structure: $H_2N{\cdot}NHC(S)NHNH_2 \leftrightarrows H_2N{\cdot}NHC(SH):NNH_2$. We are therefore assigning to the S-alkyl derivatives of thiocarbohydrazide the "isothiocarbohydrazide" terminology. The compound $H_2NNHC(SCH_3):NNH_2$ is named S-methylisothiocarbohydrazide. Symmetrically substituted 1,5-aldehyde and ketone derivatives could be designated as S-methylisothiocarbohydrazones; others would be designated by position reference, as for example, $H_2\overset{5}{N}{\cdot}\overset{4}{N}H\overset{3}{C}(SCH_3):\overset{2}{N}{\cdot}\overset{1}{N}HCONH_2$, which is given the name 1-carbamyl-S-methylisothiocarbohydrazide.

hydrazine on thiocarbohydrazide, $CS(N_2H_3)_2$. The latter contains only the C=S group which is subject to hydrazinolysis. However, the simple displacement of hydrogen sulfide from thiocarbohydrazide by hydrazine cannot be evaluated in an alkaline medium for two reasons: (a) a cyclization reaction occurs which involves essentially the loss of hydrogen sulfide and hydrazine from two molecules of thiocarbohydrazide to form 3-hydrazino-4-amino-5-mercapto-1,2,4-triazole (12) and (b) triaminoguanidine is unstable in basic solution. The hydrazinolysis of thiocarbohydrazide was therefore effected using hydrazine monohydrochloride as the source of hydrazine. Reaction in what amounts to an acidic medium prevents formation of the cyclic product and stabilizes triaminoguanidine. Refluxing an aqueous solution containing equimolar amounts (0.1 mole) of hydrazine monohydrochloride and thiocarbohydrazide for eight hours gave less than 3% triaminoguanidine hydrochloride. Most of the thiocarbohydrazide was recovered unchanged. This slow rate of reaction may be contrasted with the very rapid reaction of S-methylisothiocarbohydrazide hydriodide with hydrazine. It is furthermore pertinent to this investigation to note that attempts to hydrazinolyze carbohydrazide failed to give any triaminoguanidine.

Consideration of the experimental evidence presented in this paper demonstrates that ease of hydrazinolysis of specific functional groups increases in the order:



EXPERIMENTAL

S-Methylisothiocarbohydrazide (G). To a suspension of 12 g. of thiocarbohydrazide in 400 ml. of absolute ethanol heated under reflux, there was added dropwise a total of 18 g. of methyl iodide over a period of 30 minutes. Heating was continued until all of the thiocarbohydrazide had undergone reaction. The resulting solution was filtered hot; the desired product crystallized on cooling. A yield of 22 g. (80%) of *G* in the form of the hydriodide, (m.p. 145° with dec.) was obtained.

Anal. Calc'd for $C_2H_9IN_4S$: C, 9.68; H, 3.66; N, 22.58.
Found: C, 9.81; H, 3.63; N, 22.61.

Conversion to the *picrate* was accomplished by adding alcoholic picric acid to a solution of hydriodide in water. The product melts at 168–169°.

Anal. Calc'd for $C_8H_{11}N_7O_7S$: C, 27.51; H, 3.18; N, 28.07.
Found: C, 27.65; H, 3.24; N, 28.25.

The *dibenzaldehyde* derivative was prepared by direct combination of the appropriate reagents in a water-alcohol mixture. The product first isolated contained a non-stoichiometric amount of hydriodic acid from which it was freed by solution in a small quantity of ethanol and addition of the resulting solution to a large volume of water. Some iodine which also precipitated was removed by dissolving the product in chloroform and shaking this solution with an aqueous thiosulfate solution. The chloroform solution was evaporated to dryness and the solid product was purified by recrystallization from a 3:1 ethanol-water mixture. The free base melts at 146–147°.

Anal. Calc'd for 1,5-dibenzylidene-S-methylisothiocarbohydrazone, $C_{16}H_{16}N_4S$: C, 64.84; H, 5.44; N, 18.91.
Found: C, 64.73; H, 5.40; N, 18.71.

The dibenzaldehyde derivative may be converted to the hydriodide by treating an alcoholic solution with hydriodic acid; however, the salt (m.p. 200°) could not be obtained analytically pure.

Triaminoguanidine hydriodide. A refluxing solution of 5 g. of *G.* hydriodide in 130 ml. of ethanol was treated with 1 ml. of 95% hydrazine. The solution was heated for five minutes to assure complete reaction, then cooled. The resulting precipitate was removed and recrystallized from a 1:4 water-alcohol mixture to yield 3.8 g. (82%) of a crude product (m.p. 227°). After two recrystallizations the compound was found to melt at 232°. The product was further identified by conversion to the *picrate* [m.p. 173° (13)].

Anal. Calc'd for 1,2,3-triaminoguanidine hydriodide, CH_9IN_6: C, 5.18; H, 3.91; N, 36.22.

Found: C, 5.42; H, 4.12; N, 36.54.

1-Carbamyl-S-methylisothiosemicarbazide (*H*). A suspension of 1-carbamylthiosemicarbazide (13.4 g.) in hot ethanol (90%) was treated with 15 g. of methyl iodide and refluxed until complete solution had taken place. The desired product which crystallized on cooling as the hydriodide, was filtered off and washed with absolute alcohol. Recrystallization from 90% ethanol gave 22 g. (80%) of *H*•HI, m.p. 192–193°.

Anal. Calc'd for $C_3H_9IN_4OS$: C, 13.04; H, 3.28; N, 20.29.

Found: C, 13.44; H, 3.16; N, 20.41.

The *picrate* was prepared as a characterizing derivative and was recrystallized from water. It melts at 199°.

Anal. Calc'd for the picrate of 1-carbamyl-S-methylisothiosemicarbazide, $C_9H_{11}N_7O_8S$: C, 28.65; H, 2.94; N, 26.00.

Found: C, 28.84; H, 2.95; N, 26.03.

1-Amino-3-ureidoguanidine (*F*). A solution containing 8.3 g. of *H* as the hydriodide and 1.2 ml. of 95% hydrazine in 200 ml. of 95% ethanol was refluxed for 45 minutes during which time methyl mercaptan was evolved continuously. The solution was concentrated to 100 ml., then treated with 1.5 ml. of hydriodic acid and cooled to give 5 g. (64%) of a product melting at 187–188°. Two recrystallizations from a water-ethanol mixture failed to raise the melting point despite the fact that analytical results did not check for the hydriodide of *F*.

The *benzaldehyde* derivative of *F* was prepared by treating an alcohol-water solution of the hydriodide with benzaldehyde and heating the resulting solution. Upon cooling a white solid precipitated which gave a positive test for iodide ion indicating the formation of the hydriodide of the desired product. It was converted to the free base by treating an alcohol-water solution with concentrated ammonium hydroxide. The white solid which precipitated from this solution was recrystallized from a 1:1 water-ethanol mixture and found to melt at 210°.

Anal. Calc'd for $C_6H_{12}N_6O$: C, 49.08; H, 5.49; N, 38.16.

Found: C, 48.93; H, 5.36; N, 38.02.

The *picrate* was prepared by heating a water-ethanol solution containing equivalent amounts of *F*•HI and picric acid. The solution was cooled to precipitate the product which was then recrystallized from the minimum amount of alcohol. The picrate melts at 191°.

Anal. Calc'd for $C_9H_{11}N_9O_8$: C, 26.60; H, 3.07; N, 34.90.

Found: C, 27.02; H, 3.02; N, 34.77.

1,2-Diamino-3-ureidoguanidine (*E*). A solution containing 13.8 g. of the hydriodide of 1-carbamyl-S-methylisothiosemicarbazide (*H*) and 5.0 ml. of 95% hydrazine in 200 ml. of absolute ethanol was refluxed for 30 min. during which time methyl mercaptan and ammonia were evolved continuously and a white solid precipitated. The reaction mixture was chilled and the solid product was collected, washed with ethanol, and dried. There was obtained 10 g. of product melting at 197°. This was recrystallized from 18 ml. of water containing 10 drops of hydriodic acid to give 8 g. of product melting at 209°. Since the loss on recrystallization was considered to be excessive, a small quantity of the product was re-

crystallized from a water-alcohol mixture. The melting point was raised to 216° but analysis of the product indicated it was not yet pure. Consequently, the *picrate* was prepared as a characterizing derivative and was recrystallized from water. It melts at 200°.

Anal. Calc'd for 1,2-diamino-3-ureidoguanidine picrate, $C_8H_{12}N_{10}O_8$: C, 25.53; H, 3.22; N, 37.23.

Found: C, 25.68; H, 3.21; N, 37.24.

The identity of the product was further proven by preparation of the *dibenzaldehyde* derivative. An aqueous solution of *E*•HI was allowed to react with an excess of benzaldehyde. The resulting precipitate was dissolved in alcohol and treated with concentrated ammonium hydroxide to obtain the free base. The latter was recrystallized from a water-alcohol mixture to a constant melting point, 209–210°.

Anal. Calc'd for $C_{16}H_{17}N_7O$: C, 59.43; H, 5.30; N, 30.33.

Found: C, 59.69; H, 5.35; N, 30.23.

1-Carbamyl-S-methylisothiocarbohydrazide hydriodide (*I*). A suspension of 3.0 g. of 1-carbamylthiocarbohydrazide in 150 ml. of 95% ethanol containing 3.0 g. of methyl iodide was refluxed for 2.5 hours; small amounts of methyl iodide were added occasionally to maintain an excess of that reagent. The hot reaction mixture was then filtered to remove unreacted starting material and the filtrate was evaporated to a volume of 50 ml. The desired product precipitated when this solution was chilled in an ice-bath. After two recrystallizations from small amounts of 90% ethanol, 2.0 g. of product (41%) melting at 182° was obtained.

Anal. Calc'd for $C_3H_{10}IN_5OS$: C, 12.38; H, 3.46; N, 24.06.

Found: C, 12.63; H, 3.53; N, 24.18.

One gram of *I* and 0.5 ml. of 95% hydrazine were dissolved in 20 ml. of 95% ethanol and the solution was heated on a steam-bath until its volume had been reduced to 10 ml. The solution then was cooled to give a small quantity of pink solid, which upon recrystallization produced a white, crystalline solid melting at 216°. The latter was shown to be identical with 1,2-diamino-3-ureidoguanidine hydriodide (*E*), obtained by the hydrazinolysis of the hydriodide of 1-carbamyl-S-methylisothiosemicarbazide (H), both by a mixture melting point and by preparation of the picrate (m.p. 200°).

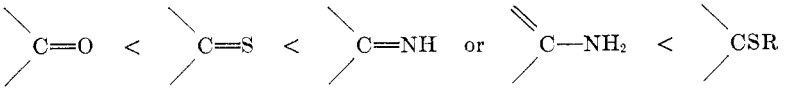
SUMMARY

Hydrazinolysis of S-alkyl derivatives of the ammono and hydrazino thiocarbonic acids affords a convenient preparative means for introduction of the hydrazide function. Hydrazinolysis reactions have led to preparation of the following compounds:

(a) triaminoguanidine from S-methylisothiocarbohydrazide
(b) 1,2-diamino-3-ureidoguanidine from the S-methyl derivative of 1-carbamylthiocarbohydrazide (and from 1-amino-3-ureidoguanidine)
(c) 1-amino-3-ureidoguanidine from the S-methyl derivative of 1-carbamylthiosemicarbazide

These substances have been isolated as the hydriodides and have been further characterized as the picrates and the benzaldehyde derivatives.

Hydrazinolysis of thiocarbohydrazide using hydrazine hydrochloride allows only limited conversion to triaminoguanidine. Other experimental evidence demonstrates that the ease of hydrazinolysis of specific functional groups increases in the order:



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