The Chemistry of 1,2,5-Thiadiazoles. II. 3,4-Disubstituted Derivatives of 1,2,5-Thiadiazole 1,1-Dioxide[1]

Richard Y. Wen, Andrew P. Komin, Robert W. Street, and Marvin Carmack*

Contribution No. 2644 from the Department of Chemistry, Indiana University, Bloomington, Indiana 47401

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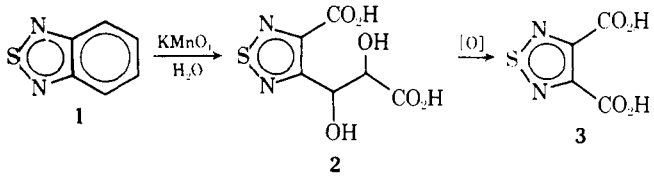
The dipotassium salt of 3,4-dihydroxy-1,2,5-thiadiazole 1,1-dioxide (**4a**) was synthesized in high yield from sulfamide and diethyl oxalate. The free acid (**7**) was prepared from **4a**, from the disilver salt (**4c**), or from 3,4-dichloro-1,2,5-thiadiazole 1,1-dioxide (**13**), the latter being synthesized from **4a** and phosphorus pentachloride. The reactive **13** was converted in methanol to the dimethoxy derivative (**12**). Either **12** or **13** reacted with ammonia to form the 3,4-diamino derivative (**14**) and with methylamine, dimethylamine, and ethylenediamine, respectively, to produce the 3,4-bis(methylamino) (**15**), the 3,4-bis(dimethylamino) (**16**), and the 3,4-piperazino (**23**) derivatives. One mole of morpholine with **12** yielded 3-morpholino-4-methoxy-1,2,5-thiadiazole 1,1-dioxide (**17**), which could be rearranged smoothly by heating to 2-methyl-3-oxo-4-morpholino-1,2,5-thiadiazoline 1,1-dioxide (**18**). Two moles of piperidine with **12** gave 3-oxo-4-piperidino-1,2,5-thiadiazoline 1,1-dioxide (**19**) and *N*-methylpiperidine. Dimethoxy derivative **12** rearranges thermally, first to 2-methyl-3-oxo-4-methoxy-1,2,5-thiadiazoline 1,1-dioxide (**10**) and then to 2,5-dimethyl-3,4-dioxo-1,2,5-thiadiazolidine 1,1-dioxide (**11**). *o*-Phenylenediamine with **12** in DMF gave the tricyclic 1,3-dihydro[1,2,5]thiadiazolo[3,4-*b*]quinoxaline 2,2-dioxide (**24**). **12** and **14** condensed in the presence of sodium methoxide to form a linear tricyclic quinonoid salt (**25a**). **13** reacted with 2 mol of anthranilic acid to yield a diamine (**26**) which was dehydrated to a linear pentacyclic bis(quinazolino)-1,2,5-thiadiazole derivative (**27**).

Previously, only alkyl or aryl disubstituted derivatives of the 1,2,5-thiadiazole 1,1-dioxide ring had been reported.[2,3] We now wish to report the synthesis and reactions of 1,2,5-thiadiazole 1,1-dioxide derivatives having chlorine, oxygen, or nitrogen substituents on the 3,4 positions.

This work has permitted us to compare the parent aromatic ring system, 1,2,5-thiadiazole,[1a] with its 1,1-dioxide in a series of functional derivatives, and to assess the relative influence of the two ring systems upon such important groups as chloro, hydroxy, and amino. For example, comparison has been made of the effects of the state of oxidation of the ring sulfur atom upon the acidic ionization constants of the 3,4-dihydroxy derivatives (or their tautomers). The amide-like character of the 3,4-diamino derivatives has been noted. A pronounced tendency of the 3,4-dialkoxyl derivatives to transfer their *O*-alkyl groups to the ring nitrogen atoms has been observed. Spectral studies have given information regarding possibilities for prototropy in the hydroxy- and amino-substituted derivatives. Finally, the dioxo compounds have been shown to be excellent precursors for building up more complex fused ring derivatives in which, at the end, the $-SO_2-$ function can be replaced with an unoxidized –S– to yield otherwise inaccessible fused-ring 1,2,5-thiadiazole derivatives of unusual character.[1b] The 1,2,5-thiadiazole 1,1-dioxide nucleus is to be regarded as alicyclic rather than aromatic. It is strongly electron withdrawing and activating but somewhat less powerful than the oxalyl group (–COCO–), with which it is compared.

Carmack et al.[1,4,5] and Pesin et al.[6] found that the neutral potassium permanganate oxidation of 2,1,3-benzothiadiazole (**1**) at 50–60° gave diacid **2**, 1,2,5-thiadiazole-3,4-dicarboxylic acid (**3**), and a small amount of the dipotassium salt of 3,4-dihydroxy-1,2,5-thiadiazole 1,1-dioxide (**4a**). Compound **4a** was obtained as the major product when the permanganate oxidation of **1** or **3** was carried out at 90°. Product **4a** could also be synthesized in low yield from sulfamide and dimethyl oxalate using potassium hydroxide in methanol–water.[1,7] Initial consideration was given to the possibility that the by-product salt might be the dipotassium salt of *N*-sulfamoyloxamic acid **5**, but this was ruled out by both chemical and spectral evidence showing that the compound is a heterocyclic derivative which crystallizes with a firmly held water of crystallization.



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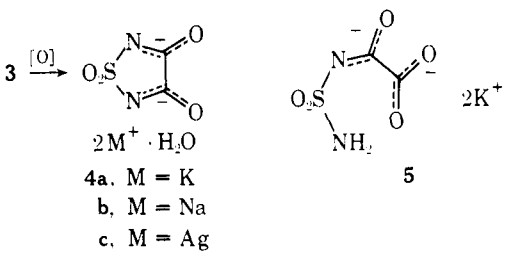
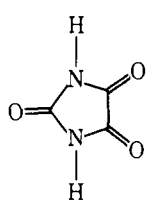


4a, M = K
b, M = Na
c, M = Ag

5

The anhydrous disodium and dipotassium salts of **4** were synthesized in high yield from sulfamide and diethyl oxalate using the respective metal methoxide in a procedure similar to the synthesis of parabanic acid (**6**).[8] The water of hydration was picked up on recrystallization from water and was evolved upon heating above 180°. The proton NMR of **4a** in Me_2SO-d_6 showed only water, identified by observing increased peak intensity upon adding water to the sample.[9] The ^{13}C NMR spectrum of **4b** in water showed one sharp singlet at 171.9 ppm, consistent with the resonating dianion structure **4**. The formation of **4** under completely anhydrous conditions further rules out structure **5**.



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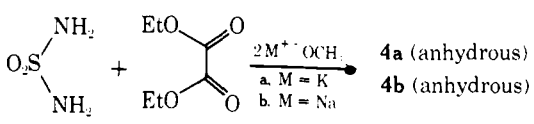
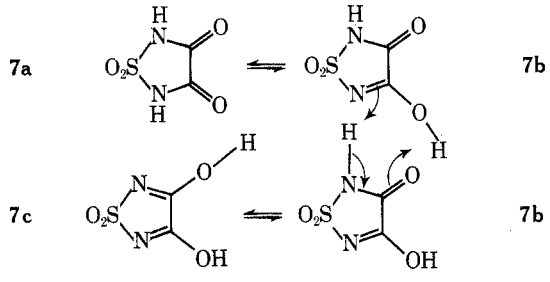


Free 3,4-dihydroxy-1,2,5-thiadiazole 1,1-dioxide (**7**) was

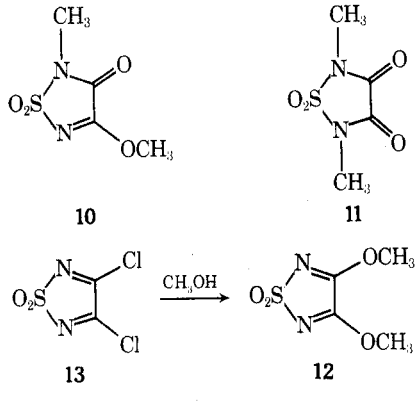
isolated from **4a** by means of a cation-exchange resin, or by the action of hydrogen sulfide on the disilver salt **4c**. Although its salts are stable, **7** itself hydrolyzed readily to sulfamide and presumably oxalic acid. Neutralization of **7** with potassium hydroxide reconverted the material to the dipotassium salt **4a**. Free dihydroxy compound **7** could exist as three tautomers (**7a–c**), whose order of stability



would be predicted to be **7a** > **7b** > **7c**. This order was arrived at from the strength of the infrared absorption bands at 5.67 and 5.80 μm, both typical of >C=O (cf. compound **11**, vide infra) and the lack of absorption in the region of 6.15 μm.

A comparison of acid strengths determined in water for 3,4-dihydroxy-1,2,5-thiadiazole (**9**), 3,4-dihydroxy-1,2,5-thiadiazole 1-oxide (**8**), and 3,4-dihydroxy-1,2,5-thiadiazole-1,1-dioxide (**7**) is shown in Table I.

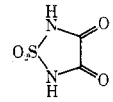
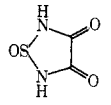
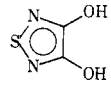
Methylation of the disilver salt **4c** in refluxing methyl iodide–benzene gave 2-methyl-3-oxo-4-methoxy-1,2,5-thiadiazoline 1,1-dioxide (**10**), mp 179–180°, and 2,5-dimethyl-3,4-dioxo-1,2,5-thiadiazolidine 1,1-dioxide (**11**), mp 118–120°, in a 2:1 ratio. The third possible dimethylated isomer, 3,4-dimethoxy-1,2,5-thiadiazole 1,1-dioxide (**12**), mp 188–189°, was synthesized from **13** by a method known to



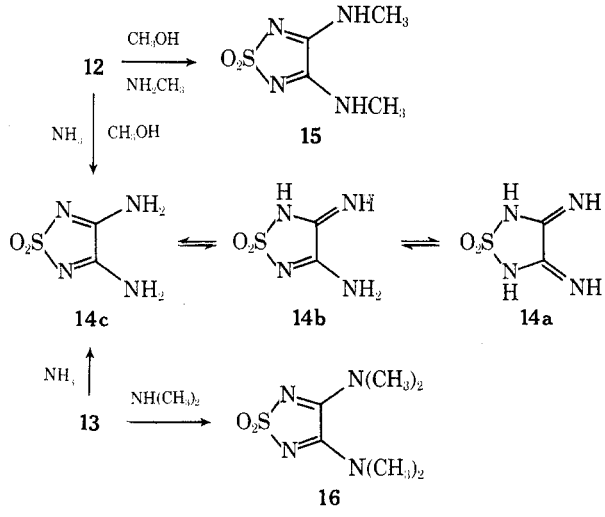
give only the 3,4-dimethoxy compound (vide infra). All three compounds gave correct analyses for $C_4H_6N_2O_4S$ and showed molecular ions at *m/e* 178 in their mass spectra. The structural assignments of **10** and **11** were made on the basis of ir and NMR spectra. The infrared spectrum of **12** showed a single band at 6.1 μm as expected for the C=N bonds, whereas **10** showed an amide carbonyl band at 5.7 μm[12] in addition to a 6.15-μm band. Compound **11** showed a pair of amide carbonyl bands at 5.54 and 5.7 μm. The proton NMR spectra of the two symmetrical compounds **11** and **12** showed singlets at δ 3.23 and 4.18, respectively. The unsymmetrical compound **10** showed two singlets, one at δ 3.28 for the *N*-methyl protons and one at δ 4.24 for the *O*-methyl protons.

Reaction of **4a** with 3–5 mol of phosphorus pentachloride at 55–60° gave 3,4-dichloro-1,2,5-thiadiazole 1,1-dioxide (**13**). Repeated elemental analyses have shown a small amount (~0.2%) of hydrogen due to the extreme sensitivity of the compound toward atmospheric moisture. However, the mass spectrum of **13** gave the correct exact mass and the expected major fragment at *m/e* 135 ($CClNO_2S$, M^+ – cyanogen chloride). Hydrolysis of **13** to **7** occurred rapidly, indicating that **13** has reactivity comparable to an acid chloride. Surprisingly, the reactions of crystalline **4a** and **4b** with phosphorus pentachloride seemed related to the degree of hydration. Most consistent good yields were obtained from **4a** monohydrate. **4b** dihydrate gave variable yields, whereas anhydrous **4b** gave no dichloride **13**.

Table I
Ionization Constants of Heterocyclic Acids

	pK_{a_1}	pK_{a_2}	Ref
	1.23	4.19	10
 7	2.20	5.55	
 8	2.62	6.58	11
 9	4.68	7.50	7, 11

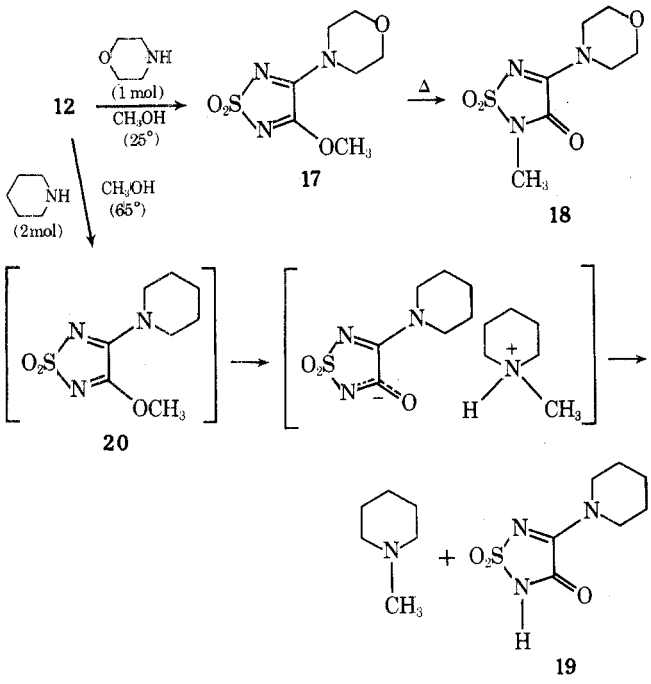
Addition of **13** to methanol gave dimethoxy compound **12** in an exothermic reaction. The corresponding 3,4-diethoxy-1,2,5-thiadiazole 1,1-dioxide was prepared from ethanol and **13**. The dimethoxy compound **12** is readily purified, yet retains reactivity at least comparable to an ester. When a methanolic solution of **12** was saturated with ammonia, 3,4-diamino-1,2,5-thiadiazole 1,1-dioxide (**14**) was formed in nearly quantitative yield. Compound **14** was obtained directly from **13** by treatment with liquid ammonia, although the work-up was longer and the yield lower than in the synthesis from **12**. The compound **14** probably has considerable imino character and should best be represented as a mixture of tautomers, **14a**, **14b**, and **14c**. The same



interpretation would apply to compounds **15**, **23**, and **26**, all of which contain 3,4 secondary nitrogens. The compounds which have protons available for tautomerization exhibit multiple infrared bands between 5.6 and 6.3 nm whereas

compounds incapable of tautomerism, such as **12** and **16**, exhibit only single bands in this region.

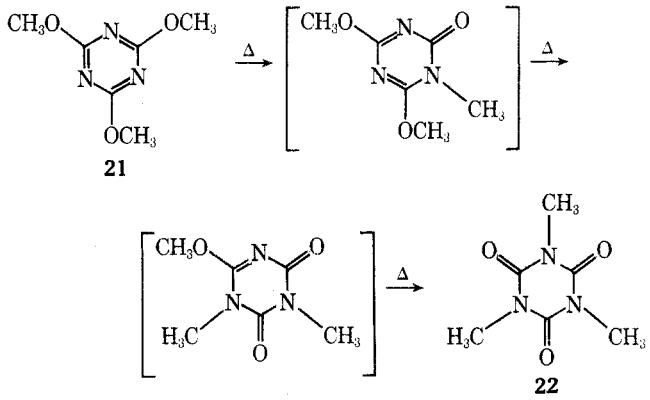
Several N-substituted analogs of **14** were prepared from amines and **12** or **13**. Methylamine with **12** gave 3,4-di-(*N*-methylamino)-1,2,5-thiadiazole 1,1-dioxide (**15**), a white solid, mp 307–308°, showing a molecular ion at *m/e* 176 in its mass spectrum. The corresponding bis(dimethylamino) derivative **16** could be prepared from **13** with excess dimethylamine in ether. The reaction of **12** with 1 mol of morpholine in methanol at 25° gave a white precipitate in which only one of the methoxy groups had been replaced to give 3-methoxy-4-morpholino-1,2,5-thiadiazole 1,1-dioxide (**17**). On rapid heating, a sample of **17** melted at ~205°, then crystallized and melted again at 260–261°, whereas slow heating gave only the higher melting point. The infrared, NMR, and mass spectra of the material obtained by melting **17** and recrystallizing the solid showed it to be 2-methyl-3-oxo-4-morpholino-1,2,5-thiadiazoline 1,1-dioxide (**18**). The mass spectra of both **17** and **18** gave molecular



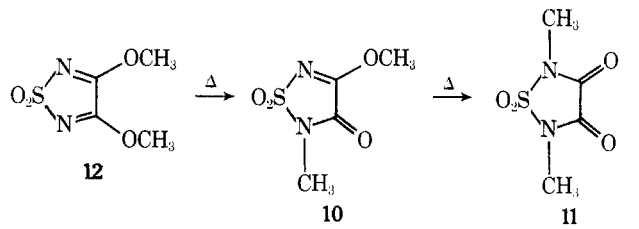
ions at *m/e* 233, although the fragmentation patterns differed considerably, suggesting that a rearrangement had taken place. The ir of **18** showed bands at 5.75 and 6.12 μm analogous to the bands at 5.7 and 6.15 μm for **10**, whereas **17** showed only a 6.2-μm band analogous to the 6.1-μm band for **12**. Thus the thermal rearrangement can be seen to involve a methyl shift from oxygen (**17**) to nitrogen (**18**). This is confirmed by the proton NMR spectra of **17** and **18**. The *O*-methyl of **17** appears at δ 4.18 (cf. the *O*-methyls of **10** and **12** at δ 4.24 and 4.18, respectively) and the *N*-methyl of **18** appears at δ 3.19 (cf. the *N*-methyls of **10** and **11** at δ 3.28 and 3.23, respectively).

An attempt to prepare the 3,4-dipiperidino derivative of **12** by refluxing a methanol solution of **12** and 2 mol of piperidine did not give the expected product, but rather 3-oxo-4-piperidino-1,2,5-thiadiazoline 1,1-dioxide (**19**) and *N*-methylpiperidine. Apparently the expected intermediate, 3-methoxy-4-piperidino-1,2,5-thiadiazole 1,1-dioxide (**20**), is attacked on the methoxy methyl group by the second equivalent of piperidine. The hydrogen of the *N*-methylpiperidinium ion is then transferred to yield **19** and *N*-methylpiperidine.

Precedent for these rearrangements is supplied by a similar thermal rearrangement of 2,4,6-trimethoxy-1,3,5-triazine (**21**) to the *N,N',N''*-trimethyl compound **22**. The isomerization of **21** has been shown to be an intermolecular reaction by isotope labeling, methyl trapping, and chemical methods.[13]

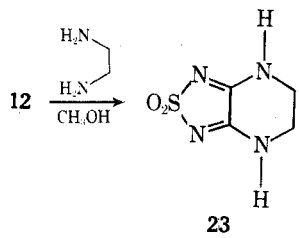


In view of the relative ease of methyl isomerization, dimethoxy compound **12** was reexamined and found to isomerize completely to **11** in less than 1 min above its melting point.[14] A mixture of all three isomers (**10**, **11**, and **12**) was



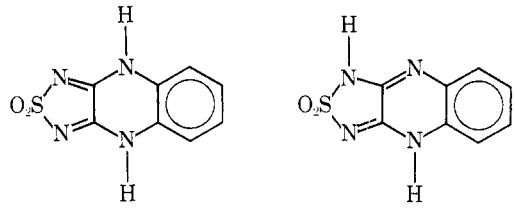
obtained by quickly melting and cooling a sample of **12**, showing that the isomerization proceeded via **10**. Evidently, the isomerization of **10** to **11** is rapid compared to the isomerization of **12** to **10**. Although Paoloni et al. could not isolate the two intermediates in the thermal isomerization of **21** to **22**, they did show that the second and third isomerizations of the intermediates occurred faster than the isomerization of **21** to the first intermediate.[13]

Formation of fused piperazine and pyrazine rings on the 1,2,5-thiadiazole 1,1-dioxide ring was readily accomplished by reaction of **12** with 1,2-diamines. Ethylenediamine in methanol reacted rapidly and quantitatively with **12** to give a precipitate of 4,5,6,7-tetrahydro[1,2,5]thiadiazolo[3,4-*b*]pyrazine 2,2-dioxide (**23**). Not unexpectedly, *o*-phenyl-

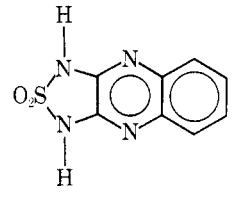


enediamine did not react readily with **12** in methanol; however, an equimolar solution of the reagents in DMF rapidly formed white crystals in a slightly exothermic reaction. The product was identified as 1,3-dihydro[1,2,5]thiadiazolo-[3,4-*b*]quinoxaline 2,2-dioxide (**24**) by its mass spectrum and analysis. Typical of a fused-ring heterocycle, the mass spectrum of **24** showed an intense molecular ion (*m/e* 222.0211, 100%) and a sparse fragmentation pattern (loss of SO_2 predominating, *m/e* 158.0592). Compound **24** would be expected to exist preferentially as tautomer **24c**, since **24c** contains the additional stabilizing factor of a quinoxaline ring.

The extremely weak basicity of the amino groups in compound **14** rendered direct condensation with the dimethoxy

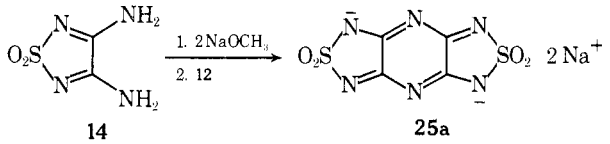


24a 24b



24c

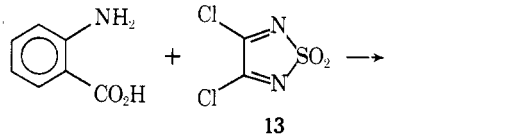
compound **12** unlikely. However, a solution of **14** in methanol containing 2 equiv of sodium methoxide reacted with **12** to give a bright yellow disodium salt, assigned a linear tricyclic structure for which **25a** would represent a preferred resonance-stabilized contributor having maximum separation of the two negative charges in a *p*-quinonoid arrangement. After the recrystallization of the sodium salt, the



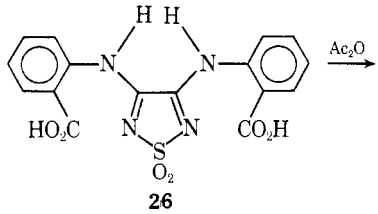
14 25a

NMR showed no protons, and an analysis indicated a C:H:N:S ratio of 2:0:3:1. When a concentrated aqueous solution of **25a** was acidified with dilute hydrochloric acid, a white, crystalline solid formed, mp >360°. A mass spectrum of the free compound (**25b**) showed a molecular ion, as predicted, at *m/e* 262 with volatilization at very high temperature.

Reaction of the dichloride **13** with excess anthranilic acid in hot acetone gave yellow needles of a product postulated to be diacid **26** in which each chlorine of **13** was replaced by an amino group of anthranilic acid. The diacid **26** was not characterized further, but rather dehydrated with acetic anhydride to **27**. Structural assignment of **27** was made on



13



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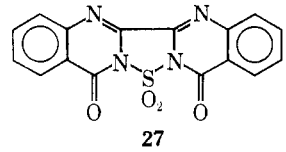

27

the basis of its chemical properties, analysis, and mass spectrum. In contrast to diacid **26**, which is soluble in dilute base, **27** is insoluble in base. Analysis showed a C:H:N ratio of 4:2:1 and a mass spectrum gave a molecular ion at *m/e* 352 (100%).

Experimental Section

General. Melting points (uncorrected) were determined in a Mel-Temp apparatus in open capillary tubes. Analyses were performed by Midwest Microlab, Indianapolis, Ind. Infrared spectra were recorded on a Perkin-Elmer 137 spectrometer. Ultraviolet spectra were recorded using a Cary 14 spectrometer. Low-resolution mass spectra (70 eV) were obtained on a Varian MAT CH-7 instrument using a heated probe. High-resolution mass spectra (70 eV) were obtained on an AEI MS-9 spectrometer. Proton NMR spectra were recorded on a Varian HR-220 instrument with internal Me_4Si as reference. The ^{13}C NMR spectra were acquired on a Varian XL-100 instrument in FT mode. Methanol and 2-propanol were distilled from calcium hydride prior to use.

Dipotassium Salt of 3,4-Dihydroxy-1,2,5-thiadiazole 1,1-Dioxide Monohydrate (4a). A potassium alkoxide solution was prepared by adding 58.7 g (1.50 mol) of potassium to 300 ml of 2-propanol and diluting the solution with 300 ml of methanol. After the solution had cooled, 72.0 g (0.75 mol) of sulfamide in 600 ml of methanol was added dropwise with vigorous mechanical stirring to give a white suspension. Diethyl oxalate (109.6 g, 0.75 mol) was added dropwide with stirring and the resulting suspension was refluxed gently for 16 hr with stirring. After cooling, the white solid was filtered, washed with methanol, and dried under high vacuum to give 158.0 g (93.0%) of anhydrous **4a**. The product was recrystallized from boiling water (2.5 ml/g): mp >360°, gas evolved above 185°; ir (KBr) 2.85, 3.00, 6.00, 6.09, 7.39, 8.01, 8.15, 8.85, 10.40, and 13.23 μm.

Anal. Calcd for $C_2K_2N_2O_4S\cdot H_2O$: C, 9.84; H, 0.83; N, 11.48; S, 13.12. Found: C, 9.75; H, 0.60; N, 11.43; S, 12.75.

Disodium Salt 4b. The above procedure was used starting with 1.0 mol of sulfamide to prepare the disodium salt **4b** in 97.5% yield except that only methanol was used to prepare the sodium methoxide. The salt was recrystallized from water and dried at 100° in vacuo: mp >360°, gas evolved above 185°; ^{13}C NMR (H_2O) 171.9 ppm (s).[15]

Anal. Calcd for $C_2Na_2N_2O_4S\cdot 2H_2O$: C, 10.44; H, 1.75. Found: C, 10.82; H, 1.79.

Repeated recrystallization of the disodium salt **4b** from saturated KCl gave dipotassium salt **4a** identical with **4a** prepared above.

Disilver Salt of 4 Monohydrate (4c). A solution of 15.0 g of silver nitrate in 100 ml of water was added dropwise to a stirred solution of **4a** (10.0 g, 41.0 mmol) in 300 ml of water at 90°. After the addition was complete, the mixture was boiled for 15 min and filtered hot. The white solid was washed with 200 ml of hot water and dried at 100° to give 14.8 g (94.5%) of **4c** containing a small amount of potassium by flame test, mp >360°. The product could not be recrystallized because of its insolubility and was therefore analyzed without purification.

Anal. Calcd for $C_2Ag_2N_2O_4S\cdot H_2O$: C, 6.29; H, 0.53; N, 7.34; S, 8.40. Found: C, 6.86, 6.70; H, 0.32, 0.24; N, 7.75; S, 8.27.

Method A. 3,4-Dihydroxy-1,2,5-thiadiazole 1,1-Dioxide Monohydrate (7). Cation Exchange in 4a. A solution of **4a** (3.00 g, 12.3 mmol) in 50 ml of water was passed through 40 ml (wet volume) of Amberlite IR-120H cation-exchange resin, and eluted with water to a pH of 6. The eluent was lyophilized to give 2.09 g of white solid, which on fractional crystallization from acetone–chloroform gave 0.555 g (26.9%) of **7** as colorless prisms: mp 159–161° dec; ir (KBr) 2.97, 3.02, 3.08, 5.67, 5.80, 7.48, and 8.75 μm. A potentiometric titration in water with NaOH gave pK_{a_1} 2.20 and pK_{a_2} 5.55.

Anal. Calcd for $C_2H_2N_2O_4S\cdot H_2O$: C, 14.29; H, 2.37; N, 16.67; S, 19.08. Found: C, 14.62; H, 2.25; N, 16.80; S, 18.88.

Concentration of the mother liquor gave 0.642 g (54.5%) of white crystals, mp 91–92°, identified as sulfamide by ir and mixture melting point with an authentic sample.

Method B. Reaction of 4c with Hydrogen Sulfide. Hydrogen sulfide was bubbled into a suspension of the disilver salt **4c** (5.00 g, 13.1 mmol) in 75 ml of THF. After 1 hr, the black silver sulfide was filtered off and the colorless filtrate was evaporated to dryness. Recrystallization from acetone–chloroform gave 0.755 g (34.3%) of **7**, mp 159–160°.

Method C. Hydrolysis of 13. Recrystallized **13** (695 mg, 3.70 mmol) was added to 15 ml of cold 6 *N* HCl with stirring. After the dichloro compound had dissolved, the solution was extracted with ether (2 × 20 ml). The combined ether extracts were dried and evaporated to a white residue, which, after two recrystallizations from ether–cyclohexane, gave 135 mg (21.7%) of **7**, mp 162–163°. The infrared spectra of **7** prepared by all three methods were identical.

Methylation of Disilver Salt 4c. A suspension of **4c** (5.00 g, 13.1 mmol) in 20 ml of redistilled methyl iodide and 100 ml of benzene was refluxed for 20 hr with good stirring. The yellow silver iodide was filtered from the hot solution and washed with 20 ml of hot chloroform. The combined filtrate was evaporated under vacuum to give 2.65 g of faint yellow solid. Fractional crystallization from chloroform–cyclohexane gave two white products. The major product, 831 mg (35.6%), was identified as 2-methyl-3-oxo-4-methoxy-1,2,5-thiadiazoline 1,1-dioxide (**10**): mp 179–180° (see text and ref 14); ir (KBr) 5.70, 6.15, 7.40, 7.52, 8.27, 8.50, 9.62, 10.90, and 14.25 μm; uv (ethanol) λ_{max} 218 nm (log ε 3.88); NMR ($CDCl_3$) δ 3.28 (s), 4.24 (s); mass spectrum *m/e* (rel intensity) 178 (41), 106 (11), 58 (100), 57 (40), 56 (30), 29 (13), and 28 (22).

Anal. Calcd for $C_4H_6N_2O_4S$: C, 26.98; H, 3.40; N, 15.71; S, 18.00. Found: C, 27.39; H, 3.48; N, 15.85; S, 17.83.

The minor product, 425 mg (18.2%), was identified as 2,5-dimethyl-3,4-dioxo-1,2,5-thiadiazolidine 1,1-dioxide (**11**): mp 118–120°; ir (KBr) 5.54, 5.70, 7.34, 7.85, 8.56, 9.50, 10.13, 10.78, and 11.65 μm; uv (ethanol) only end absorption; NMR ($CDCl_3$) δ 3.23 (s); mass spectrum *m/e* (rel intensity) 178 (28), 106 (6), 94 (11), 93 (9), 86 (10), 58 (100), 57 (53), 56 (55), 29 (28), and 28 (58).

Anal. Calcd for $C_4H_6N_2O_4S$: C, 26.98; H, 3.40; N, 15.71. Found: C, 27.13; H, 3.50; N, 16.03.

3,4-Dichloro-1,2,5-thiadiazole 1,1-Dioxide (13). An intimate mixture of **4a** (10.0 g, 41.0 mmol, recrystallized from water, dried at 80° for 4 hr, and finely powdered) and 43.0 g (0.206 mol) of powdered PCl_5 was heated at 55–60° in a flask with a short condenser and drying tube. Magnetic stirring was begun as soon as enough $POCl_3$ had formed. After 12 hr, the $POCl_3$ was evaporated off under vacuum at less than 40°. The dry solid was sublimed at 42–43° (0.3 mm) to give 5.85 g of colorless crystals. Recrystallization from cyclohexane yielded 3.34 g (43.5%) of **13** as needles: mp 103–104°; ir (Nujol) 6.30, 6.41, 7.19, 8.34, 8.73, 9.60, 12.64, 13.15, and 14.52 μm; mass spectrum *m/e* (rel intensity) 186 (2 ^{35}Cl, 1), 125 (1 Cl, 86), 90 (62), 87 (1 Cl, 24), 64 (99), 63 (60), 61 (1 Cl, 100), 52 (18), and 48 (67).

Exact Mass. Calcd for $C_2{}^{35}Cl_2N_2O_2S$: 185.9058. Found: 185.9062.

Anal. Calcd for $C_2Cl_2N_2O_2S$: C, 12.85; H, 0.00; Cl, 37.93. Found: C, 13.21; H, 0.20; Cl, 37.12.

Method A. 3,4-Dimethoxy-1,2,5-thiadiazole 1,1-Dioxide (12) and the Diethoxy Analog. From Recrystallized 13. A solution of 166 mg (0.887 mmol) of recrystallized **13** in 10 ml of anhydrous ether was added to 15 ml of methanol. The mixture was heated on a steam bath for 15 min and then refrigerated overnight to give 119 mg (75.5%) of **12** as colorless needles: mp 188–189° (methanol) (see text and ref 14); ir (KBr) 3.36, 6.10, 6.95, 7.18, 7.50, 7.70, 7.85, 8.44, 10.44, 11.00, and 13.40 μm; uv (ethanol) only end absorption.

Anal. Calcd for $C_4H_6N_2O_4S$: C, 26.96; H, 3.40; N, 15.72; S, 18.00. Found: C, 26.92; H, 3.45; N, 15.84; S, 18.29.

A similar experiment using ethanol in place of methanol gave 83% of the 3,4-diethoxy derivative as white plates from ethanol, mp 178–179.5° (see ref 14).

Anal. Calcd for $C_6H_{10}N_2O_4S$: C, 34.94; H, 4.89. Found: C, 34.71; H, 4.73.

Method B. From 4a via Crude 13. A mixture of 20.0 g (82.0 mmol) of **4a** and 60.0 g (0.288 mol) of PCl_5 was heated as described above. The mixture was filtered and washed with anhydrous ether (3 × 120 ml). The ether extract was added to 140 ml of methanol over 15 min (exothermic), and refluxed for 30 min. On cooling, the white, crystalline precipitate of **12** was collected. Additional crops were recovered by concentrating the mother liquor and cooling to give 7.80 g (53.4%) of **12**, which was recrystallized from methanol: mp 188–189° (see text and ref 14); NMR ($CDCl_3$) δ 4.18 (s); mass spectrum *m/e* (rel intensity) 178 (53), 147 (17), 121 (15), 114 (9), 106 (29), 105 (12), 95 (16), 90 (23), 85 (23), 84 (79), 79 (23), 72 (75), 69 (34), 64 (34), 58 (85), 57 (100), 56 (30), 48 (18), 44 (14), 42 (21), 41 (13), 31 (9), 30 (11), 29 (14), and 28 (27).

Exact Mass. Calcd for $C_4H_6N_2O_4S$: 178.0058. Found: 178.0061.

The infrared and mass spectra of **12** prepared by both methods were identical.

3,4-Diamino-1,2,5-thiadiazole 1,1-Dioxide (14). Method A. Reaction of 12 with Ammonia. An ice-cooled solution of **12** (14.6 g, 82.0 mmol) in 1.2 l. of methanol was bubbled with ammonia for 1 hr. The ice bath was removed and ammonia was bubbled into the solution for an additional 1 hr. Much of the methanol was removed on a rotary evaporator, and, after cooling, the product was filtered. Further concentration and cooling gave a nearly quantitative yield of **14**: mp 284–286° dec; uv (ethanol) λ_{max} 240 nm (log ε 3.93); ir (KBr) 2.92, 3.10, 5.90, 5.97, 6.18, 7.36, 7.70, 7.82, 8.60, 11.25, and 13.80 μm.

Anal. Calcd for $C_2H_4N_4O_2S$: C, 16.21; H, 2.72; N, 37.82. Found: C, 16.15; H, 2.90; N, 37.95.

A similar replacement by ammonia on the 3,4-diethoxy analog of **12** in ethanol gave an identical product.

Method B. Reaction of 13 with Ammonia. A solution of **13** (3.50 g, 18.7 mmol) in 50 ml of anhydrous ether was added dropwise to 5 ml of liquid ammonia at −78°. The mixture was allowed to warm to room temperature and evaporated to dryness under vacuum. The light yellow solid was extracted with THF for 36 hr in a Soxhlet apparatus. The product was filtered from the THF and recrystallized from DMF–chloroform to give 1.14 g (41.2%) of **14**: mp 286–288° dec; ir (KBr) identical with that of **14** prepared from **12**.

3,4-Bis(dimethylamino)-1,2,5-thiadiazole 1,1-Dioxide (16). A solution of **13** (387 mg, 2.07 mmol) in 10 ml of anhydrous ether was added dropwise to a solution of 2 ml of dimethylamine in 20 ml of anhydrous ether. The dimethylamine and ether were evaporated to give a yellow solid which was extracted repeatedly with 10-ml portions of hot acetone. The combined extracts were treated with carbon and filtered. The product was crystallized by addition of hexane to give 158 mg (37.5%) of **16** as colorless crystals: mp 183–185°; uv (ethanol) λ_{max} 280 nm (log ε 3.93); ir (KBr) 3.35, 6.23, 7.14, 7.72, 8.10, 8.73, 9.40, 10.55, 12.06, 13.04, and 14.10 μm.

Anal. Calcd for $C_6H_{12}N_4O_2S$: C, 35.27; H, 5.92; N, 27.43. Found: C, 35.42; H, 5.91; N, 27.44.

3,4-Bis(methylamino)-1,2,5-thiadiazole 1,1-Dioxide (15). A solution of **12** (1.78 g, 10.0 mmol) in 250 ml of methanol was cooled on ice while methylamine was bubbled in for 30 min. The ice bath was removed and the mixture was stirred for 1 hr. The solution was evaporated to dryness and the white product was recrystallized from acetone to give a nearly quantitative yield of **15**: mp 307–308° slow dec; ir (KBr) 3.15, 6.10, 6.40, 7.05, 7.40, 7.82, 8.70, 10.90, and 13.10 μm; mass spectrum *m/e* (rel intensity) 176 (26), 84 (29), 57 (100), 56 (73), 55 (63), 28 (21).

Exact Mass. Calcd for $C_4H_8N_4O_2S$: 176.0368. Found: 176.0368.

Anal. Calcd for $C_4H_8N_4O_2S$: C, 27.26; H, 4.58. Found: C, 27.53; H, 4.82.

3-Methoxy-4-morpholino-1,2,5-thiadiazole 1,1-Dioxide (17). Morpholine (470 mg, 5.40 mmol) in 10 ml of methanol was added at room temperature to a solution of **12** (890 mg, 5.00 mmol) in 100 ml of methanol. A white solid soon precipitated. After 3 hr, the product was filtered, washed with 50 ml of methanol, and dried under high vacuum to give 1.03 g (88.5%) of **17**: mp ~205° and 260–261° (see text); ir (KBr) 6.20, 6.96, 7.60, 7.90, 8.65, 9.00, 9.58, 10.25, 10.83, 11.05, 11.57, 12.42, and 13.85 μm; mass spectrum *m/e* (rel intensity) 233 (41), 218 (52), 176 (30), 168 (18), 154 (44), 139 (18), 112 (23), 86 (49), 85 (19), 58 (40), 57 (20), 56 (100), 55 (61), 54 (41), 53 (15), 42 (89), 29 (20), 28 (92), 27 (22), and 15 (42); NMR ($CDCl_3$) δ 3.76 (t, 2 H, *J* = 5 Hz), 3.81 (s, 4 H), 4.02 (t, 2 H, *J* = 5 Hz), 4.18 (s, 3 H).

Exact Mass. Calcd: 233.0470. Found: 233.0474.

Anal. Calcd for $C_7H_{11}N_3O_4S$: C, 36.04; H, 4.75. Found: C, 35.94; H, 4.71.

2-Methyl-3-oxo-4-morpholino-1,2,5-thiadiazoline 1,1-Dioxide (18). Recrystallized (methanol) **17** (ca. 150 mg) was placed in a small test tube and warmed over a small flame until completely melted. After cooling, the white solid was recrystallized from methanol to give **18**: mp 260–261°; ir (KBr) 5.75, 6.12, 6.98, 7.35, 7.50, 7.65, 7.80, 8.20, 8.40, 8.93, 9.30, 9.72, 9.90, 10.23, 10.83, 11.10, 11.55, and 12.26 μm; mass spectrum *m/e* (rel intensity) 233 (42), 169 (33), 139 (15), 126 (14), 85 (52), 57 (12), 56 (27), 55 (100), 54 (24), 42 (58), and 28 (56); NMR ($CDCl_3$) δ 3.19 (s, 3 H), 3.78 (t, 2 H, *J* = 5 Hz), 3.82 (s, 4 H), 4.45 (t, 2 H, *J* = 5 Hz).

Exact Mass. Calcd: 233.0470. Found: 233.0474.

Anal. Calcd for $C_7H_{11}N_3O_4S$: C, 36.04; H, 4.75. Found: C, 35.61; H, 4.72.

3-Oxo-4-piperidino-1,2,5-thiadiazoline 1,1-Dioxide (19). Piperidine (410 μl, 4.15 mmol) in 2 ml of methanol was added to dimethoxy compound **12** (356 mg, 2.00 mmol) dissolved in 40 ml of methanol. After refluxing for 45 min, the methanol was removed by distillation through a 6-in. helices-packed column. The remaining oil was distilled to give a drop of *N*-methylpiperidine, identified by comparison of its mass spectrum with literature data:[16,17] mass spectrum *m/e* (rel intensity) 99 (33), 98 (100), 84 (14), 71 (8), 70 (19), 58 (12), 57 (11), 56 (6), 55 (7), 44 (12), 43 (46), 42 (29), 41 (8), and 39 (7); at ~18 eV, 99 (100). The residue was precipitated twice from methylene chloride with hexane to give **19** as a pale yellow oil: ir (KBr) 3.50, 6.00, 6.25, 7.98, 8.76, 10.13, 11.69, and 12.34 μm; mass spectrum *m/e* (rel intensity) 217 (11), 153 (19), 109 (8), 84 (17), 83 (100), 69 (10), 57 (9), 56 (12), 55 (55), 54 (12), and 53 (8).

Isomerization of 12 to 10. Recrystallized **12** (ca. 180 mg) was placed in a small test tube and immersed in an oil bath at 200°. After all the solid had melted, heating was continued for an additional 60 sec. The melt was cooled and scratched to induce crystallization. An infrared spectrum (KBr) showed only **10**, which after recrystallization from chloroform–cyclohexane was identical with **10** prepared by the methylation of **4c**.

Another sample of **12** was heated in an oil bath at 190° until melted and immediately cooled on ice. An infrared spectrum of the solid showed characteristic bands for each of the three methyl isomers, **10**, **11**, and **12**.

4,5,6,7-Tetrahydro[1,2,5]thiadiazolo[3,4-*b*]pyrazine 2,2-Dioxide (23). A solution of ethylenediamine (680 μl, 10.0 mmol) in 10 ml of methanol was added to a solution of **12** (1.78 g, 10.0 mmol) in 200 ml of methanol. Almost immediately a white solid began to precipitate. After the mixture had been stirred for 30 min, the solid was filtered, washed with 50 ml of methanol, and dried under high vacuum to give 1.74 g (100%) of **23**: mp >360°; ir (KBr) 6.13, 7.20, 7.74, 8.70, and 10.80 μm.

Anal. Calcd for $C_4H_6N_4O_2S$: C, 27.58; H, 3.47. Found: C, 26.92; H, 4.02.

1,3-Dihydro[1,2,5]thiadiazolo[3,4-*b*]quinoxaline 2,2-Dioxide (24). Freshly purified *o*-phenylenediamine (540 mg, 5.00 mmol) and recrystallized **12** (890 mg, 5.00 mmol) were dissolved in 5 ml of DMF. The light yellow solution warmed slightly and within 5 min crystalline **24** began to precipitate. After standing at room temperature for 3 hr, the crystals were collected and vacuum dried to give 675 mg of **24**. An additional 407 mg (total 97.5%) was obtained by concentrating the mother liquor under vacuum, filtering the solid, washing with 5 ml of acetone, and vacuum drying. The product was soluble in dilute sodium hydroxide and could be precipitated by adding dilute hydrochloric acid. An analytical sample was recrystallized from DMF: mp >360° (some darkening); ir (KBr) 3.26, 6.02, 6.27, 6.71, 7.20, 7.70, 8.61, 10.72, 11.96, and 13.24 μm; mass spectrum *m/e* (rel intensity) 222 (100), 158 (90), 131 (18), 105 (41), 104 (31), 90 (16), 78 (17), 77 (17), 64 (11), 53 (10), 52 (14), and 51 (14).

Exact Mass. Calcd for $C_8H_6N_4O_2S$: 222.0211. Found: 222.0211. Calcd for $C_8H_6N_4$ ($M^+ - SO_2$): 158.0592. Found: 158.0592.

Anal. Calcd for $C_8H_6N_4O_2S$: C, 43.24; H, 2.72. Found: C, 43.22; H, 2.83.

25a. A sodium methoxide solution was prepared from 276 mg (12.0 mmol) of sodium and 300 ml of methanol. After cooling, **14** (888 mg, 6.00 mmol) was added and stirred until dissolved. Dimethoxy compound **12** (1.068 g, 6.00 mmol) was added and the mixture was allowed to stir for 12 hr at room temperature. The bright yellow salt was filtered and dried to give 1.39 g (75.8%) of **25a**. Additional material of lesser purity was obtained by concentrating the mother liquor. After recrystallization from methanol, **25a** showed mp >360°; NMR [D_2O–TMSP (sodium 3-(trimethylsilyl)propanesulfonate)] no protons; ir (KBr) 6.54, 7.18, 7.70, 8.68, 8.91, 10.20, 11.43, 12.43, and 13.32 μm.

Anal. Calcd for $C_4Na_2N_6O_4S_2$: C, 15.69; H, 0.00. Found: C, 15.78; H, 0.00.

25b. The parent acid of disodium salt **25a** (**25b**) was prepared by acidifying a concentrated aqueous solution of **25a** with 5 *N* HCl and filtering the crystals after 4 hr: mp >360° (darkening); mass spectrum *m/e* 262 (100%).

26 and 27. An acetone solution (20 ml) of **13** (187 mg, 1.00 mmol) and anthranilic acid (550 mg, 4.00 mmol) was refluxed for 30 min to give 514 mg of yellow solid. The solid was dissolved in dilute NH_4OH and after neutralization to pH 6 with HCl, 280 mg of **26** crystallized as fine yellow needles, mp 340–350° dec. Compound **26** was dehydrated by refluxing in 10 ml of acetic anhydride for 15 min. The pale yellow crystalline precipitate was filtered off and dried to give 152 mg of **27**. An analytical sample was recrystallized twice from DMF–water: mp 351–353° (sealed tube); ir (KBr) 5.78, 6.12, 6.28, 6.83, 7.09, 7.50, 7.77, 8.13, 8.34, 8.63, 9.24, 12.40, 12.83, 13.00, 13.46, and 14.50 μm; mass spectrum *m/e* 352 (100%).

Anal. Calcd for $C_{16}H_8N_4O_4S$: C, 54.55; H, 2.29; N, 15.91. Found: C, 54.36; H, 2.41; N, 15.61.

Registry No.—**4a**, 35036-06-7; **4b**, 55904-78-4; **4c**, 55904-79-5; **7**, 55904-80-8; **10**, 55904-81-9; **11**, 55904-82-0; **12**, 55904-83-1; **12** diethoxy analog, 55904-84-2; **13**, 55904-85-3; **14**, 55904-35-3; **15**, 55904-86-4; **16**, 55904-87-5; **17**, 55904-86-6; **18**, 55904-89-7; **19**, 55904-90-0; **23**, 55904-91-1; **24**, 55904-92-2; **25a**, 55925-85-4; **25b**, 55904-93-3; **26**, 55904-94-4; **27**, 55904-95-5; sulfamide, 7803-58-9; diethyl oxalate, 95-92-1.

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