NMR ($CDCl_3/Me_4Si$, 250 MHz) δ 1.54 (d, 3 H, J = 7 Hz), 2.26 (s, 3 H), 4.98 (d, 1 H), 5.12 (t, 1 H), 5.43 (t, 1 H), 6.17 (d, 1 H, aromatic), 5.00 (m, 1 H), 7.17 (5 H, aromatic), 7.57 (d, 1 H, NH), 8.02 (s, 1 H, imine), 10.12 (s, 1 H, NH): $[\alpha]_D$ +1013° (c 0.76, $CHCl_3$). Anal. Calcd for $C_{21}H_{19}CrN_3O_5$: C, 56.63; H, 4.30. Found: C, 56.80; H, 4.39.

Diastereomer II (**7a-II**): mp 166–168 °C; R_f 0.46 (EE/PE 90:10); IR ($CHCl_3$) and NMR ($CDCl_3/Me_4Si$) are identical with those of diastereomer **7a-I**; $[\alpha]_D$ −1195° (c 0.69, $CHCl_3$).

Semioxamazone 7b: yield, 90%; chromatography solvent, diethyl ether.

Diastereomer I (**7b-I**): mp > 190 °C dec; R_f 0.75 (ether); IR ($CHCl_3$) ν_{NH} 3380, 3300, $\nu_{C\equiv O}$ 1975, 1905, ν_{amide} 1680 cm^{-1}; ^1H NMR ($CDCl_3/Me_4Si$, 250 MHz) δ 1.60 (d, 3 H, $J \simeq 7$ Hz), 3.81 (s, 3 H), 4.98 (t, 1 H, aromatic), 5.09 (d, 1 H, aromatic), 5.12 (m, 1 H), 5.70 (t, 1 H, aromatic), 6.54 (d, 1 H, aromatic), 7.35 (s, 5 H aromatic), 7.78 (br d, 1 H, NH), 8.28 (s, 1 H), 10.4 (s, 1 H, NH); $[\alpha]_D$ +986° (c 0.07, $CHCl_3$). Anal. Calcd for $C_{21}H_{19}CrN_3O_6$: C, 54.66; H, 4.12; N, 9.11. Found: C, 54.86; H, 4.35; N, 9.30.

Diastereomer II (**7b-II**): mp 99–101 °C; R_f 0.57 (ether); IR ($CHCl_3$) and NMR ($CDCl_3/Me_4Si$) are identical with those of diastereomer **7b-I**; $[\alpha]_D$ −959° (c 0.07, $CHCl_3$).

Semioxamazone 7c: yield, 70%; chromatography solvent, diethyl ether.

Diastereomer II (**7c-I**): mp 96–98 °C; R_f 0.72 (ether); IR ($CHCl_3$) ν_{NH} 3380, 3310, $\nu_{C\equiv O}$ 1970, 1900, ν_{amide} 1680 cm^{-1}; ^1H NMR ($CDCl_3/Me_4Si$, 250 MHz) δ 1.50 (d, 3 H), 3.75 (s, 3 H), 3.85 (s, 3 H), 5.20 (m, 1 H, also 2 H aromatic) 5.75 (d, 1 H, aromatic), 7.25 (s, 5 H, aromatic), 7.65 (d, 1 H, NH), 8.30 (s, 1 H), 10.45 (br s, 1 H, NH): $[\alpha]_D$ +556° (c 0.06, $CHCl_3$). Anal. Calcd for $C_{22}H_{21}CrN_3O_7$: C, 53.77; H, 4.28; N, 8.55. Found: C, 53.67; H, 4.31; N, 8.55.

Diastereomer II (**7c-II**): mp 118–120 °C; R_f 0.57 (ether); IR ($CHCl_3$) and ^1H NMR ($CDCl_3/Me_4Si$) are identical with those of diastereomer **7c-I**; $[\alpha]_D$ −415° (c 0.05, $CHCl_3$).

Semioxamazone 7d: yield, 70%; chromatography solvent, diethyl ether.

Diastereomer I (**7d-I**): mp 108–110 °C; R_f 0.59 (ether); IR ($CHCl_3$) ν_{NH} 3380, 3300, $\nu_{C\equiv O}$ 1970, 1895, ν_{amide} 1680 cm^{-1}; ^1H NMR ($CDCl_3/Me_4Si$, 250 MHz) δ 1.60 (d, 3 H), 3.75 (s, 6 H), 5.00 (m, 1 H), 5.15 (s, 2 H, aromatic), 5.90 (s, 1 H, aromatic), 7.20 (s, 5 H, aromatic), 7.75 (br, 1 H, NH), 7.80 (s, 1 H), 10.90 (br s, 1 H NH); $[\alpha]_D$ +450 (c 0.09, $CHCl_3$). Anal. Calcd for $C_{22}H_{21}CrN_3O_7$: C, 53.77; H, 4.28; N, 8.55. Found: C, 53.85; H, 4.38; N, 8.59.

Diastereomer II (**7d-II**): mp 105–107 °C; R_f 0.39 (ether); IR ($CHCl_3$) and ^1H NMR ($CDCl_3/Me_4Si$) are identical with those of diastereomer **7d-I**; $[\alpha]_D$ −479° (c 0.10, $CHCl_3$).

Optically Active Complexes. 3a: mp 99–100 °C; R_f 0.95 (ether/hexane 9:1); IR ($CHCl_3$) ν_{CHO} 2860, 2720 (vw), $\nu_{C\equiv O}$ 1970, 1895, ν_{CO} 1680 cm^{-1}; ^1H NMR ($CDCl_3/Me_4Si$) δ 2.45 (s, 3 H), 4.95 (d, 1 H, aromatic), 5.12 (t, 1 H, aromatic), 5.62 (t, 1 H, aromatic), 5.95 (d, 1 H aromatic), 9.72 (s, 1 H); from **7a-I**, $[\alpha]_D$ +665° (c 0.22, $CHCl_3$); from **7a-II**, $[\alpha]_D$ −664° (c 0.26, $CHCl_3$) (lit.[3] $[\alpha]_D$ −660°).

3b: mp 98–99 °C; R_f 0.89 (ether); IR ($CHCl_3$) ν_{OMe} and ν_{CHO} 2840, 2810 (w), $\nu_{C\equiv O}$ 1975, 1900, ν_{CO} 1675 cm^{-1}; ^1H NMR ($CDCl_3/Me_4Si$) δ 3.80 (s, 3 H), 4.95 (t, 1 H, aromatic), 5.0 (d, 1 H, aromatic), 5.75 (t, 1 H, aromatic), 6.15 (d, 1 H, aromatic), 10.1 (s, 1 H); from **7b-I**, $[\alpha]_D$ +1015° (c 0.06, $CHCl_3$); from **7b-II**, $[\alpha]_D$ −1020° (c 0.09, $CHCl_3$) (lit.[8] $[\alpha]_D$ −1000°).

3c: mp 59–61 °C; R_f 0.94 (ether); IR ($CHCl_3$); ν_{OMe} ν_{CHO} 2860, 2820 (w), $\nu_{C\equiv O}$ 1975, 1900, ν_{CO} 1680 cm^{-1}; ^1H NMR ($CDCl_3/Me_4Si$) δ 3.75 (s, 3 H), 3.95 (s, 3 H), 5.10 (t, 1 H, aromatic), 5.45 (d, 1 H aromatic), 5.60 (d, 1 H aromatic), 10.05 (s, 1 H); from **7c-I**, $[\alpha]_D$ +360° (c 0.12, $CHCl_3$); from **7c-II**, $[\alpha]_D$ −387° (c 0.19, $CHCl_3$).

3d: mp 83–85 °C; R_f 0.93 (ether); IR ($CHCl_3$) ν_{OMe} 2810, ν_{CHO} 2810, 2720 (vw), $\nu_{C\equiv O}$ 1970, 1885, ν_{CO} 1675 cm^{-1}; ^1H NMR ($CDCl_3/Me_4Si$) δ 3.75 (s, 3 H), 3.80 (s, 3 H), 5.15 (d, 1 H, aromatic), 5.55 (d, 1 H, aromatic), 5.85 (s, 1 H, aromatic), 9.30 (s, 1 H); from **7d-I**, $[\alpha]_D$ +793° (c 0.60, $CHCl_3$); from **7d-II**, $[\alpha]_D$ −818° (c 0.77, $CHCl_3$).

Acknowledgment. We thank Dr. D. Picken (laboratory of Professor G. Ourisson) for translating our manuscript.

(8) R. Dabard and G. Jaouen, *Tetrahedron Lett.*, 3391 (1969).

Registry No. (±)-**3a**, 32734-21-7; (+)-**3a**, 33152-66-8; (−)-**3a**, 33152-65-7; (±)-**3b**, 12181-92-9; (+)-**3b**, 36249-94-2; (−)-**3b**, 71327-35-0; (±)-**3c**, 71243-02-2; (+)-**3c**, 71243-03-3; (−)-**3c**, 71243-04-4; (±)-**3d**, 71243-05-5; (+)-**3d**, 71243-06-6; (−)-**3d**, 71243-07-7; **6**, 6152-25-6; **7a**, 71243-08-8; **7a-I**, 71276-52-3; **7a-II**, 71276-53-4; **7b**, 71250-01-6; **7b-I**, 71300-53-3; **7b-II**, 71300-54-4; **7c**, 71250-02-7; **7c-I**, 71300-55-5; **7c-II**, 71300-56-6; **7d**, 71250-03-8; **7d-I**, 71300-57-7; **7d-II**, 71300-58-8; 2-methylbenzaldehyde, 529-20-4; 2-methoxybenzaldehyde, 135-02-4; 2,3-dimethoxybenzaldehyde, 86-51-1; 3,4-dimethoxybenzaldehyde, 120-14-9; 1,2-ethanediol, 107-21-1; 2-methylbenzaldehyde cyclic ethylene acetal, 64380-54-7; 2-methoxybenzaldehyde cyclic ethylene acetal, 4420-21-7; 2,3-dimethoxybenzaldehyde cyclic ethylene acetal, 71242-97-2; 3,4-dimethoxybenzaldehyde cyclic ethylene acetal, 71242-98-3; chromium carbonyl ($Cr(CO)_6$), 13007-92-6; 2-methylbenzaldehyde cyclic ethylene acetal chromium complex, 71250-04-9; 2-methoxybenzaldehyde cyclic ethylene acetal chromium complex, 71250-05-0; 2,3-dimethoxybenzaldehyde cyclic ethylene acetal chromium complex, 71276-89-6; 3,4-dimethoxybenzaldehyde cyclic ethylene acetal chromium complex, 71250-06-1.

Synthesis of 1,2,6-Thiadiazine 1,1-Dioxides via Isoxazolylsulfamides

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Received June 28, 1979

A variety of synthetic procedures have been devised for the synthesis of 1,2,6-thiadiazine 1,1-dioxides.[1] The logical extension of direct methods by which 2-pyrimidones are prepared, with the substitution of sulfamide for urea, provides the rationale for much of this work. However, although the analogy to the 2-pyrimidones has been recognized,[2] the analogues **3a** and **7a** of cytosine and thymine, respectively, in which the 2-carbonyl is replaced by the bioisosteric[3] SO_2 linkage have heretofore not been reported. The published procedures, while providing synthetic access to 1,2,6-thiadiazine 1,1-dioxides with a limited variety of substitution patterns, are not sufficiently general to be successfully adapted to the preparations of **3a** and **7a**. This paper describes the synthesis of these and related compounds by a new general method through the intermediacy of isoxazolylsulfamides.

Cytosine analogue **3a** was prepared according to Scheme I. Reaction of 3-isoxazolamine[4] (**1a**) with sulfamoyl chloride and triethylamine in benzene gave sulfamide **2a**, which was then hydrogenated in methanol, with Raney nickel catalyst, in the presence of sodium methoxide. Hydrogenolysis of the isoxazole nucleus was accompanied by spontaneous ring closure to give **3a**. Compatible spectral data are summarized in the Experimental Section; in addition, a single-crystal X-ray analysis confirmed the structure (Figure 1).

Crystals of **3a** are monoclinic, space group $P2_1/a$, with a = 15.845 (3), b = 5.313 (1), and c = 7.252 (1) Å and β =

(1) (a) Lawson, A.; Tinkler, R. B. *Chem. Rev.* **1970**, *70*, 593 and references therein. (b) Die, R.; Diez, J.; Garcia-Muñoz, G.; Madoñero, R.; Stud, M., *J. Heterocycl. Chem.* **1972**, *9*, 973. (c) Diez, J.; Garcia-Muñoz, G.; Madoñero, R.; Stud, M. *Ibid.* **1973**, *10*, 469. (d) Garcia-Muñoz, G.; Ochoa, C.; Stud, M.; Pfleiderer, W. *Ibid.* **1977**, *14*, 431. (e) Garcia-Muñoz, G.; Ochoa, C.; Stud, M. *Ibid.* **1976**, *13*, 793. (f) Ochoa, C.; Stud, M. *Ibid.* **1978**, *15*, 221. (g) Goya, P.; Stud, M. *Ibid.* **1978**, *15*, 253.

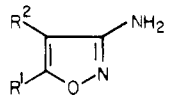
(2) Pagani, G. A. *J. Chem. Soc., Perkin Trans. 1* **1974**, 2050.

(3) Burger, A. In "Medicinal Chemistry", 3rd ed; Burger, A., Ed.; Wiley-Interscience: New York, **1970**; pp 72–8.

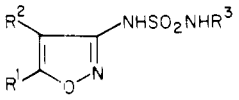
(4) Klötzer, W.; Bretschneider, H.; Fitz, E.; Reiner, R.; Bader, B. *Monatsh. Chem.* **1970**, *101*, 1109.

0022-3263/79/1944-4191$01.00/0

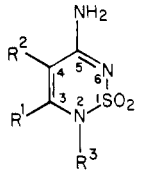
Scheme I



1a, R^1 = H; R^2 = H
b, R^1 = Me; R^2 = H



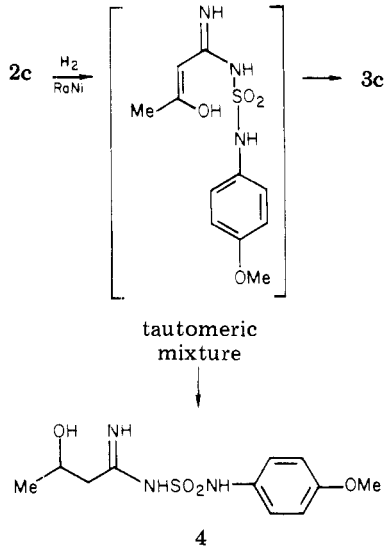
2a, R^1 = H; R^2 = H; R^3 = H
b, R^1 = Me; R^2 = H; R^3 = Et
c, R^1 = Me; R^2 = H; R^3 = 4-$MeOC_6H_4$



3a, R^1 = H; R^2 = H; R^3 = H
b, R^1 = Me; R^2 = H; R^3 = Et
c, R^1 = Me; R^2 = H; R^3 = 4-$MeOC_6H_4$

103.04 (1)°. A total of 1105 accessible reflections were measured for $\theta < 70°$ (Ni filtered Cu Kα radiation), of which 1021 were considered to be observed. The data were corrected for absorption (μ = 41.4 cm^{-1}). All five hydrogen atoms were found on a difference map calculated after anisotropic refinement of the heavier atoms. The structure was refined by full-matrix least-squares methods to R = 0.048 and R_w = 0.071 (heavier atoms anisotropic, hydrogens isotropic and not refined).

The substitution pattern of the thiadiazine product can be tailored by appropriate choice of starting materials. Intermediate sulfamides are prepared generally by reaction of 3-isoxazolamines with N-substituted sulfamoyl chlorides or azides. For example, the reaction of **1b** with ethylsulfamoyl chloride gave **2b**, which on hydrogenation yielded **3b**. Similarly, the reaction of **1b** with (4-methoxyphenyl)sulfamoyl azide gave **2c**, which yielded **3c** on hydrogenation. This latter reaction illustrates the necessity for hydrogenating in the presence of base. When sodium methoxide is omitted from the reaction mixture, uptake of 2 mol of hydrogen occurs with formation of 4.



tautomeric mixture

4

Thymine analogue **7a** was prepared according to Scheme II. The reaction of 4-methyl-5-isoxazolamine (**5a**) with sulfamoyl chloride and triethylamine in methylene chloride

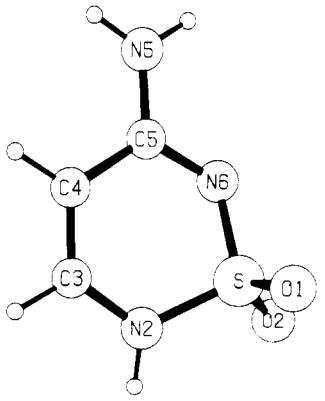
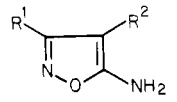
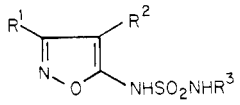


Figure 1. Perspective drawing of a molecule of **3a**. The six carbon and nitrogen atoms are nearly coplanar (rms deviation 0.03 Å). The sulfur atom is 0.4 Å out of this plane.

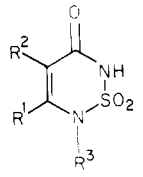
Scheme II



5a, R^1 = H; R^2 = Me
b, R^1 = Me; R^2 = H



6a, R^1 = H; R^2 = Me; R^3 = H
b, R^1 = Me; R^2 = H; R^3 = Et
c, R^1 = Me; R^2 = H; R^3 = 4-$MeOC_6H_4$



7a, R^1 = H; R^2 = Me; R^3 = H
b, R^1 = Me; R^2 = H; R^3 = Et
c, R^1 = Me; R^2 = H; R^3 = 4-$MeOC_6H_4$

gave **6a** in rather poor yield due to formation of 2-cyanopropanamide as a major byproduct. Being unsubstituted in the 3-position, **5a** readily underwent ring opening to the nitrile and proved quite vulnerable to acid. The stability of the isoxazole nucleus was markedly enhanced by incorporation into the sulfamide **6a**. Hydrogenation of **6a** in DMF over Raney nickel followed by heating at 100 °C gave **7a**.

Again, the substitution pattern of the product can be varied according to the choice of starting materials. The reaction of **5b** with ethylsulfamoyl chloride gave **6b**, which on hydrogenation yielded **7b**. In a similar sequence, reaction of **5b** with (4-methoxyphenyl)sulfamoyl azide gave **6c**, which was hydrogenated to yield **7c**. The hydrogenation product in these reactions did not spontaneously cyclize, but the ring closure was readily accomplished by heating. After hydrogenation, evaporation of the DMF under reduced pressure with heating on a steam bath was sufficient to yield the thiadiazines.

Experimental Section

General. Melting points were determined in a Thomas-Hoover apparatus and are uncorrected. Proton NMR spectra were recorded at 60 MHz on a JEOL C60H spectrometer or at 100 MHz on a Varian HA-100 spectrometer. Chemical shifts are reported as δ (parts per million) relative to tetramethylsilane as internal

standard, with the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. IR spectra were recorded on a Digilab FTS-14 or a Perkin-Elmer 621 spectrophotometer. UV spectra were determined on a Cary-14 recording spectrophotometer. Mass spectra were recorded on a Varian MAT CH5 spectrometer with a Varian 620i computer for data acquisition. Elemental and spectral analyses and the X-ray structure determination were carried out by the Physical Chemistry Department, Hoffmann-La Roche Inc. All hydrogenations were carried out in a Parr apparatus at an initial gauge pressure of 50 psi, by using Raney nickel catalyst which had been prewashed with the specified solvent, and were complete within 1 h.

3-Isoxazolylsulfamide (2a). 3-Isoxazolamine[4] (12.6 g, 0.15 mol) was added dropwise to a solution of 17.4 g (0.15 mol) of sulfamoyl chloride[5] in 150 mL of benzene at 5 °C. The mixture, containing a gummy precipitate, was allowed to warm to 15 °C during 15 min. With the mixture cooled in ice, 15.2 g (0.15 mol) of triethylamine was then added at 5–10 °C. The mixture was allowed to warm spontaneously and reached a maximum of 30 °C after 1 h. Aqueous 5 N sodium hydroxide (60 mL) was then added, with cooling to maintain the reaction at 15–20 °C. The aqueous phase was filtered, chilled in ice, and acidified with concentrated hydrochloric acid. Crystals of **2a** separated rapidly: 14.0 g (57%), mp 131–133 °C. The analytical sample was recrystallized from ethanol: NMR (Me_2SO-d_6) δ 6.53 (s, 1 H), 7.41 (s, 2 H), 8.62 (s, 1 H), 10.52 (s, 1 H); IR (KBr) 3370, 3290, 1323, 1154 cm^{-1}; UV max (2-propanol) 207 nm (ϵ 4880).

Anal. Calcd for $C_3H_5N_3O_3S$: C, 22.06; H, 3.09; N, 25.76. Found: C, 22.21; H, 3.03; N, 25.59.

5-Amino-2*H*-1,2,6-thiadiazine 1,1-Dioxide (3a). A solution of 12.2 g (0.075 mol) of **2a** and 4.46 g (0.083 mol) of sodium methoxide in 225 mL of methanol was hydrogenated over Raney nickel catalyst. After filtration of the catalyst, the solvent was evaporated under reduced pressure. The residue was dissolved in 20 mL of water and the solution filtered, cooled in ice, and acidified with concentrated hydrochloric acid. Crystallization occurred to yield **3a**: 8.33 g (77%), mp 179–181 °C. The analytical sample was crystallized from ethanol: mp 182–183 °C; NMR (Me_2SO-d_6) δ 5.25 (d, J = 8 Hz, 1 H), 7.12 (d, J = 8 Hz, 1 H), 7.32 (s, 2 H), 10.8 (br s, 1 H); on addition of D_2O, the three hydrogens on nitrogen (δ 7.32, 10.8) exchanged immediately; over a period of about 10 min, the hydrogen at position 4 of the ring (δ 5.25) exchanged, and the doublet at δ 7.12 due to the hydrogen at position 3 collapsed to a singlet; IR (KBr) 3410, 3340, 3270, 3220, 1662, 1290, 1130 cm^{-1}; UV max (pH 7) 224 nm (ϵ 4820), 300 (9050); pK_a = 5.24 ± 0.05;[6] mass spectrum, m/e 147 (M^+).

Anal. Calcd for $C_3H_5N_3O_2S$: C, 24.49; H, 3.43; N, 28.56. Found: C, 24.46; H, 3.47; N, 28.42.

***N*-Ethyl-*N'*-(5-methyl-3-isoxazolyl)sulfamide (2b).** A solution of 18.3 g (0.187 mol) of **1b** and 18.9 g (0.187 mol) of triethylamine in 190 mL of acetonitrile was stirred with cooling in ice, and 26.8 g (0.187 mol) of ethylsulfamoyl chloride[7] was added dropwise in 30 min. The ice bath was removed and stirring continued for 1.5 h before filtering. The solvent was evaporated under reduced pressure and the residue triturated with cold water to obtain 32.2 g of product, which on crystallization from aqueous ethanol yielded **2b**: 27.2 g (71%), mp 147–150 °C; NMR (Me_2SO-d_6) δ 1.05 (t, J = 7 Hz, 3 H), 2.83 (s, 3 H), 2.91 (m, 2 H), 5.94 (s, 1 H), 7.33 (t, J = 6 Hz, 1 H); IR (KBr) 3305, 1620, 1472, 1340, 1168 cm^{-1}.

Anal. Calcd for $C_6H_{11}N_3O_3S$: C, 35.11; H, 5.40; N, 20.48. Found: C, 35.21; H, 5.61; N, 20.43.

5-Amino-2-ethyl-3-methyl-2*H*-1,2,6-thiadiazine 1,1-Dioxide (3b). A solution of 20.5 g (0.10 mol) of **2b** and 6.00 g (0.11 mol) of sodium methoxide in 225 mL of methanol was hydrogenated over Raney nickel catalyst. After filtration of the catalyst, 10 mL of acetic acid was added and the solvent evaporated under reduced pressure. A solution of the residue in 100 mL of water was filtered, and allowed to crystallize to obtain **3b**; 14.4 g (76%), mp 202–204 °C. The analytical sample was recrystallized from methanol: mp 202–204 °C; NMR (Me_2SO-d_6) δ 1.22 (t, J = 7, 3 H), 2.16 (s, 3 H), 3.72 (q, J = 7, 2 H), 5.32 (s, 1 H), 7.32 (s, 2 H); IR (KBr) 3405, 3305, 3195, 1638, 1603, 1345, 1305, 1176 cm^{-1}; UV max (2-propanol) 243 nm (ϵ 5720), 289 (11 200).

Anal. Calcd for $C_6H_{11}N_3O_2S$: C, 38.08; H, 5.86; N, 22.21. Found: C, 38.18; H, 6.00; N, 22.02.

***N*-(4-Methoxyphenyl)-*N'*-(5-methyl-3-isoxazolyl)sulfamide (2c).** To a solution of 28.0 g (0.288 mol) of **2** in 650 mL of pyridine was added 65.0 g (0.288 mol) of (4-methoxyphenyl)sulfamoyl azide[8] dropwise. The mixture was stirred overnight and concentrated under reduced pressure. The residual oil was agitated with 750 mL of water and the mixture made strongly alkaline by addition of 10% aqueous NaOH. After filtration, the mixture was acidified with concentrated hydrochloric acid and the precipitated product extracted into ether. The ether was dried ($MgSO_4$) and concentrated under reduced pressure; the residue was crystallized from benzene to obtain **2c**: 31.6 g (39%), mp 132–134 °C; NMR (Me_2SO-d_6) δ 2.31 (s, 3 H), 3.67 (s, 3 H), 6.08 (s, 1 H), 6.82 (d, J = 9 Hz, 2 H), 7.03 (d, J = 9 Hz, 2 H), 9.84 (s, 1 H), 10.79 (s, 1 H); IR (KBr) 3190, 1326, 1160, 1140 cm^{-1}; UV max (2-propanol) 229 nm (ϵ 14 950), 281 (1430).

Anal. Calcd for $C_{11}H_{13}N_3O_4S$: C, 46.69; H, 4.62; N, 14.83. Found: C, 46.73; H, 4.43; N, 14.67.

5-Amino-2-(4-methoxyphenyl)-3-methyl-2*H*-1,2,6-thiadiazine 1,1-Dioxide (3c). A solution of 1.41 g (5.0 mmol) of **2c** and 0.27 g (5.0 mmol) of sodium methoxide in 250 mL of methanol was hydrogenated over Raney nickel. The catalyst was filtered, the solvent evaporated under reduced pressure, and the solution of the residue in water cleared by filtration. Acidification with hydrochloric acid precipitated the product, which was recrystallized from ethanol to yield **3c**: 0.60 g (45%), mp 246–248 °C; NMR (Me_2SO-d_6) δ 1.73 (s, 3 H), 3.75 (s, 3 H), 5.45 (s, 1 H), 6.99 (d, J = 9 Hz, 2 H), 7.21 (d, J = 9 Hz, 2 H), 7.51 (br s, 2 H); IR (KBr) 3415, 3320, 3210, 1643, 1507 cm^{-1}; UV max (2-propanol) 230 nm (ϵ 12 650), 288 (12 980).

Anal. Calcd for $C_{11}H_{13}N_3O_3S$: C, 49.43; H, 4.90; N, 15.72. Found: C, 49.40; H, 5.28; N, 16.07.

***N*-(4-Methoxyphenylsulfamoyl)-3-hydroxybutanamidine (4).** A solution of 700 mg (2.5 mmol) of **2c** in 100 mL of methanol was hydrogenated over Raney nickel. After filtration of the catalyst, the solution was concentrated under reduced pressure and the residue recrystallized twice from ethyl acetate to obtain **4**: 200 mg (28%), mp 116–118 °C; NMR (Me_2SO-d_6) δ 0.95 (d, J = 6.5 Hz, 3 H), 2.20 (d, J = 9 Hz, 2 H), 3.68 (s, 3 H), 3.85 (m, 1 H), 4.63 (br s, 1 H), 6.81 (d, J = 9 Hz, 2 H), 7.10 (d, J = 9 Hz, 2 H), 7.53 (br s, 1 H), 8.33 (br s, 1 H), 9.00 (br s, 1 H); IR (KBr) 3430, 3245, 3180, 1673 cm^{-1}; UV max (2-propanol) 229 nm (ϵ 14 980), 281 (4200).

Anal. Calcd for $C_{11}H_{17}N_3O_4S$: C, 45.98; H, 5.96; N, 14.62. Found: C, 46.17; H, 5.77; N, 14.50.

4-Methyl-5-isoxazolylsulfamide (6a). A solution of 5.78 g (0.05 mol) of sulfamoyl chloride[5] in 25 mL of methylene chloride was added dropwise during 20 min to a solution of 4.90 g (0.05 mol) of **5a**[9] in 25 mL of methylene chloride, with cooling to maintain the reaction of 10 °C. The mixture was allowed to warm slightly and stirred for 45 min at 15 °C. A 5.05-g portion (0.05 mol) of triethylamine was then added dropwise at 10–15 °C and the mixture stirred for another 45 min at 15 °C. With the mixture cooled at 5–10 °C, 20 mL of 5 N NaOH was added, and the aqueous phase was acidified with concentrated hydrochloric acid and extracted with three 25-mL portions of ethyl acetate. The combined extracts were dried (Na_2SO_4) and concentrated under reduced pressure, and the residue was crystallized from ethanol–methylene chloride to obtain **6a**: 1.18 g (13%), mp 109.5–110.5 °C; NMR ($CDCl_3$) δ 1.95 (s, 3 H), 6.28 (br s, 2 H), 8.02 (s, 1 H), 9.43 (br s, 1 H); IR (KBr) 3355, 3265, 1653, 1340, 1173 cm^{-1}; UV

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(9) Compound **5a** was prepared in 60% yield from 4-methylisoxazole by reaction with sodium methoxide in methanol (2 h) followed by addition of hydroxylamine hydrochloride and a further 16 h at room temperature. This compound has also been prepared by peroxide oxidation of 3-amino-2-methylpropanenitrile: Matsumura, K.; Saraie, T.; Kawarro, Y.; Hashimoto, N.; Morita, K., *Takeda Kenkyusho Ho* **1971**, *30*, 475.

max (2-propanol) 234 nm (ε 5930).

Anal. Calcd for $C_4H_7N_3O_3S$: C, 27.12; H, 3.98; N, 23.72. Found: C, 27.25; H, 4.12; N, 23.45.

The filtrate from the crystallization of **6a** was concentrated under reduced pressure to leave a partially crystalline residue. An NMR spectrum of this residue suggested that a mixture of **6a** and 2-cyanopropanamide in a molar ratio of approximately 1:4 was present. The crystalline portion of the residual mixture was sublimed (0.01 kPa) to obtain 2-cyanopropanamide: mp 90–94 °C (lit.[10] mp 96–98 °C); NMR (Me_2SO-d_6) δ 1.37 (d, J = 7 Hz, 3 H), 3.62 (q, J = 7 Hz, 1 H), 7.26 (br s, 1 H), 7.58 (br s, 1 H); IR (KBr) 3360, 3195, 2255, 1720, 1670, 1638 cm^{-1}.

4-Methyl-2*H*-1,2,6-thiadiazin-3(6*H*)-one 1,1-Dioxide (7a). A solution of 8.90 g (0.05 mol) of **6a** in 225 mL of DMF was hydrogenated over Raney nickel. After filtration, the solution was concentrated under reduced pressure on the steam bath; heating was continued for 1 h after the solvent had evaporated. The residue was partitioned between 100 mL of water and 110 mL of ethyl acetate and the mixture made strongly alkaline with 10% aqueous NaOH. The aqueous phase was washed with ethyl acetate, acidified with 6 N hydrochloric acid, and extracted with three 150-mL portions of ethyl acetate. After drying (Na_2SO_4) and evaporation of the ethyl acetate under reduced pressure, the residue was triturated with methylene chloride to obtain **7a**: 3.80 g (47%), mp 156–158 °C. The analytical sample was recrystallized from ethanol–methylene chloride: mp 156–158 °C; NMR (Me_2SO-d_6) δ 1.77 (s, 3 H), 7.24 (s, 1 H), 11–12 (br s, 2 H); IR (KBr) 3215, 1660, 1645, 1345, 1160 cm^{-1}; UV max (2-propanol) 210 nm (ε 5280), 280 (4020); pK_a 2.55 and 8.23 (±0.05);[5] mass spectrum, m/e 162 (M^+).

Anal. Calcd for $C_4H_6N_2O_3S$: C, 29.63; H, 3.73; N, 17.28. Found: C, 29.57; H, 3.63; N, 17.23.

***N*-Ethyl-*N'*-(3-methyl-5-isoxazolyl)sulfamide (6b).** Ethylsulfamoyl chloride (43.2 g, 0.30 mol) was added dropwise to a solution of 29.4 g (0.30 mol) of **5b** in 200 mL of pyridine at 5–10 °C. The mixture was stirred overnight at room temperature and concentrated under reduced pressure. The residue was stirred with 600 mL of water, and the solution was cleared by filtration and acidified with 6 N hydrochloric acid; **6b** crystallized rapidly: 46.2 g (75%), mp 133–136 °C. The analytical sample was recrystallized from aqueous ethanol: mp 133–135 °C; NMR (Me_2SO-d_6) δ 1.03 (t, J = 7.5 Hz, 3 H), 2.12 (s, 3 H), 2.90 (m, 2 H), 5.63 (s, 1 H), 7.71 (t, J = 6 Hz, 1 H), 11.13 (br s, 1 H); IR (KBr) 3290, 2705, 1618 cm^{-1}; UV max (2-propanol) 232 nm (ε 10 100).

Anal. Calcd for $C_6H_{11}N_3O_3S$: C, 35.11; H, 5.40; N, 20.48. Found: C, 35.24; H, 5.14; N, 20.68.

6-Ethyl-5-methyl-2*H*-1,2,6-thiadiazin-3(6*H*)-one 1,1-Dioxide (7b). A solution of 20.5 g (0.10 mol) of **6b** in 225 mL of DMF was hydrogenated over Raney nickel. After filtration, the solution was concentrated under reduced pressure on the steam bath. The residue was first washed with petroleum ether (bp 30–60 °C) and then triturated with 100 mL of tetrahydrofuran. The resultant solid was dissolved in water and the solution acidified with 6 N hydrochloric acid to precipitate **7b**: 4.10 g (20%), mp 147.5 °C; NMR (Me_2SO-d_6) δ 1.27 (t, J = 7 Hz, 3 H), 2.28 (s, 3 H), 3.83 (q, J = 7 Hz, 2 H), 5.52 (s, 1 H), 12.7 (br s, 1 H); IR (KBr) 3090, 1648, 1600 cm^{-1}; UV max (2-propanol) 218 nm (ε 4800), 293 (7810).

Anal. Calcd for $C_6H_{10}N_2O_3S$: C, 37.89; H, 5.30; N, 14.73. Found: C, 37.92; H, 5.46; N, 14.77.

***N*-(3-Methyl-5-isoxazolyl)-*N'*-(4-methoxyphenyl)sulfamide (6c).** This compound was prepared in 33% yield from **5b** by a procedure similar to that used to prepare **2c**. The analytical sample of **6c** was recrystallized from benzene: mp 120.5–122 °C; NMR (Me_2SO-d_6) δ 2.15 (s, 3 H), 3.70 (s, 3 H), 5.71 (s, 1 H), 6.86 (d, J = 9 Hz, 2 H), 7.06 (d, J = 9 Hz, 2 H), 10.07 (s, 1 H), 11.54 (br s, 1 H); IR (KBr) 3265, 1353, 1174, 1155 cm^{-1}; UV max (2-propanol) 231 nm (ε 20 300), 281 (1480).

Anal. Calcd for $C_{11}H_{13}N_3O_4S$: C, 46.64; H, 4.63; N, 14.83. Found: C, 46.84; H, 4.49; N, 14.63.

6-(4-Methoxyphenyl)-5-methyl-2*H*-1,2,6-thiadiazin-3(6*H*)-one 1,1-Dioxide (7c). A solution of 2.83 g (0.01 mol) of **6c** in 100 mL of DMF was hydrogenated over Raney nickel. After filtration, the solution was concentrated under reduced pressure on the steam bath, and heating was continued for 1 h after the solvent had evaporated. The residue was dissolved in dilute aqueous sodium hydroxide, the solution cleared by filtration, and the product precipitated by addition of hydrochloric acid. A second reprecipitation from aqueous solution yielded **7c**: 1.00 g (37%), mp 182–185 °C; NMR (Me_2SO-d_6) δ 1.85 (s, 3 H), 3.79 (s, 3 H), 5.61 (s, 1 H), 7.01 (d, J = 9 Hz, 2 H), 7.76 (d, J = 9 Hz, 2 H); IR (KBr) 3000 (br), 1660, 1614, 1353, 1343, 1180 cm^{-1}; UV max (2-propanol) 228 nm (ε 16 200), 293 (9750).

Anal. Calcd for $C_{11}H_{12}N_2O_4S$: C, 49.25; H, 4.51; N, 10.44. Found: C, 49.32; H, 4.80; N, 10.80.

Registry No. **1a**, 1750-42-1; **1b**, 1072-67-9; **2a**, 71565-64-5; **2b**, 71565-65-6; **2c**, 71565-66-7; **3a**, 71565-67-8; **3b**, 71565-68-9; **3c**, 71565-69-0; **4**, 71565-70-3; **5a**, 35143-75-0; **5b**, 14678-02-5; **6a**, 71565-71-4; **6b**, 71565-72-5; **6c**, 71565-73-6; **7a**, 71565-74-7; **7b**, 71565-75-8; **7c**, 71565-76-9; sulfamoyl chloride, 7778-42-9; ethylsulfamoyl chloride, 16548-07-5; *p*-methoxyphenylsulfamoyl azide, 71565-77-0; 2-cyanopropanamide, 71565-78-1; 4-methylisoxazole, 6454-84-8; hydroxylamine hydrochloride, 5470-11-1.

Supplementary Material Available: Tables of the final atomic parameters, bond lengths, bond angles, and ring torsion angles for **3a** (5 tables, 2 pages). Ordering information is given on any current masthead page.

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Acetoxyl Group Migration in 2-Acetoxy-4-(methylthio)-3,5-xylenol. A Novel Catechol to Phenol Transformation

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While pursuing synthetic studies aimed at preparation of a ring-hydroxylated methyl [4-(methylthio)-3,5-xylyl]carbamate analogue,[1] we observed an unusual catechol to phenol transformation. 2-Acetoxy-4-(methylthio)-3,5-xylenol (**3**) [prepared from rearrangement of 4-(methylsulfinyl)-3,5-xylenol (**1**)[2]] when treated with *N*-methyl isothiocyanate in the presence of triethylamine yielded a quantitative amount of a new compound that still contained acetoxyl and phenolic moieties but was devoid of any carbamate substituents.

Results and Discussion

The normal procedure for preparation of *N*-methyl carbamates entails reaction of a hydroxylic moiety with *N*-methyl isothiocyanate in the presence of a suitable catalyst, i.e., boron trifluoride etherate or triethylamine.

Initial treatment of **3** with *N*-methyl isothiocyanate in the presence of boron trifluoride etherate (at 0 °C) gave a mixture of compounds and obvious polymerization. Upon substituting triethylamine for boron trifluoride etherate and refluxing the mixture overnight, we obtained a quantitative yield of a new compound. (It was later demonstrated that the presence or absence of *N*-methyl isothiocyanate had no bearing on the end result of this reaction.) On the basis of its NMR spectrum which indicated retention of the acetoxyl group, the presence of two aro-

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