Preparation of Halomethyl-1,3,4-thiadiazoles. Conversion to 2-Amino-5-(1-methyl-5-nitro-2-imidazolyl)-1,3,4-thiadiazole, an Important Antimicrobial Agent.

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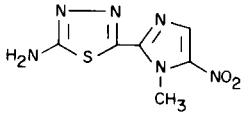
A new route for the synthesis of 2-amino-5-(1-methyl-5-nitro-2-imidazolyl)-1,3,4-thiadiazole (**1**) is described. This route was based upon the preparation of 2-amino-5-halomethyl-1,3,4-thiadiazoles by condensation of haloacetic acids with thiosemicarbazide. One of these intermediates, 2-acetamido-5-dichloromethyl-1,3,4-thiadiazole (**4**), was hydrolyzed to the corresponding 5-amino-2-carboxaldehyde **6**, which was trapped as its oxime **5**. 5-Acetamido-1,3,4-thiadiazole-2-carbonitrile (**7**), formed upon dehydration of **5**, was then converted into 2-amino-5-(2-imidazolyl)-1,3,4-thiadiazole (**11**) by a route based on the Pinner amidine synthesis. Methylation and nitration of the imidazole moiety then completed the preparation of **1**.

Discussion.

Recently Berkelhammer and Asato reported the synthesis and antimicrobial activity of 2-amino-5-(1-methyl-5-nitro-2-imidazolyl)-1,3,4-thiadiazole (**1**) (1). This compound shows not only the outstanding antiprotozoal activity characteristic of certain nitroimidazoles, but also important oral activity against both Gram-negative and Gram-positive bacteria in experimental animals. It therefore occupies a unique place among antimicrobial agents.



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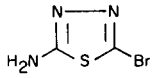
Although the original synthesis of **1** is reasonably straightforward from 1,2-dimethyl-5-nitroimidazole (1,2), the potential importance of **1** is sufficient that an investigation of alternative syntheses seemed desirable. This article describes a route based upon the prior development of the thiadiazole ring, followed by the introduction and elaboration of the nitroimidazole ring. Of particular interest is the thiadiazole chemistry which made this route possible.

One of the better methods (3) for synthesis of an imidazole is based upon conversion, by the Pinner method, of a nitrile into an amidine (4) bearing a potential aldehyde group, followed by liberation of the aldehyde and cyclization. Therefore, we sought to prepare a 1,3,4-thiadiazole (*e.g.* **7**) substituted with a cyano group and an amino (or potential amino) group. No cyanothiadiazoles were known prior to the present investigation, but their preparation from other thiadiazoles seemed possible. To this end a number of attempts at nucleophilic displacement of halogen, nitro, and methylsulfonyl groups from thiadiazoles by sodium cyanide or silver cyanide were tried, but these were unsuccessful (5,6). Efforts to obtain a cyanothiadiazole by treatment of the diazonium salt derived from 2-amino-5-bromo-1,3,4-thiadiazole (**2**) with cuprous cyanide and potassium cyanide were also fruitless under a variety of conditions.



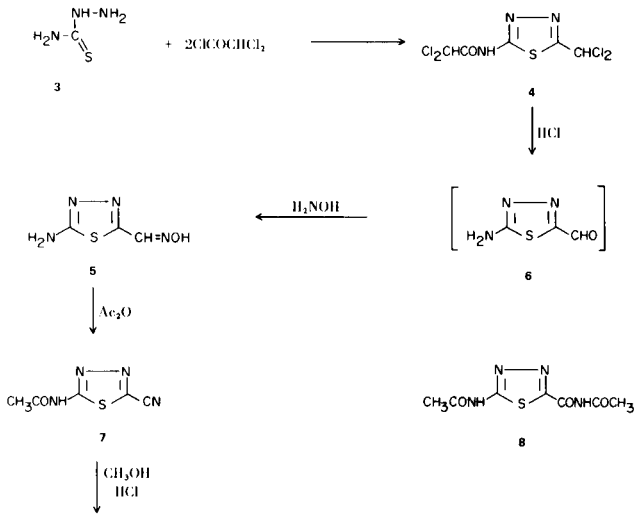
2

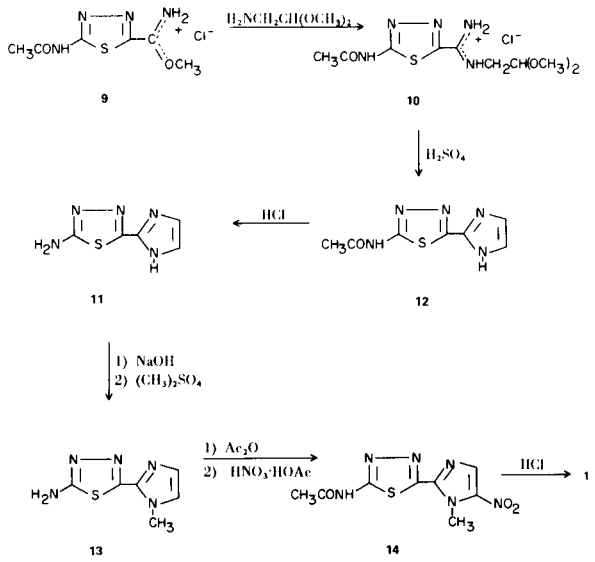
We also investigated the preparation of a cyanothiadiazole from the corresponding carboxaldehyde by way of the oxime. 5-Amino-1,3,4-thiadiazole-2-carboxaldehyde (6) had been prepared by ozonolysis of a nitrostyryl derivative of 5-amino-2-methyl-1,3,4-thiadiazole (7), and it readily gave oxime **5** upon treatment with hydroxylamine. Conversion of **5** to the nitrile was then effected by heating with acetic anhydride at reflux temperature. Some of the imide **8** was also formed, but fortunately, it could be readily removed because of its insolubility in acetic anhydride.

A more attractive route to aminoaldehyde **6** appeared available by the hydrolysis of an appropriate thiadiazole bearing a dihalomethyl substituent. No thiadiazoles substituted with halomethyl groups were known in the

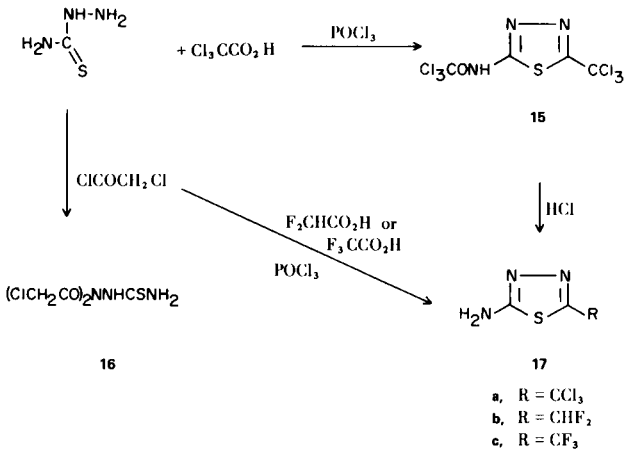
literature, but it appeared likely that they could be formed by condensation of thiosemicarbazide with suitable derivatives of haloacetic acids. Ample precedent for this type of condensation is found in the syntheses of 2-amino-5-alkyl-1,3,4-thiadiazoles from thiosemicarbazide and alkanoyl chlorides or anhydrides (8). These syntheses are sometimes carried out in excess acid chloride or anhydride as solvent. However, only two equivalents of such reagents are theoretically required; one to acylate the thiosemicarbazide, and the other to effect cyclization of the resulting acylthiosemicarbazide. It is also possible to substitute an inorganic cyclizing agent, such as phosphorus oxychloride or concentrated sulfuric acid, for the second equivalent of acid chloride or anhydride.

In our initial experiment, thiosemicarbazide (**3**) was heated with one equivalent of dichloroacetyl chloride and one equivalent of phosphorus oxychloride. This procedure afforded 2-dichloroacetamido-5-dichloromethyl-1,3,4-thiadiazole (**4**) in 15% yield, based upon the thiosemicarbazide. Since one equivalent of dichloroacetyl chloride was evidently consumed in acylating the 2-amino-group of **4**, it appeared necessary in this case to use two equivalents for a better conversion of thiosemicarbazide. A second experiment was based upon generation, *in situ*, of two equivalents of dichloroacetyl chloride from the relatively inexpensive dichloroacetic acid and phosphorus oxychloride. It gave a 44% yield of **4**, which represents a substantial improvement over the first method. In later preparations (described below), wherein the dihalomethylthiadiazole was not isolated but was instead converted into the corresponding carboxaldehyde oxime (*e.g.*, **5**), we found that only one equivalent of dichloroacetic acid and two equivalents of phosphorus oxychloride provided an even more efficient thiadiazole formation. Since the overall yields of **5** exceeded 50% it appears that in this case the 2-amino group was not acylated in the intermediate dichloromethyl thiadiazoles. Preparation of **4** from thiosemicarbazide and two equivalents of dichloroacetic anhydride proceeded in 53% yield.





Other halomethylthiadiazoles were also prepared by these procedures. Trichloroacetic acid and phosphorus oxychloride afforded 2-trichloroacetamido-5-trichloromethyl-1,3,4-thiadiazole (**15**) which was readily hydrolyzed by hydrochloric acid to the corresponding amine **17a**. When difluoroacetic acid and trifluoroacetic acid were treated under the same conditions the amides formed were too unstable to survive the workup. The free amines **17b** and **17c** were obtained instead (9). It was not possible to obtain a monochloromethylthiadiazole by condensing chloroacetyl chloride with thiosemicarbazide. Only 1,1-bis(chloroacetyl)thiosemicarbazide (**16**) could be isolated (42%).



Returning to the problem of converting dichloromethylthiadiazole **4** into the corresponding nitrile *via* aldehyde **6**, we examined its acid hydrolysis under a

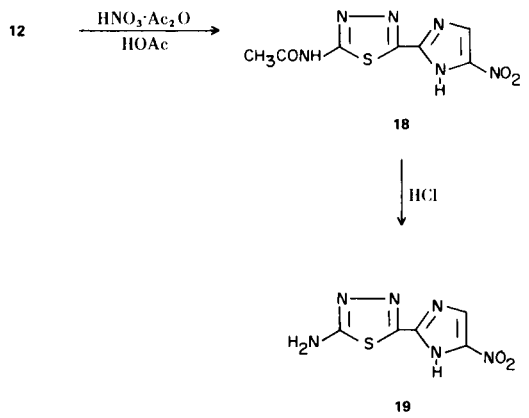
variety of conditions; however a useful procedure for the preparation of **6** could not be found. Only polymeric products were obtained. One possible mode of polymerization was acid-catalyzed Schiff's base formation from **6**. If this were actually the case, then polymerization might have been prevented by trapping the carboxaldehyde as its oxime before it had a change to react with itself. Therefore, we prepared **4** by the above-described route from dichloroacetic acid and thiosemicarbazide and, without isolation, hydrolyzed it with hydrochloric acid in the presence of excess hydroxylamine. This method succeeded in suppressing polymerization, and a 55% yield of oxime **5** was obtained. Samples of **5** prepared in this manner were suitable for direct conversion to nitrile **7**, provided they were first thoroughly dried in a vacuum. When this precaution was not taken, relatively high proportions of imide **8** were formed along with **7**.

With a convenient and efficient route to **7** (two steps in 42% overall yield from dichloroacetic acid) thus established, development of the nitrile group into an imidazole ring was investigated next. As we had hoped, the method (3) based upon a Pinner amidine synthesis proved effective for this purpose. Thus, the nitrile was first converted into imino ether hydrochloride **9** by methanol and anhydrous hydrogen chloride in tetrahydrofuran. It was necessary throughout to keep the mixture below 5° to prevent methanolysis of **9**. Treatment of **9** with aminoacetaldehyde dimethylacetal in ethanol then furnished amidine hydrochloride **10**, which was washed well with ether and converted directly into the desired imidazole (**12**) by sulfuric acid. The overall yield from nitrile **7** was 56%.

Final elaboration of the imidazole ring of **12** by methylation and nitration was now required to complete the synthesis of **1**. Since the amide nitrogen of **12** was relatively acidic the preferential base-catalyzed methylation of an imidazole ring nitrogen presented difficulties. It was necessary, therefore, to hydrolyze **12** to the free amine **11**. Treatment of **11** with dilute sodium hydroxide solution afforded its sodium salt (proton removed from imidazole nitrogen), which was then readily alkylated in the imidazole ring.

Nitration of an *N*-methylimidazole at C-5 presents a considerable problem because, under most conditions, the nitro group is introduced at the 4-position (in conjugation with the methylated nitrogen) (10). Both steric and electronic factors appear to favor the C-4 nitration. However, after trying a variety of procedures, we found one which was highly specific for nitration at C-5. This method consisted of heating **13** with acetic anhydride to form its acetamido derivative and then adding acetic acid and several equivalents of 70% nitric acid. A vigorous reaction occurred, accompanied by evolution of oxides of nitrogen. Workup of the resulting solution afforded a mixture which contained 5-nitro derivative **14**, some non-nitrated imidazole, and unidentified by-products. Acid hydrolysis of this mixture afforded **1**, which could be separated from the by-products by precipitation at different values of *p*H. At *p*H 1 the by-products came out of solution, whereas **1** was precipitated at *p*H 7. When prepared in this manner, **1** contained only a small amount of **13** which could be removed by chromatography or recrystallization. The yield for nitration and hydrolysis was 27%.

It was also possible to nitrate unmethylated imidazole **13** by the above-described procedure. In this case, dilution of the acetic anhydride with acetic acid was particularly important in moderating the vigorous reaction. Yields up to 45% of nitro derivative **18** were obtained and fewer by-products were noted. Hydrolysis of **18** furnished the demethyl analog **19** of **1** in 30% overall yield from **13**. This homolog is of interest because it is the major metabolite of **1** found in the urine of the dog (11).



EXPERIMENTAL

Melting points were determined on a Mel-Temp apparatus and are corrected. Ultraviolet spectra were determined in methanol solution with a Cary recording spectrophotometer. Infrared spectra were determined in potassium bromide disks with a Perkin-Elmer Model 21 spectrophotometer. Nuclear magnetic resonance spectra were determined in dimethylsulfoxide-d_6 (unless otherwise specified) with a Varian A-60 spectrometer. Solutions were dried over anhydrous magnesium sulfate and concentrated under reduced pressure on a rotary evaporator.

5-Amino-1,3,4-thiadiazole-2-carboxaldehyde Oxime (**5**).

A. From Pure **6**.

An aqueous solution of hydroxylamine, prepared from 0.695 g. (10 mmoles) of hydroxylamine hydrochloride, 40 ml. of water, and 2 ml. of 5 *N* sodium hydroxide was treated with 1.29 g. (10 mmoles) of 5-amino-1,3,4-thiadiazole-2-carboxaldehyde (**6**) and 5 ml. of ethanol. The mixture was warmed on a steam bath for 25 minutes and then cooled. Yellow crystals (820 mg., 64%),

which melted with decomposition at 240°, separated from the resulting solution. An analytical sample, recrystallized from methanol-water had m.p. 242° dec.; λ max 3.1, 3.2, 3.7 μ; λ max 301 mμ (ε, 11,500).

Anal. Calcd. for $C_3H_4N_4OS$: C, 25.00; H, 2.80; N, 38.88; S, 22.22. Found: C, 25.17; H, 2.90; N, 38.72; S, 21.88.

B. From Dichloroacetic Acid.

To an ice-cooled mixture of 9.11 g. (0.1 mole) of thiosemicarbazide and 12.89 g. (0.1 mole) of dichloroacetic acid was added slowly, with vigorous stirring, 30.67 g. (18 ml., 0.2 mole) of phosphorus oxychloride. After this addition was complete the ice bath was replaced by a water bath, and the temperature was raised gradually to 70°. Vigorous evolution of hydrogen chloride ensued as the temperature neared 70° and the mixture was briefly cooled to control foaming. After *ca.* 70 minutes, gas evolution ceased. The resulting viscous solution was stirred at 70° for an additional hour and then cooled in an ice bath. A solution of 30 g. of hydroxylamine hydrochloride in 50 ml. of water was added, and 20 ml. of concentrated hydrochloric acid was added immediately afterward. The mixture was stirred at 70° for 5 hours, then cooled and filtered to remove some excess hydroxylamine hydrochloride. When the *p*H of the filtrate was adjusted to 6.0 by addition of 5 *N* sodium hydroxide, the oxime crystallized as brownish prisms. It was washed with cold water and dried under a vacuum. A 10.8 g. (55%) yield of material suitable for direct conversion to the nitrile was obtained. It had m.p. 136-138° and an ir spectrum superimposable with that of **5** prepared from pure **6**.

5-Acetamido-1,3,4-thiadiazole-2-carbonitrile (**7**).

A suspension of 10.8 g. of 5-amino-1,3,4-thiadiazole-2-carboxaldehyde oxime (**5**) in 100 ml. of acetic anhydride was stirred and heated at reflux temperature for 18 hours. The resulting amber solution was cooled, whereupon a small amount (560 mg.) of tan solid separated. The mixture was filtered and the filtrate was concentrated. Crystallization of the solid residue from methanol-water afforded 8.5 g. (76%) of nitrile **7** as nearly white prisms, m.p. 226-230°. An analytical sample, recrystallized from tetrahydrofuran-hexane had m.p. 230-234°; λ max 4.50 (weak, CN), 5.90 (CO) μ; λ max 280 mμ (ε, 10,000).

Anal. Calcd. for $C_5H_4N_4OS$: C, 35.72; H, 2.40; S, 19.03. Found: C, 35.72; H, 2.43; S, 18.63.

The solid which formed upon cooling the acetic anhydride solution, was recrystallized from methanol. It had m.p. 263-265°; λ max 5.85 (CO) μ; λ max 284 mμ (ε, 11,000); nmr, methyl groups at δ 2.20 and 2.12 ppm, which confirms the structure 5-acetamido-1,3,4-thiadiazole-2-(*N*-acetylcarboxamide) (**8**).

Anal. Calcd. for $C_7H_8N_4O_3S$: C, 36.84; H, 3.53; N, 24.55; S, 14.05. Found: C, 36.56; H, 3.46; N, 25.24; S, 14.54.

2-Acetamido-5-(2-imidazolyl)-1,3,4-thiadiazole (**12**).

A mixture of 8.40 g. (50 mmoles) of 5-acetamido-1,3,4-thiadiazole-2-carbonitrile (**7**) and 80 ml. of tetrahydrofuran was filtered to remove a small amount of insoluble material, treated with 4.05 ml. (3.20 g., 100 mmoles) of methanol, chilled in an ice bath and saturated with anhydrous hydrogen chloride. A solid formed during this saturation process. The mixture was kept at 5° for 22 hours and then filtered. The solid imino ether hydrochloride (**9**) was washed well with ether and added directly to an ice-cooled mixture of 5.25 g. (50 mmoles) of aminoacetaldehyde dimethylacetal and 100 ml. of methanol. After the resulting mixture had been heated at reflux temperature for 19 hours, it was concentrated under reduced pressure. The gummy residue was triturated with ether containing a little methanol until the amidine hydrochloride (**10**) had crystallized. It was washed with ether, air dried, and then added in portions to 20 ml. of concentrated sulfuric acid. The mixture, which foamed and became warm, was cooled in a water bath when necessary. When complete solution was obtained it was poured onto 100 g. of ice and the resulting solution (filtered if necessary) was brought to *p*H 6 with 5 *N* sodium hydroxide (ice cooling). The precipitate that formed was washed with water and dried in air. This procedure gave 5.75 g. (56%) of **12** as yellow solid that did not melt below 320°. In order to obtain an analytically pure sample it was necessary to chromatograph this product on diatomaceous earth with a system composed of 85 heptane:100 ethyl acetate:40 dimethylformamide:8 water. Snow white needles which decomposed above 380° were obtained. They had λ max 3.80 (CO) μ; 304 mμ (ε, 16,500); nmr, methyl group at δ 2.24 ppm; two aromatic (imidazole) hydrogens at 7.26 ppm.

Anal. Calcd. for $C_7H_7N_5OS$: C, 40.19; H, 3.37; N, 33.48. Found: C, 39.98; H, 3.22; N, 33.22.

2-Amino-5-(2-imidazolyl)-1,3,4-thiadiazole (**11**).

A suspension of 4.18 g. (20 mmoles) of 2-acetamido-5-(2-imidazolyl)-1,3,4-thiadiazole in 50 ml. of concentrated hydrochloric acid was heated at reflux temperature until a clear solution resulted (40 minutes). It was then concentrated under reduced pressure and the residue was dissolved in 10 ml. of water and neutralized to *p*H 5 with sodium hydroxide. The white solid that formed was washed with water and air dried. A 2.20 g. (66%) yield of material that decomposed above 285° was obtained. For analysis the dihydrochloride was prepared and recrystallized from concentrated hydrochloric acid. It had m.p. 222-227°; λ max 3.1-4.0 (broad) μ; 317 mμ (ε, 12,000).

Anal. Calcd. for $C_5H_5N_5S \cdot 2HCl$: C, 25.01; H, 2.94; Cl, 29.53. Found: C, 24.77; H, 3.00; Cl, 29.79.

2-Amino-5-(1-methyl-2-imidazolyl)-1,3,4-thiadiazole (**13**).

A mixture of 307 mg. (1.85 mmoles) of 2-amino-5-(2-imidazolyl)-1,3,4-thiadiazole and 3.8 ml. of 0.5 *N* sodium hydroxide was stirred and filtered to remove some insoluble material. The filtrate was treated with 0.17 ml. (1.85 mmoles) of dimethyl sulfate and stirred for 45 minutes. The solid that separated was washed with water and dried in air. This procedure gave 124 mg. (37%) of nearly white crystals, m.p. 246-251°; λ max 3.1-3.3 (NH) μ; λ max 308 mμ (ε, 16,700); nmr, NH_2 at δ 7.44 ppm, two hydrogens on imidazole carbons at 7.28 and 6.98 ppm, methyl group at 3.95 ppm.

Anal. Calcd. for $C_6H_7N_5S$: C, 39.78; H, 3.89; S, 17.67. Found: C, 39.82; H, 4.01; S, 17.88.

2-Amino-5-(1-methyl-5-nitro-2-imidazolyl)-1,3,4-thiadiazole (**1**).

A mixture of 1.12 g. of 2-amino-5-(1-methyl-2-imidazolyl)-1,3,4-thiadiazole, 10 ml. of acetic acid, 5 ml. of acetic anhydride, and 0.5 ml. of 70% nitric acid was warmed on a steam bath. An additional 0.4 ml. of the nitric acid was added to promote reaction. This reaction afforded evolution of heat and brown fumes. When a clear solution was obtained it was concentrated *in vacuo* and the residue was treated with water. The solid that formed weighed 624 mg. after drying in air. Thin-layer chromatography showed it to contain 2-acetamido-5-(1-methyl-5-nitro-2-imidazolyl)-1,3,4-thiadiazole (**14**), since the largest spot had an R_f value identical with that of **14** prepared by acetylation of authentic **1**. This solid was heated with 2 ml. of concentrated hydrochloric acid on a steam bath for 15 minutes. The resulting solution was cooled and diluted, whereupon a yellow solid separated. The mixture was

filtered and the filtrate was brought to *p*H 7. A yellow precipitate formed and it was washed with water and dried in air. This precipitate (370 mg.) was identical in ir and uv spectra and behavior upon chromatography with an authentic sample of **1** (1), except that a small amount of **13** was also present. Partition chromatography on diatomaceous earth with a heptane, ethyl acetate, methanol, water system (70:30:15:6) afforded pure **1**.

2-Amino-5[5(4)-nitro-2-imidazolyl]-1,3,4-thiadiazole (**19**).

A suspension of 2.09 g. (10 mmoles) of 2-acetamido-5-(2-imidazolyl)-1,3,4-thiadiazole in 5 ml. of acetic anhydride and 15 ml. of acetic acid was treated with 0.6 ml. of 70% nitric acid. The mixture was heated on a steam bath for 30 minutes, treated with an additional 0.3 ml. of nitric acid and heated for 15 minutes. It was then cooled and filtered, and the filtrate was concentrated. The solid residue was triturated with water, washed well with more water, and dried in air. Without further purification the resulting 2-acetamido-5[5(4)-nitro-2-imidazolyl]-1,3,4-thiadiazole (**18**, 795 mg.) was converted to **19**. A mixture of **18** and 4 ml. of concentrated hydrochloric acid was heated on a steam bath for 30 minutes, cooled and diluted with 50 ml. of water. The mixture was filtered and the filtrate was brought to *p*H 7 with 5 *N* sodium hydroxide. The yellow solid that separated was washed with water and dried in air, yield 640 mg. (30%). An analytical sample, recrystallized from dimethylformamide-water, did not melt below 330°. It had λ max 6.2 μ (NH_2); λ max 298 (ε, 7,850), 370 mμ (ε, 9,750).

Anal. Calcd. for $C_5H_4N_6O_2S$: C, 28.30; H, 1.90; N, 39.60; S, 15.11. Found: C, 28.64; H, 2.00; N, 39.68; S, 14.93.

2-Dichloroacetamido-5-dichloromethyl-1,3,4-thiadiazole (**4**).

A. From Dichloroacetyl Chloride.

A mixture of 1.47 g. (10 mmoles) of dichloroacetyl chloride, 0.91 g. (10 mmoles) of thiosemicarbazide and 1.53 g. (10 mmoles) of phosphorus oxychloride was heated at 60° for 6 hours, cooled and triturated with ether. The resulting mixture was filtered and the filtrate was concentrated. When the residual oil was dissolved in methanol, the solution became quite warm. Gradual addition of water caused white crystals to separate from this solution. A 436 mg. (15%) yield of material with m.p. 180-182° was obtained. Recrystallization from methanol-water gave white crystals, m.p. 183-187°; λ max 5.85 μ (CO); λ max 266 mμ (ε, 10,000); nmr, δ 7.95 ppm ($CHCl_2$ on nucleus), 6.77 ppm ($CHCl_2$ of amide).

Anal. Calcd. for $C_5H_3Cl_4N_3OS$: C, 20.36; H, 1.02; Cl, 48.07; N, 14.24; S, 10.86. Found: C, 20.27; H, 1.07; Cl, 47.64; N, 14.21; S, 11.05.

B. From Dichloroacetic Anhydride.

A mixture of 0.91 g. (10 mmoles) of thiosemicarbazide and 4.78 g. (20 mmoles) of dichloroacetic anhydride was warmed at 60° for 3 hours and then cooled and poured onto cracked ice. This procedure gave a gummy precipitate, which changed to a light tan solid upon addition of methanol. The solid was washed with a little petroleum ether. It then had m.p. 175-180° and an ir spectrum superimposable with that of **4** prepared by Method A, yield 1.51 g. (53%).

C. From Dichloroacetic Acid.

To an ice-cooled mixture of 64.5 g. (0.5 mole) of dichloroacetic acid and 22.8 g. (0.25 mole) of thiosemicarbazide was added slowly 76.8 g. (0.5 mole) of phosphorus oxychloride. The resulting suspension was then gradually warmed. As the temperature neared 70° vigorous evolution of hydrogen chloride ensued and the suspension was briefly cooled in ice to control foaming. Warming was carefully controlled until hydrogen chloride evolution was nearly completed and then the mixture was kept at 70° for an additional hour. It was then cooled and treated with a large amount of ice water. A gum formed initially but soon changed to fine particles. This solid was resuspended in water, which was brought to *p*H 6 with sodium hydroxide. The solid was dried in air and then dissolved in hot ethyl acetate. This solution was decolorized and concentrated. A pale yellow solid, m.p. 170-177°, ir identical with material prepared by Method A, was obtained in a 32.3 g. (44%) yield.

2-Trichloroacetamido-5-trichloromethyl-1,3,4-thiadiazole (**15**).

This compound was prepared by Method C described for **4**, except that a temperature of 80° was necessary. From 18.23 g. of thiosemicarbazide and 68.63 g. of trichloroacetic acid was obtained 57.8 g. (79%) of **15** with m.p. 179-182°; λ max 5.82 μ (CO), λ max 282 mμ (ε, 7,800).

Anal. Calcd. for $C_5HCl_6N_3OS$: C, 16.50; H, 0.28; Cl, 58.46; N, 11.55; S, 8.81. Found: C, 16.28; H, 0.28; Cl, 58.70; N, 11.62; S, 8.92.

2-Amino-5-trichloromethyl-1,3,4-thiadiazole Hydrochloride (**17a**).

A mixture of 10.94 g. of 2-trichloroacetamido-5-trichloromethyl-1,3,4-thiadiazole (**15**) and 70 ml. of concentrated hydrochloric acid was heated on a steam bath until a clear solution resulted. It was then chilled at 5°. White crystals (3.63 g. (47%) of **17a** crystallized from this solution. They showed indefinite decomposition when heated; λ max 3.0-3.8, 6.12 μ (NH_2); λ max 250 mμ (ε, 6,900).

Anal. Calcd. for $C_3H_2Cl_3N_3S{\cdot}HCl$: C, 14.13; H, 1.18; Cl, 55.63; N, 16.48; S, 12.58. Found: C, 14.15; H, 1.09; Cl, 55.27. N, 16.38; S, 12.83.

2-Amino-5-difluoromethyl-1,3,4-thiadiazole (**17b**).

This compound was prepared from 4.62 g. of thiosemicarbazide and 10.22 g. of difluoroacetic acid by method C for **4**. The solid initially obtained upon pouring the reaction mixture onto ice was dissolved in the aqueous mixture by warming and stirring. Adjusting the *p*H to 6 then afforded precipitation of pure **17b**, m.p. 184-187° in 6.33 g. (82%) yield; λ max 3.0, 3.2, 6.10 μ (NH_2); λ max 268 mμ (ε, 6,200).

Anal. Calcd. for $C_3H_3F_2N_3S$: C, 23.84; H, 2.00; F, 25.14; N, 27.80; S, 21.22. Found: C, 23.94; H, 2.15; F, 25.23; N, 28.02; S, 20.96.

2-Amino-5-trifluoromethyl-1,3,4-thiadiazole (**17c**).

This compound was prepared by the same technique used for **17b**. From 9.11 g. of thiosemicarbazide and 24.0 g. of trifluoroacetic acid was obtained 12.75 g. (75%) of white crystals, m.p. 220-225°. Recrystallization from ethyl acetate gave m.p. 216-219°; λ max 3.0, 3.2, 6.09 μ (NH); λ max 273 mμ (ε, 6,200).

Anal. Calcd. for $C_3H_2F_3N_3S$: C, 21.30; H, 1.19; F, 33.70; N, 24.84; S, 18.96. Found: C, 21.62; H, 1.20; F, 33.98; N, 25.01; S, 19.15.

1,1-Bis(chloroacetyl)thiosemicarbazide (**16**).

A mixture of 5.1 g. of thiosemicarbazide and 20 ml. of chloroacetyl chloride was gradually warmed on a steam bath until hydrogen chloride evolution began and warming was continued until this evolution was finished. The resulting solid was cooled and washed well with ether. It was then suspended in acetone, which removed some gummy red material. The acetone-insoluble white solid product was then crystallized two times from methanol-

ether. This procedure gave 5.7 g. (42%) of **16** as white needles, m.p. 225° dec.; λ max 5.55, 5.75 μ; λ max 235 mμ (ε, 4,880).

Anal. Calcd. for $C_5H_7Cl_2N_3O_2S$: C, 24.60; H, 2.89; Cl, 29.05; N, 17.22; S, 13.14. Found: C, 24.99; H, 3.04; Cl, 28.78; N, 17.02; S, 13.21.

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