δ 1.73 (m, 14 H), 2.02 (s, 3 H), 2.82 (p, $J \approx 7$ Hz, 2 H), 5.22 (t, $J \approx 7$ Hz, 1 H); HRMS, observed m/z 224.1410; $C_{13}H_{20}O_3$ requires 224.1411.

2β-Acetoxybicyclo[4.4.1]undecan-11-one (6). Using the above method for **5**, we obtained the desired product in >95% yield on a 0.5-mmol scale: IR 2930, 2860, 1732, 1690, 1238 cm^{-1}; NMR δ 1.6–2.1 (m, 14 H), 2.02 (s, 3 H), 2.6–3.2 (m, 2 H), 4.88 (m, 1 H); HRMS, observed m/z 224.1411; $C_{13}H_{20}O_3$ requires 224.1414.

2α-Hydroxybicyclo[4.4.1]undecan-11-one (7). A solution of 1.07 g (4.8 mmol) of **5** and 4.0 g of tetra-*n*-butylammonium hydroxide in methanol was allowed to stir for 24 h at ambient temperature. Dilution of this solution with 50 mL of water and completion of the standard workup left 0.70 g (80.5%) of alcohol **7**: 3420, 2940, 2875, 1675 cm^{-1}; NMR δ 1.80 (m, 14 H), 2.60 (s, exchanges with D_2O, 1 H), 2.85 (br m, 2 H), 4.00 (m, 1 H); mass spectrum (70 eV), m/z 182 (M^+, 5), 180 (8), 164 ($M^+ - H_2O$, 63), 112 (100); HRMS, observed m/z 182.1293; $C_{11}H_{18}O_2$ requires 182.1304.

Other hydrolysis conditions afforded substantial amounts of an additional compound assigned structure **9**: NMR (partial) δ 9.50 (s).

2β-Hydroxybicyclo[4.4.1]undecan-11-one (8). To a solution of the acetate (100 mg, 0.45 mmol) in 20 mL of methanol was added 470 mg (0.45 mmol) of a 25% solution of tetra-*n*-butylammonium hydroxide in methanol. After stirring for 20 h at room temperature, 15 mL of water was added, and the resulting solution was extracted with 4 × 15 mL of Et_2O. The combined ether layers were dried over $MgSO_4$, and the solvent was removed to leave 63 mg of the alcohol (78%) contaminated with a small amount of aldehyde (<5%): IR 3420, 2940, 2870, 1690 cm^{-1}; NMR δ 1.20–2.10 (m, 14 H), 2.40–3.10 (m, 2 H), 3.88 (m, 1 H); HRMS, observed m/z 182.1302; $C_{11}H_{18}O_2$ requires 182.1304.

(*E*)-5-Cyclodecenyl-1-methanol (3). According to the procedure of Crossland and Servis,[11] 0.101 g (0.55 mmol) of **7** was added to 0.125 mL of triethylamine in 3 mL of methylene chloride (CH_2Cl_2) at 0 °C. This mixture was then treated with 0.055 mL (0.69 mmol) of methanesulfonyl chloride over a 15-min period. The mixture was then stirred for 20 min, diluted with 10 mL of CH_2Cl_2, and washed successively with 10 mL of cold water, 10% HCl, saturated Na_2CO_3, and brine. Completion of the standard workup provided 0.148 g of mesylate **10**: NMR δ 1.80 (m, 14 H), 2.80 (m, 2 H), 3.05 (br s, 3 H), 5.10 (br m, 1 H).

A solution of 0.139 g (0.53 mmol) of this crude mesylate in 10 mL of dry THF was treated with 0.070 g of $LiAlH_4$. The resulting suspension was heated at reflux for 7 h, cooled, and processed as usual to give 0.072 g (78% yield) of **3**: IR 3350, 2900, 2850, 1458, 1030, 983 cm^{-1}; NMR δ 1.00–2.10 (m, 15 H), 2.30 (br s, exchanges with D_2O, 1 H), 3.40 (d, J = 6 Hz, 2 H), 5.47 (br m, 2 H); mass spectrum (20 eV), m/z 168 (M^+, 41), 150 (18), 137 (100), 135 (41); HRMS, observed m/z 168.151; $C_{11}H_{20}O$ requires 168.151.

(*Z*)-5-Cyclodecenyl-1-methanol (4). Using the procedure for **3**, we obtained the crude mesylate in 80% yield on a 0.3-mmol scale: IR 2965, 2860, 1685, 1355, 1170 cm^{-1}; NMR δ 1.50–2.20 (m, 14 H), 2.65 (m, 2 H), 3.00 (s, 3 H), 4.70 (m, 1 H). Crude **11** (0.105 g) afforded 0.057 g (49%) of crude **4**. An analytical sample of **4** (29% yield) was obtained by purification on silica gel: IR 3370 (br), 2940, 2850, 1630, 1450, 1030, 735, 695 cm^{-1}; NMR δ 1.10–1.70 (m, 15 H), 3.45 (m, 2 H), 5.39 (m, 2 H); HRMS, observed m/z 168.1514; $C_{11}H_{20}O$ requires 168.1512.

Bicyclo[4.4.1]undecane-2,11-dione (12). A solution of 0.30 g of **7** in 30 mL of reagent-grade acetone at 0 °C was treated with Jones reagent until the red color persisted. The suspension was stirred for 10 min, treated with 2-propanol (1 mL), and filtered through solid sodium carbonate. The filtrate was condensed, and the residue was dissolved in ether. Completion of the standard workup afforded 0.29 g (98%) of **12**: IR 1700 cm^{-1}; NMR δ 1.0–2.4 (m, 12 H), 2.45 (t, J = 6 Hz, 2 H), 2.75 (m, 1 H), 3.38 (t, J = 6 Hz, 2 H).

Methyl 4-(2-Oxo-1-cycloheptyl)butyrate (14).[15] A solution of 0.51 g of diketone **12** in 40 mL of 10% aqueous sodium hydroxide was heated at reflux for 2 h. The solution was cooled, acidified with 10% aqueous hydrochloric acid, and washed with ether (4 × 50 mL). Completion of the standard workup on the pooled ether layers afforded 0.53 g (94% yield) of a yellow oil: IR 3400–2500 (br), 2490, 2860, 1700 (br), 1450, 1250 cm^{-1}; NMR δ 1.2–1.9 (m, 12 H), 2.3 (t, J = 6 Hz, 2 H), 2.4 (m, 3 H); mass spectrum (70 eV), m/z 198 (M^+).

The keto acid (0.53 g, 2.7 mmol) was dissolved in 40 mL of anhydrous methanol and treated with freshly distilled boron trifluoride etherate (0.70 mL, 5.7 mmol). This mixture was heated at reflux for 24 h, cooled, and diluted with 20 mL of 5% aqueous sodium bicarbonate. Most of the methanol was removed with a rotary evaporator. The residue was extracted with ether (4 × 50 mL). Completion of the standard workup of the pooled ether layers provided 0.47 g (83% yield) of **14**: IR 2920, 2965, 1745, 1715, 1450, 1175 cm^{-1}; NMR δ 1.2–2.0 (m, 12 H), 2.2–2.6 (m, 5 H), 3.6 (s, 3 H); ^{13}C NMR δ 215.8, 173.9, 51.9, 51.5, 42.9, 34.0, 31.6, 31.3, 29.5, 28.6, 24.4, 22.7; mass spectrum (70 eV), m/z 212 (M^+), 112 (base); HRMS, observed m/z 212.1406; $C_{12}H_{20}O_3$ requires 212.1409.

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Registry No. **1**, 82614-26-4; **2**, 82659-79-8; **3**, 82614-27-5; **4**, 82614-28-6; **5**, 82614-29-7; **6**, 82659-80-1; **7**, 82614-30-0; **8**, 82659-81-2; **9**, 82614-34-4; **10**, 82614-31-1; **11**, 82659-82-3; **12**, 82614-32-2; **13**, 33366-38-0; **14**, 82614-33-3; (*Z*)-1-acetoxy-1,3-butadiene, 35694-19-0; (*E*)-1-acetoxy-1,3-butadiene, 35694-20-3; cycloheptatrienone, 539-80-0.

(15) We are grateful to W. McBride for obtaining some of the spectral data as a part of a rotation project, Winter Quarter, 1980.

Elimination–Addition Reactions of 3-[2-(Arylthio)ethyl]sydnones. Displacement of the Sulfide by an Ether Group

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During a metabolism study[1] of some antiinflammatory sydnones, **1**,[2] in the rat, we observed that these sydnones tended to decompose in solutions containing strong bases.[3,4] We investigated the reaction of **1** in CD_3OD containing CD_3ONa. The ^1H NMR spectrum of **1b** (at probe temperature) changed quickly and dramatically after the concentration of CD_3ONa reached about 2 N. At that point, the triplet at 4.46 ppm (CH_2N) disappeared with the simultaneous collapse of the triplet to a singlet at 3.33 ppm (CH_2S) (measured downfield from tetramethylsilane). At the same time, new singlets began to appear at 2.13, 3.63, and 3.82 ppm whose intensity grew with time. Also, the symmetrical sets of signals arising from the arene protons (AA′BB′) became diffuse, with the appearance of new lines. The reaction was about 80% complete after 2 h.

(1) To be reported elsewhere.

(2) (a) Wagner, H.; Hill, J. B. *J. Med. Chem.* **1974**, *17*, 1337–1338. (b) Hill, J. B.; Ray, R. E.; Wagner, H.; Aspinall, R. L. *Ibid.* **1974**, *18*, 50–53.

(3) During routine isolation procedures, a chloroform solution of **1** may be washed repeatedly with cold aqueous sodium hydroxide solutions without appreciately destroying any sydnone. As a matter of fact, when **1** in $CDCl_3$ is shaken repeatedly with 1.5 N NaOD in D_2O, no active methylene H–D exchange occurs.

(4) Hot aqueous sodium hydroxide hydrolyzes sydnones to the starting *N*-nitroso acids (Garret, E. R. *J. Pharm. Sci.* **1964**, *53*, 42–43).

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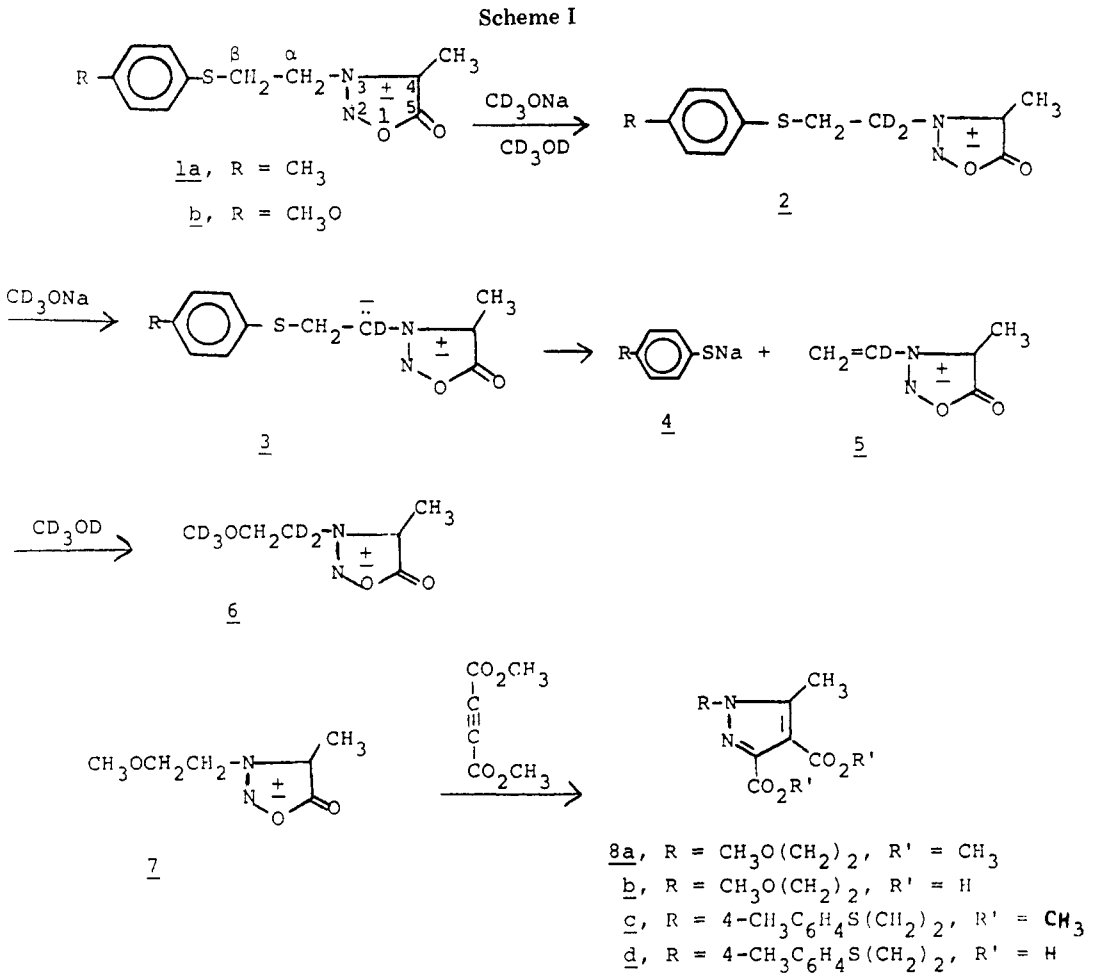
Scheme I



We interpret these spectral changes in the following way. The disappearance of the triplet at 4.46 ppm is due to an H–D exchange of weakly acidic active methylene protons (1 → 2, Scheme I). Then, in this CD_3OD/CD_3ONa solution, the sulfide is displaced by an OCD_3 group to generate **6**, presumably via elimination–addition reactions. Since no *N*-vinylsydnone (**5**) was detected (on the NMR time scale), it is postulated that a relatively slow β-elimination of thiophenoxide ion from **3** is followed by a fast addition of alkoxide ion to furnish **6**. The final mixture from the reaction of **1b** with CD_3OD/CD_3ONa consists of **6** and **4** (R = CH_3O). The new CH_3 (sydnone) and OCH_2 singlets at 2.13 and 3.82 ppm arise from **6**, while that at 3.63 ppm comes from the OCH_3 of sodium 4-methoxythiophenoxide. Furthermore, acidification of this reaction mixture and subsequent analysis by GC/MS (OV-1 column) confirmed the presence of **6** and 4-methoxythiophenol (retention times and mass spectra). Similar elimination–displacement reactions took place when **1a** was placed in a solution of CD_3OD containing CD_3ONa to form **6** and **4** (R = CH_3).

In another NMR experiment, after the reaction of 1 → **6** was virtually complete, water was introduced into the CD_3OD solution containing CD_3ONa. With increasing quantities of water, the N–CD_2 group of **6** commenced a D–H exchange which finally gave rise to a multiplet characteristic of the OCH_2CH_2N spin system.

The reverse elimination–addition reaction from the ether to the sulfide (e.g., **7** → **1**) could not be effected. On boiling **7** with ArSH/ArSNa in either benzene or tetrahydrofuran (1.5 h) did not produce **1** (GC/MS). Apparently, the anion of **7** does not eliminate alkoxide ion to produce **5**, which would be the logical precursor for thiophenol addition to form **1**.

On a preparative scale, **1b** was reacted with sodium methoxide in methanol to produce **7**. After column chromatography or vacuum distillation, pure samples of **7** were obtained (^1H NMR, TLC) which failed to provide completly satisfactory microanalyses (C,H, and N on a particular sample). This sydnone began to decompose at −5 °C during 24 h as witnessed by the appearance of impurities in TLC, lower N analyses, and extra ^1H NMR signals. A sample of this sydnone **7** was also synthesized independently from 1-amino-2-methoxyethane by standard methods. Alkylation of this amine with ethyl 2-bromopropanoate furnished the required N-substituted alanine, which was nitrosated. Cyclization of this nitroso acid in acetic anhydride afforded **7**.

It was possible to characterize **7** readily by first subjecting it to a 1,3-dipolar cycloaddition[5,6] with methyl acetylenedicarboxylate to form an oil, **8a**, which was hydrolyzed to the crystalline pyrazoledicarboxylic acid (**8b**). A similar sequence of reaction on **1b** produced the crystalline acid **8d**.

Experimental Section

Melting points were determined on a Thomas-Hoover Unimelt apparatus and are uncorrected. Elemental analyses were performed by Micro-Tech Laboratories, Skokie, IL. Proton NMR

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(6) (a) Gotthardt, H.; Reiter, F. *Chem. Ber.* **1981**, *114*, 2450–2464. (b) Padwa, A.; Burgess, E. M.; Gingrich, H. L.; Rous' , D. M. *J. Org. Chem.* **1982**, *47*, 786–791.
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spectra were determined on a Varian T-60 spectrometer equipped with a Nicolet TT-7 Fourier transform accessory. Chemical shifts are reported in parts per million (δ) downfield from tetramethylsilane as internal standard. These abbreviations are used to report peak multiplicity: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broadened. Unless otherwise indicated gas chromatography and mass spectrometry were performed with a Finnigan 3300 quadrupole mass spectrometer (MS) interfaced to a Finnigan 9500 gas chromatograph (GC). The mass spectrometer was equipped for chemical ionization (CI) and with a pulsed positive, negative ion chemical ionization (PPNICI) module. CI spectra were generated at 100 eV, using methane as the reagent gas. Electron-impact (EI) spectra were generated at 70 eV. Only major ions (usually above 20%) are reported except when deemed significant. The ion intensity is given in parentheses. For GC, a 5 ft, 2 mm i.d. U-shaped glass column was used, packed with 3% OV-1 on Chromosorb W H.P., 80–100 mesh. The carrier gas was helium for EI at a flow rate to generate an analyzer pressure of 5×10^{-6} torr. For CI the carrier gas was methane at a flow rate to generate an analyzer pressure of 3×10^{-5} torr and a source pressure of 500 torr. The GC/MS system was controlled by a Finnigan 6100 Data System equipped with an LSI computer. Thin-layer chromatography (TLC) was carried out with Brinkmann Polygram sheets, sil G/UV 254, 0.25-mm silica gel precoated on plastic sheets.

All solvents were reagent grade and distilled prior to use except for dichloromethane, which was purchased from Burdick and Jackson and was used without further purification. All other reagents unless otherwise stated were purchased from Aldrich Chemical Co. and used as such.

3-[2-[(4-Methylphenyl)thio]ethyl]-4-methylsydnone (1a). Some of the steps in this sydnone preparation were modified from those reported in the literature.

The starting amino thioether was synthesized essentially by the method of Wehrmeister.[7] An equimolar (0.16 mol) mixture of 4-methylthiophenol (20.2 g), propanoic acid (12.1 g), and 2-aminoethanol (9.95 g) in benzene (50 mL) was heated under an 18-in. Snyder column with slow azeotropic removal of water. The temperature of the pot rose from 135 to 198 °C in 3.5 h. The residue was cooled and dissolved in ethanol (200 mL), and the product was precipitated by water (600 mL). *N*-[2-[(4-Methylphenyl)thio]ethyl]propanamide (47.8 g, 89%) was recrystallized from chloroform–hexane (160 mL, 1:10): mp 66.5–67.5 °C; ^{1}H NMR ($CDCl_3$) δ 1.11 (t, CH_3CH_2, J = 7.2 Hz), 2.16 (q, CH_2CO), 2.31 (s, CH_3Ar), 3.00 (m, CH_2S), 3.38 (m, CH_2N), 5.90 (br, NH), 6.93–7.35 (m, Ar H); mass spectrum (EI), m/e 223 (8, M^+), 150 (100), 125 (55), 123 (15), 100 (20).

This amide (14.0 g, 0.063 mol) was refluxed with 8 N HCl (50 mL) for 3 h. The solution was cooled and made alkaline with 9 N NaOH. The base was extracted into benzene (3 × 10 mL) and dried (Na_2CO_3). The benzene solution was filtered and HCl gas was bubbled through to form 2-[[(4-methylphenyl)thio]amino]-ethane hydrochloride (12.0 g, 93%). The salt was filtered and washed with acetone (30 mL): mp 131–133 °C (lit. mp 132 °C,[8] 155–156 °C[9]); ^{1}H NMR (D_2O) δ 2.17 (s, CH_3Ar), 3.04 (s, CH_2CH_2), 6.77–7.54 (m, ArH); mass spectrum (EI), m/e 167 (20, M^+ free base), 138 (100), 123 (18).

We found that the following alkylation produced consistent and higher yields than the one reported in the literature.[2] To an aqueous solution of the amine hydrochloride (15.1 g, 0.074 mol in 50 mL) was added 40% NaOH (10 mL). The amine was extracted with benzene (3 × 30 mL), dried (Na_2CO_3), and then added to 2-bromopropanoic acid (3.66 g, 0.024 mol) in benzene (30 mL). The mixture was stirred for 18 h at 25 °C and then extracted with 10% NaOH (30 mL). The alkaline solution was washed once with benzene (50 mL). The pH was adjusted to 5 with 36% HCl. 2-[[2-[(4-Methylphenyl)thio]ethyl]amino]-propanoic acid (4.6 g, 81%) was filtered off, washed with water, and dried: mp 165–168 °C dec; ^{1}H NMR (D_2O, 4% NaOH) δ 1.14 (d, CH_3CH, J = 6.9 Hz), 2.27 (s, CH_3Ar), 2.73 (m, CH_2N), 2.90 (m, CH_2S), 3.06 (q, CH), 6.83–7.65 (m, Ar H); mass spectrum (EI), m/e 239 (3, M^+), 138 (92), 123 (35), 102 (75), 55 (100).

A mixture of the amino acid (4.8 g, 0.02 mol) and sodium nitrite (2.07 g, 0.026 mol) in water (35 mL) and dichloromethane (35 mL) was stirred at 0 °C. Dilute HCl (10 mL, 8.8%, 0.029 mol) was added dropwise over 1 h. After the mixture was stirred an additional 2 h at 0 °C, the dichloromethane layer was lifted and the aqueous phase extracted with dichloromethane (50 mL). The organic phase was dried (Na_2SO_4) and then evaporated in vacuo. The resultant yellow oil was used immediately in the next step.

This oil was dissolved in freshly distilled acetic anhydride (150 mL) and allowed to stand at 25 °C for 4 days in the dark. Solvents were evaporated in vacuo (maximum temperature 40 °C) and the residue dissolved in dichloromethane (100 mL). This solution was washed with ice-cold 10% $NaHCO_3$ until CO_2 evolution ceased, dried (Na_2CO_3), and evaporated in vacuo. The product was triturated with hexane (75 mL) and then recrystallized from ether (100 mL) to furnish pure **1a** (3.9 g, 78%): mp 95–96 °C; ^{1}H NMR ($CDCl_3$) δ 2.01 (s, CH_3syd), 2.35 (s, CH_3Ar), 3.33 (t, CH_2S, J = 6.9 Hz), 4.33 (t, CH_2N), 7.05–7.40 (m, Ar H); ^{1}H NMR (CD_3OD) δ 2.00 (s, CH_3syd), 2.28 (s, CH_3Ar), 3.40 (t, CH_2S, J = 7.0 Hz), 4.48 (t, CH_2N), 7.04–7.40 (m, Ar H); mass spectrum (EI), m/e 250 (3, M^+), 151 (50), 123 (100), (CI pos) 251 [5, $(M + H)^+$], 151 (100), (CI neg) 99 (100). Anal. Calcd for $C_{12}H_{14}N_2O_2S$: C, 57.58; H, 5.64; N, 11.19. Found: C, 57.57; H, 5.64; N, 11.08.

It should be noted that it is the corresponding sulfoxide that is reported in Table III of ref 2b.

3-[2-[(4-Methoxyphenyl)thio]ethyl]-4-methylsydnone (1b). The preparation followed the one reported above for the methyl analogue. 4-Methoxythiophenol was converted in 89% yield to *N*-[2-[(4-methoxyphenyl)thio]ethyl]propanamide: mp 95–96 °C; ^{1}H NMR ($CDCl_3$) δ 1.11 (t, CH_3CH_2, J = 7.2 Hz), 2.16 (q, CH_2CO), 2.93 (m, CH_2S), 3.38 (m, CH_2N), 3.78 (s, CH_3O), 6.0 (br, NH), 6.76–7.44 (m, Ar H); mass spectrum (EI), m/e 239 (12, M^+), 166 (100), 151 (20), 139 (32), 100 (70).

Hydrolysis of this amide provided 2-[(4-methoxyphenyl)-thio]-1-aminoethane hydrochloride (95%): mp 138–139 °C (lit.[9] mp 125 °C); ^{1}H NMR (D_2O) δ 3.05 (s, CH_2CH_2), 3.73 (s, CH_3O), 6.80–7.45 (m, Ar H); mass spectrum (EI), m/e 183 (32 M^+ of amine), 154 (100), 139 (55).

Alkylation of the amine with 2-bromopropanoic acid furnished 2-[[2-[(4-methoxyphenyl)thio]ethyl]amino]propanoic acid (83%): mp 163–166 °C; ^{1}H NMR (D_2O, 4% NaOH) δ 1.13 (d, CH_3CH, J = 6.9 Hz), 2.68 (m, CH_2N), 2.83 (m, CH_2S), 3.05 (q, CH), 3.75 (s, CH_3O), 6.82–7.45 (m, Ar H); mass spectrum (EI), m/e 255 (8%, M^+), 154 (70), 139 (55), 102 (70), 55 (100).

Nitrosation and subsequent cyclization gave **1b** (65%): mp 62–63 °C (lit.[2] mp 60–61 °C); ^{1}H NMR ($CDCl_3$) δ 2.01 (s, CH_3syd), 3.28 (t, CH_2S, J = 6.6 Hz), 3.80 (s, CH_3O), 4.32 (t, CH_2N), 6.80–7.48 (m, Ar H); ^{1}H NMR (CD_3OD) δ 2.00 (s, CH_3syd), 3.33 (t, CH_2S, J = 6.6 Hz), 3.77 (s, CH_3O), 4.46 (t, CH_2N), 6.79–7.44 (m, Ar H), mass spectrum (EI), m/e 266 (2, M^+), 167 (10), 139 (100), (CI pos) 267 [5, $(M + H)^+$], 167 (100), (CI neg) 99 (100).

3-(2-Methoxyethyl)-4-methylsydnone (7). A. From Sydnone 1a. ^{1}H NMR studies indicated that both **1a** and **1b** when treated with CD_3ONa in CD_3OD afforded the same product. A preparative run is described. A solution of **1a** (10.6 g, 0.04 mol) in methanol containing sodium methoxide (2.3 g of sodium in 100 mL) was refluxed for 0.75 h. Periodic examination of the reaction mixture by GC/MS, temperature programmed from 140–270 °C at 12 °C/min, indicated the rapid disappearance of the sydnone **1a**, retention time (t_R) 8.2 min, with the appearance of the new sydnone **7**, t_R 3.9 min, and 4-methoxythiophenol, t_R 0.7 min. The reaction was 50% complete at 4 min as measured by the relative amounts of thiophenol and new sydnone produced. The reaction mixture was cooled, neutralized with 6 N HCl (10 mL), and evaporated in vacuo. The residue was dissolved in dichloromethane (150 mL) and washed with 2 N NaOH (50 mL) to remove thiophenol. The dichloromethane extract was dried and evaporated in vacuo to yield 5.2 g (82%) of a golden oil: TLC ($CHCl_3$–MeOH, 95:5) R_f 0.24; ^{1}H NMR ($CDCl_3$) δ 2.18 (s, CH_3syd), 3.39 (s, CH_3O), 3.87 (m, CH_2O), 4.37 (m, CH_2N); mass spectrum (EI), m/e 158 (25, M^+), 100 (20), 59 (100), (CI pos) 159 [100, $(M + H)^+$], (CI neg) 158 (42, M^-), 99 (100); mass spectrum of deuterio analogue **6**, (EI) m/e 163 (15, M^+), 105 (12), 64 (100), (CI pos) 164 [100, $(M + H)^+$]. Distillation of the product (5 g) produced several fractions; the largest single and most uniform one (2 g) boiled at 145 °C (1.5 torr). A 70-mg sample of **7** was chromatographed on a 30 cm × 1 cm silica gel column (100–200 mesh, Sargent Welch, high purity, chromatographic grade). Elution by benzene (70 mL) to give some 4-methoxyphenyl disulfide was followed by chloroform (350 mL) and then by methanol (120 mL).

Anal. Calcd for $C_6H_{10}N_2O_3$: C, 45.56; H, 6.37. Found: C, 46.03; H, 6.03. Acceptable microanalysis for N could not be obtained.

B. Synthesis by Standard Methods. To a stirred solution of 2-methoxyethylamine (60.0 g, 0.80 mol) in benzene (200 mL) at 25 °C was added (over 0.5 h) ethyl 2-bromopropanoate (69.7 g, 0.39 mol) and the mixture stirred for 12 h. The mixture was then diluted with ethyl acetate (200 mL), washed with 140 mL of 10% NaOH, and distilled to produce ethyl 2-[(2-methoxyethyl)amino]propanoate (52.5 g, 78%): bp 90 °C (18 torr); ^{1}H NMR ($CDCl_3$) δ 1.27 (t, CH_3CH_2, J = 7.1 Hz), 1.30 (d, CH_3CH, J = 6.9 Hz), 1.88 (s, NH), 2.74 (m, CH_2N), 3.35 (s, CH_3O) 3.40 (m, $CHCH_3$), 3.48 (m, CH_2O), 4.19 (q, CH_2CH_3); mass spectrum (EI), m/e 176 [10, $(M + 1)^+$], 130 (47), 102 (100), 70 (45), 56 (72).

The ester (30 g, 0.17 mol) was hydrolyzed with boiling 15% NaOH (50 mL) for 0.5 h. The mixture was acidified (pH 5) with 36% HCl (17 mL) and evaporated in vacuo. The residue was extracted with cold chloroform–1-butanol (4:1, 3 × 70 mL) to remove inorganic solids. The organic extract was evaporated in vacuo and the residue dissolved in a pH 5.5 phosphate buffer (30 mL). This solution was again evaporated in vacuo. Extraction of the residue with chloroform–1-butanol (4:1, 2 × 50 mL) provided 2-[(2-methoxyethyl)amino]propanoic acid (20.2 g, 81%): mp 223–225 °C dec; ^{1}H NMR (D_2O) δ 1.21 (d, CH_3CH, J = 7.2 Hz), 2.95 (m, CH_2N), 3.11 (s, CH_3O), 3.37 (m, $CHCH_3$), 3.46 (m, CH_2O); mass spectrum (EI), m/e 147 (1, M^+), 129 [1, $(M - CO_2)^+$], 102 (100), 56 (70). Anal. Calcd for $C_6H_{13}NO_3$: C, 48.97; H, 8.90; N, 9.52. Found: C, 48.86; H, 8.70; N, 9.50.

The unrecrystallized amino acid hydrochloride served well in these next steps. The salt (27.5 g, 0.15 mol) was dissolved in water (50 mL) containing 36% HCl (1 mL). An aqueous solution of sodium nitrite (13.8 g, 0.2 mol in 10 mL) was added dropwise over 0.5 h. The temperature of the reaction mixture was kept between 0 and −5 °C. After an additional 0.5 h of stirring, the mixture was extracted with ethyl acetate (50 mL), dried (Na_2SO_4), and evaporated in vacuo.

The crude *N*-nitroso acid was immediately dissolved in freshly distilled acetic anhydride (150 mL) and stored in the dark at 25 °C for 4 days. Solvents were removed in vacuo at 45 °C (or less) and the residue dissolved in dichloromethane (100 mL). The organic phase was washed with 10% $NaHCO_3$ (until no further CO_2 evolution was observed) and dried (Na_2CO_3). Vacuum evaporation furnished **7** (9.5 g), which was identical in all respects with the product from preparation A. This product was used in the next step.

1-(2-Methoxyethyl)-5-methyl-3,4-pyrazoledicarboxylic Acid (8b). A solution of **7** (10 g, 0.063 mol) and methyl acetylenedicarboxylate (10 g, 0.07 mol) in benzene (100 mL) was refluxed for 18 h. Fractional distillation yielded **8a** (13.1 g, 81%): bp 216–218 °C (30 torr); ^{1}H NMR ($CDCl_3$) δ 2.51 (s, CH_3C), 3.28 (s, CH_3OCH_2), 3.78 (m, CH_2O), 3.84, 3.92 (s, ester CH_3's), 4.27 (m, CH_2N); mass spectrum (EI), m/e 256 (5, M^+), 226 (20), 225 (52), 194 (100), 167 (55), 166 (56), 59 (27), 58 (67).

This ester (13.1 g, 0.051 mol) was hydrolyzed in boiling methanol (10 mL) containing 7 N NaOH (35 mL) for 4 h. After **8a** was absent (TLC; chloroform–methanol, 9:1, R_f 0.56), the solution was concentrated in vacuo and extracted with dichloromethane (2 × 50 mL). The aqueous layer was acidified with 36% HCl (30 mL) and evaporated in vacuo. The residue was triturated several times with methanol–chloroform (1:1, 200 mL). The organic extract yielded **8b**, which was recrystallized from water (8.6 g, 74%): mp 163.5–164.5 °C; TLC (ethyl acetate–ethanol–acetic acid, 85:15:5), R_f 0.24; ^{1}H NMR ($CDCl_3$) δ 2.65 (s, CH_3C), 3.29 (s, CH_3O), 3.77 (m, CH_2O), 4.36 (m, CH_2N), 7.58 (br, OH); mass spectrum (EI), m/e 228 (1, M^+), 180 (47), 58 (100), 45 (86). Anal. Calcd for $C_9H_{12}N_2O_5$: C, 47.37; H, 5.30; N, 12.27. Found: C, 47.44; H, 5.24; N, 12.23.

1-[2-[(4-Methylphenyl)thio]ethyl]-5-methyl-3,4-pyrazoledicarboxylic Acid (8d). A solution of **1a** (2.8 g, 0.011 mol) and methyl acetylenedicarboxylate (1.7 g, 0.012 mol) in benzene (35 mL) was refluxed for 18 h. Solvents were evaporated in vacuo to yield an oily residue. Attempts to distill the ester (0.15 torr) caused partial decomposition although GC/MS analysis showed that **8c** was the major product. Mass spectrum (EI), m/e 348 (5, M^+), 151 (100), 135 (60), 123 (25). The residual oil was hydrolyzed by refluxing for 1 h in a mixture of methanol (20 mL) and 0.5 N NaOH (60 mL) and then the mixture was allowed to stand overnight (25 °C). Partial evaporation in vacuo and addition of 36% HCl (3 mL) precipitated **8d**. The product was filtered, washed with benzene (2 × 100 mL), and recrystallized from water (2.9 g, 81%): mp 198.5–199.5 °C; ^{1}H NMR ($CDCl_3$, 20% CD_3OD) δ 2.31 (s, CH_3Ar), 2.54 (s, CH_3C), 3.39 (t, CH_2S, J = 6.5 Hz), 4.38 (t, CH_2N), 6.98–7.32 (m, Ar H); mass spectrum (EI), m/e 320 (2, M^+), 151 (100), 135 (60), 44 (100). Anal. Calcd for $C_{15}H_{16}N_2SO_4$: C, 56.24; H, 5.03; N, 8.74. Found: C, 56.50; H, 5.08; N, 8.82.

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1,3-Butadiene-1,1,4-tricarboxylic Acids

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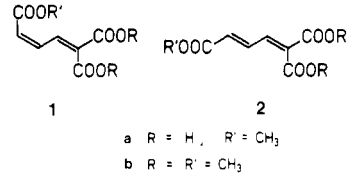
(1*E*,3*Z*)-1,3-Butadiene-1,2,4-tricarboxylic (β-carboxy-*cis*,*cis*-muconic) acid is of considerable biochemical importance as an intermediate in catabolism of aromatic compounds by bacteria and fungi, being formed by intradiol oxidative ring cleavage of 3,4-dihydroxybenzoate.[2] A characteristic and early-recognized[3] property of this triacid is its very rapid stereomutation to the 3*E* isomer under acidic conditions.[4] In this paper we describe the isomeric 1,3-butadiene-1,1,4-tricarboxylic (α-carboxymuconic) acids. The characteristic feature of the *Z* isomer, a potential product of enzymatic degradation of 2,3-dihydroxybenzoate, is its rapid, reversible lactonization in neutral or acidic solutions.

The oxidation of 2-hydroxy-3-methoxybenzaldehyde with chlorous acid to the monoester **1a** of (*Z*)-1,3-butadiene-1,1,4-tricarboxylic acid has been described elsewhere.[5] Diazomethane methylation of **1a** afforded triester **1b**. The corresponding derivatives **2a** and **2b** of (*E*)-1,3-butadiene-1,1,4-tricarboxylic acid were obtained by light- or heat-induced isomerization of **1a** and **1b**, respectively, in the presence of catalytic amounts of iodine. The change of stereochemistry caused characteristic changes in ^{1}H NMR and UV spectra (Tables I and II), reflecting planar conformations[6] of both series.



Hydrolysis of **2a** with alkali, followed by acidification, gave triacid **2c**. However, similar treatment of **1a** yielded the lactone **3** rather than the triacid **1c**. The trianion of **1c**, formed initially by saponification of **1a**, was stable in the presence of excess base and could be characterized by ^{1}H NMR and UV spectroscopy (Tables I and II), but

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