2.96 g, 10.0 mmol), lithium diisopropylamide (1.5 M in cyclohexane; 7.0 mL, 10.5 mmol) and freshly distilled benzoyl chloride (1.41 g, 10.0 mmol) gave 1-phenyl-3,3-dimethyl-1,2-butanedione (1.41 g, 74% yield from benzoyl chloride).

2,2,5,5-Tetramethyl-3,4-hexanedione. The reaction of diethyl 1-*tert*-butyl-1-(trimethylsiloxy)methanephosphonate (**1b**; 2.96 g, 10.0 mmol), lithium diisopropylamide (1.5 M in cyclohexane; 7.0 mL, 10.5 mmol), and trimethylacetyl chloride (1.21 g, 10.0 mmol) gave 2,2,5,5-tetramethyl-3,4-hexanedione (0.70 g, 41% yield from trimethylacetyl chloride) as a colorless liquid, bp 76–77 °C (3.0 mm). IR (neat): 1720 (s) cm^{-1}. ^{13}C NMR (50 MHz, $CDCl_3$): δ 210.46 (s), 37.51 (s), 26.06 (q). ^1H NMR (200 MHz, $CDCl_3$): δ 0.90 (s). GC/MS (70 eV): *m/e* 170 (M^+, 4.9), 85 (19.3), 57 (100.0). Anal. Calcd for $C_{10}H_{18}O_2$: C, 70.59; H, 10.59. Found, C, 70.54; H, 10.68.

1-(1′-Adamantyl)-3,3-dimethyl-1,2-butanedione. The reaction of diethyl 1-*tert*-butyl-1-(trimethylsiloxy)methanephosphonate (**1b**; 2.96 g, 10.0 mmol), lithium diisopropylamide (1.5 M in cyclohexane; 7.0 mL, 10.5 mmol), and 1-adamantanecarbonyl chloride (1.99 g, 10.0 mmol) gave 1-(1′-adamantyl)-3,3-dimethyl-1,2-butanedione (0.84 g, 34% yield from 1-adamantanecarboxylic acid chloride) as colorless microcrystals, mp (from petroleum ether) 82–83 °C. IR (KBr): 1740 (s), 1745 (s), cm^{-1}. ^{13}C NMR (50 MHz, $CDCl_3$): δ 210.33 (s), 209.31 (s), 46.31 (s), 38.02 (t), 36.00 (t), 35.48 (s), 28.03 (d), 26.92 (q). ^1H NMR (200 MHz, $CDCl_3$): δ 2.59–2.20 (n, 15 H), 0.91 (s, 9 H). GC/MS (70 eV): *m/e* 248 (M^+, 1.3), 163 (13.2), 135 (100.0), 85 (9.2), 57 (33.2). Anal. Calcd for $C_{16}H_{24}O_2$: C, 77.42; H, 9.68. Found: C, 77.65; H, 9.41.

Diethyl 1-(1′-Adamantyl)-1-(trimethylsiloxy)methanephosphonate. A mixture of 1-adamantanecarbaldehyde[11] (16.4 g, 0.1 mol), freshly distilled triethyl phosphite (16.6 g, 0.1 mol), and freshly distilled chlorotrimethylsilane (10.9 g, 0.1 mol) was warmed at 120 °C for 8 h to give diethyl 1-(1′-adamantyl)-1-(trimethylsiloxy)methanephosphonate (**1c**; 35.9 g, 96% yield from 1-adamantanecarbaldehyde). Bp: 178–180 °C (0.05 mm) colorless oil. IR (neat): 1245 (m) cm^{-1}. ^{31}P NMR (81 MHz, D_3PO_4): δ −23.03. ^{13}C NMR (50 MHz, $CDCl_3$): δ 76.64 (CH, d, J_{cp} = 164.3 Hz), 60.78 (CH_2, d, J_{cp} = 7.5 Hz), 60.06 (CH_2, d, J_{cp} = 7.5 Hz), 43.03 (quat, C, d, J_{cp} = 4.8 Hz), 42.18 (CH_2, d, J_{cp} = 5.8 Hz), 36.85 (CH_2), 28.99 (CH), 16.33 (CH_3, d, J_{cp} = 2.4 Hz), 16.21 (CH_3, d, J_{cp} = 2.4 Hz), 0.16 (CH_3). ^1H NMR (200 MHz, $CDCl_3$): δ 3.98 (CH_2, q, 4 H, J = 6.8 Hz), 3.81 (CH, d, 1 H, J_{HP} = 8.6 Hz), 2.30–2.71 (m, 15 H), 1.20 (CH_3, t, 6 H, J = 6.8 Hz), 0.01 (CH_3, s, 9 H). GC/MS (70 eV): *m/e* 374 (M^+ 0.6), 237 (74.4), 210 (100.0), 195 (10.5), 183 (10.4), 135 (37.6), 121 (16.5), 91 (10.2), 73 (82.6). Anal. Calcd for $C_{18}H_{35}O_4PSi$: C, 57.75; H, 9.36; O, 17.11. Found: C, 57.46; H, 9.39; O, 16.98.

1-(1′-Adamantyl)-2-phenyl-1,2-ethanedione. The reaction of diethyl 1-(1′-adamantyl)-1-(trimethylsiloxy)methanephosphonate (**1c**; 3.74 g, 10.0 mmol), lithium diisopropylamide (1.5 M in cyclohexane; 7.0 mL, 10.5 mmol), and benzoyl chloride (1.41 g, 10.0 mmol) with subsequent aqueous workup gave 1-(1′-adamantyl)-2-phenyl-1,2-ethanedione (1.90 g, 71% yield from benzoyl chloride).

1-(1′-Adamantyl)-3,3-dimethyl-1,2-butanedione. the rection of diethyl 1-(1′-adamantyl)-1-(trimethylsiloxy)methanephosphonate (**1c**; 3.74 g, 10.0 mmol), lithium diisopropylamide (1.5 M in cyclohexane; 7.0 mL, 10.5 mmol), and trimethylacetyl chloride (1.21 g, 10.0 mmol) and subsequent aqueous workup gave 1-(1′-adamantyl)-3,3-dimethyl-1,2-butanedione (0.84 g, 34% yield from trimethylacetyl chloride).

1,2-Di-1′-adamantyl-1,2-ethanedione. The reaction of diethyl 1-(1′-adamantyl)-1-(trimethylsiloxy)methanephosphonate (**1c**; 3.74 g, 10.0 mmol), lithium diisopropylamide (1.5 M in cyclohexane; 7.0 mL, 10.5 mmol), and 1-adamantanecarbonyl chloride (1.99 g, 10.0 mmol) with subsequent aqueous workup gave 1-(1′-adamantyl)-2-phenyl-1,2-ethanedione (0.75 g, 23% yield from 1-adamantanecarbonyl chloride). Mp: 76–77 °C. The spectral data was identical with that reported for 1,2-di-1′-adamantyl-1,2-ethanedione.[14]

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The Crystal Structure of 2,3-Dithia-8-(*p*-nitrobenzoyl)bicyclo[3.2.1]octane and the First Bridged Bicyclic Thiosulfinate Ester

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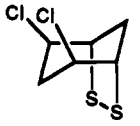
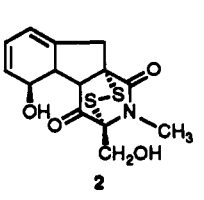
Bridged bicyclic disulfides are unique among the many examples of disulfides; the relatively rigid framework of the bicyclo-backbone forces the dihedral angle about the sulfur–sulfur bond (θ) to become, of necessity, close to 0°. Few systematic studies concerning the reactivity and structure of these compounds have been reported. The preferred conformation for the disulfide linkage has θ in the range of 90°, which minimizes the interaction between the two pairs of 3p, nonbonding electrons on the sulfur atoms. With θ near 0°, the chemical behavior of this class of compounds becomes markedly different from disulfides that have a larger dihedral angle, which absorb light at longer wavelengths in the ultraviolet[1] and have lower ionization potentials.[2] In fact, the first reported photoelectron spectrum of a bridged bicyclic disulfide, 2,4-dichloro-6,7-dithiabicyclo[3.2.1]octane (**1**), showed the largest sulfur lone pair energy gap ever observed for a simple, nonaromatic disulfide.[3]



1

Nature provides many examples of disulfides; naturally occurring bridged bicyclic disulfides are less common but one of the best known may be found in the family of fungal toxins characterized by the epidithiodioxopiperazine ring system. The crystal structure of gliotoxin (**2**), the first member of this family to be isolated,[4] has been reported,[5] and the dihedral angles were found to be 8.8° and 15.8° for the two distinct molecules in the unit cell. Other biologically active examples of bridged bicyclic disulfides may be found in the prostaglandin derivatives. The sulfur analogue of 13,14-dehydro-PGH_2 (**3**) has been synthesized[6] and found to have platelet aggregating properties.



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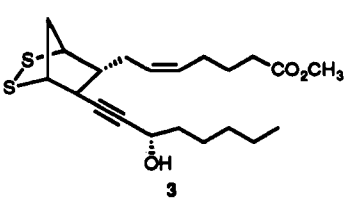

3

The synthesis of the relatively simple bridged bicyclic disulfide **4** has been achieved in only four steps from readily available precursors.[7] However, the stereochemistry of the OH group and the monomeric nature of the molecule was correctly inferred but not unambiguously

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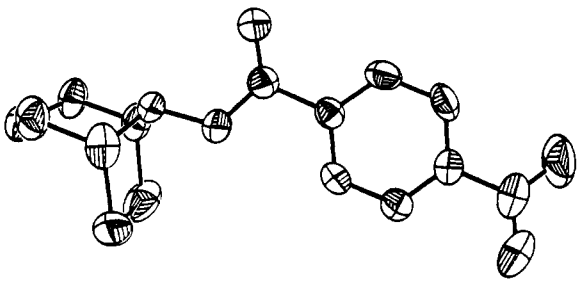


Figure 1.

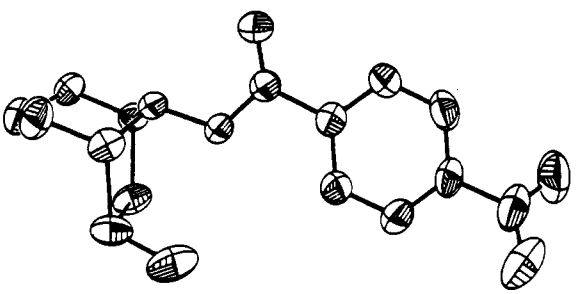
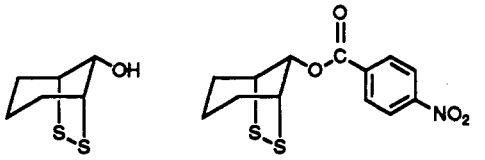


Figure 2.

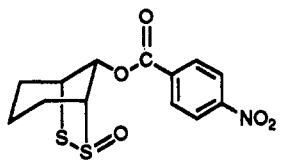
determined. An X-ray crystallographic investigation of 4 was therefore initiated. The parent disulfide itself did not provide suitable crystals for X-ray analysis. The *p*-nitrobenzoyl derivative 5 was then synthesized, and an X-ray structure was obtained.



4 5

An ORTEP[8] drawing of the molecular geometry of 5 is shown in Figure 1. The dihedral angle was found to be −1.3 (2)° and the S–S bond length was slightly longer than normal aliphatic disulfides[9] at 2.08 Å.[10] The stereochemistry of the OH group at the C1 position was unequivocally determined to be syn to the disulfide linkage.

Compound 5 is an excellent model compound for use in a thorough investigation of the chemical behavior of this unique class of compounds. One interesting example of their chemical reactivity is illustrated by the monooxidation of 5 to the corresponding thiosulfinate ester using MCPBA. The resulting product (6) is the first example of a bridged bicyclic thiosulfinate ester. Thiosulfinate



6

compounds have been reported to possess tumor inhibiting,[11] antiviral,[12] antithrombotic,[13] and antifungal and antibacterial[14] properties. Also, some biologically active five-membered-ring cyclic thiosulfinates have been isolated from young asparagus plants[15] and from the plant *Brugiera conjugata*[16] (Rhizophoracea). The *S*-oxide of lipoic acid, a 1,2-dithiolane best known for its participation in oxidative decarboxylation as a coenzyme in the transfer of acetyl groups from pyruvic acid to coenzyme A, has also been found in various biological systems.[17] The *S*-oxide is believed to be a metabolite of lipoic acid.[17,18]

Thiosulfinate esters are chiral at the sulfinyl sulfur, thus one would expect two diastereomers from the oxidation of 5. However, ^1H and ^{13}C NMR evidence indicates the presence of only one isomer.[19] In order to determine the orientation of the sulfinyl oxygen, X-ray analysis was again utilized. The molecular configuration of 6 is shown in Figure 2, and, as in the case of disulfide 5, the dihedral angle about the S–S bond is near 0° at a value of 1.5°. The orientation of the sulfinyl oxygen is in the exo configuration; the S–S bond length is slightly longer (2.10 Å) than that of disulfide 5.[20]

Oxidation of the underivatized bridged bicyclic disulfide 4 also gives only one diastereoisomer which has been proven to be in the exo configuration via derivatization with *p*-nitrobenzoyl chloride and comparison of its spectral data with that of 6.

Dialkyl thiosulfinates have a reputation for being malodorous and unstable;[21] cyclic thiosulfinates have been reported and proven to be exceptions to this trend. Pad-

(1) For example: open chain disulfide: $\theta \sim 90°$, $\lambda = \sim 250$ mμ (Barltrop, J. A.; Hayes, P. M.; Calvin, M. *J. Am. Chem. Soc.* **1954**, *76*, 4384). 1,2-Dithiane: $\theta \sim 60°$, $\lambda \sim 286$ mμ (*Ibid.*). 1,2-Dithiolane: $\theta \sim 27°$, $\lambda = 330$ mμ (*Ibid.*). gliotoxin (2): $\theta \sim 14°$, $\lambda = 340$ mμ (Beecham, A. F.; Mathieson, A. McL. *Tetrahedron Lett* **1966**, 3130). 1α,5α-Epidithioandrostane-3α,17β-diol: $\theta \sim 0°$, $\lambda = 370$ mμ (Bergson, G.; Sjöberg, B.; Tweit, R. C.; Dodson, R. M. *Acta Chem. Scand.* **1960**, *14*, 222). 2,3-Dithiabicyclo[3.2.1]octan-8-ol (4): $\theta \sim 0°$, $\lambda = 367$ mμ (this work), 369 mμ (ref 7).

(2) Moreau, W. M.; Weiss, K. *J. Am. Chem. Soc.* **1966**, *88*, 204.

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(9) Foss, O. In *Organic Sulfur Compounds*, Vol. 1; Kharasch, N., Ed.; Pergamon Press: Oxford, 1961; p 77. The usual range is 2.04–2.065 Å.

(10) Analysis by PCMODEL (Serena Software, Box 3076, Bloomington, IN 47402-3076) gives a dihedral angle for the C–S–S–C linkage of 1.54° and a S–S length of 2.08 Å.

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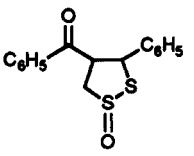
(18) Furr, H. C. *Diss. Abst. Int. B.* **1978**, *38*, 5902. Furr, H. C.; McCormick, D. B. *Int. J. Vit. Nutr. Res.* **1978**, *48*, 165. McCormick, D B. In *Nat. Sulfur Compd. [Proc. Int. Meet.] 3rd. 1979*, Cavallini, D., Gaull, G. E., Zappia, V., Eds.; Plenum: New York, 1980; p 423.

(19) The sample may contain another minor product if a slight excess of MCPBA is used. This has been proven to be the thiosulfonate ester via synthesis of an authentic sample.

(20) PCMODEL analysis (see ref 12) showed a C—S—S(=O)—C dihedral angle of 1.82° and a S–S bond length of 2.06 Å.

(21) Block, E.; O'Connor, J. *J. Am. Chem. Soc.* **1974**, *96*, 3921.

wa[22] first reported that the cyclic thiosulfinate 7 is configurationally stable up to 166 °C. The bridged bicyclic



7

thiosulfinates from this investigation are well-behaved compounds that may be purified by column chromatography on silica gel. Compound 6 is stable at room temperature for several weeks in the presence of oxygen, light, and air and has no unpleasant odor. These compounds are also easily deoxgenated with triphenylphosphine and/or Si_2Cl_6. This transformation leads to the possibility of using the oxidation step as a form of "protection" for the sensitive disulfide moiety during storage or other reactions.

Experimental Section

Melting points were determined on a Gallenkamp melting point apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were obtained on Varian XL-200 and XL-300 MHz spectrometers and the chemical shifts are quoted in ppm as referenced to the internal deuterated solvent downfield from TMS. Microanalyses were obtained from Canadian Microanalytical Service Inc., Vancouver, B.C. Mass spectra were recorded on a Kratos MS25RFA mass spectrometer. IR spectra were obtained on an Analect Instruments ASQ-18 FTIR spectrometer equipped with an Analect Instruments MAP-67 data system and an Analect Instruments RAM-567 color display.

2,3-Dithia-8-[(*p*-nitrobenzoyl)oxy]bicyclo[3.2.1]octane (5). 2,3-Dithiabicyclo[3.2.1]octan-8-ol (4) (0.169 g, 1.04 mmol) was dissolved in freshly distilled pyridine (2 mL), and *p*-nitrobenzoyl chloride (0.193 g, 1.04 mmol) in pyridine (2 mL) was added under an atmosphere of nitrogen. The reaction mixture was heated over a steam bath for 5 min, after which distilled water (5 mL) was added and the yellow precipitate formed was collected and washed several times with 5% $NaHCO_3$ and distilled water. The solid was then recrystallized from ethanol to give 5 as fine orange needles: 0.15 g (47%); mp 143–144 °C; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.8–2.3 (m, 6 H), 4.13 (br s, 2 H, H1 and H4), 5.66 (t, J = 1.8 Hz, 1 H, H8), 8.26 (q, 4 H, aromatics); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 16.49 (C6), 33.26 (C5 and C7), 54.36 (C1 and C4), 83.21 (C8), 123.62 (C3′ and C7′), 131.02 (C4′ and C6′), 135.16 (C2′), 150.66 (C5′), 163.66 (C1′). Anal. Calcd for $C_{13}H_{13}O_4NS_2$: C, 50.14; H, 4.20; N, 4.50; S, 20.60. Found: C, 49.94; H, 4.05; N, 4.60; S, 20.77.

(22) Wudl, F.; Gruber, R.; Padwa, A. *Tetrahedron Lett.* **1969**, 2133.

Crystal data for 5: $C_{13}H_{13}O_4NS_2$, M = 311.36, orthorhombic, space group $Pbn2_1$ (no. 33), a = 7.215 (2), b = 10.654 (4), and c = 18.076 (5) Å, U = 1388.8 (7) Å^3, Z = 4, D_c = 1.489 mg m^{-3}, μ = 3.78 cm^{-1}. Data were collected at room temperature on a Nicolet R3 four-circle diffractometer with graphite-monochromated Mo Kα radiation (λ = 0.709 26 Å) using ω scans ($2\theta_{max}$ 60°). An extinction correction was applied and the structure solved by direct methods (see: Sheldrick, G. M. *SHELXTL. An Integrated System for Solving, Refining and Displaying Crystal Structures from Diffraction Data*, Revision 5.1, University of Gottingen, Federal Republic of Germany, 1985) and refined by full-matrix least-squares methods to residuals of R = 0.057 and R_w = 0.038 for 1375 observed reflections with $I > 3\sigma(I)$ and with 181 variables.

MCPBA Oxidation of 5. Disulfide 5 (100 mg, 0.321 mmol) was dissolved in CH_2Cl_2 (5 mL), and MCPBA (69 mg, 0.321 mmol of 85% mixture) in CH_2Cl_2 (5 mL) was added dropwise at 0 °C. The solution was then warmed to room temperature and stirred for a further hour, at which time $NaHSO_3$ (25 mg) in distilled water (25 mL) was added and the organic layer was separated, washed with 10% $NaHCO_3$ (3×), dried over $MgSO_4$, and evaporated to dryness under reduced pressure to give a white solid. Recrystallization from ethanol gave clear crystals of 6: 83 mg (83%); mp 168.5–170 °C; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.8–2.3 (m, 6 H), 4.14 (br s, 1 H, H4), 4.78 (br s, 1 H, H1), 5.83 (t, J = 1.64 Hz, 1 H, H8), 8.27 (q, 4 H, aromatics); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 17.4 (C6), 24.8 (C5), 30.0 (C7), 59.4 (C4), 75.3 (C1), 84.2 (C8), 123.6 (C3′ and C7′), 131.5 (C4′ and C6′), 134.8 (C2′), 151.8 (C5′), 164.0 (C1′); IR (KBr) 1725 (C=O), 1530 (NO_2), 1355 (S=O), 1270 (NO_2), 1069 (S=O), 722 (NO_2) cm^{-1}; MS 327 ($M^{\bullet+}$, 13%).

Crystal data for 6: $C_{13}H_{13}O_5NS_2$, M = 327.37, monoclinic, space group $P2_1/c$ (no. 14), a = 10.753 (3), b = 10.811 (3), and c = 13.396 (3) Å, β = 112.67 (2), U = 1436.9 (6) Å^3, Z = 4, D_c = 1.513 mg m^{-3}, μ = 3.74 cm^{-1}. Data were collected on a Nicolet R3 four-circle diffractometer with graphite-monochromated Mo Kα (λ = 0.709 26 Å) using ω scans ($2\theta_{max}$ 60°). The structure was solved by direct methods (see: Sheldrick, G. M. *SHELXTL. An Integrated System for Solving, Refining and Displaying Crystal Structures from Diffraction Data*, Revision 5.1, University of Gottingen, Federal Republic of Germany, 1985) and refined by blocked cascade least squares to residuals of R = 0.059, R_w = 0.059 for 2268 observed reflections with $I > 2.5\sigma(I)$ and with 203 variables.

Acknowledgment. We thank the Natural Sciences and Research Council of Canada and F.C.A.R. (Québec) for financial support of this work. We acknowledge the work of Dr. Donald Montecalvo for preliminary synthetic work on this project. Further, we acknowledge useful discussions with Dr. J. P. Snyder (G. D. Searle, Skokie, IL) on aspects of the preliminary work in this area and Professor Kosta Steliou on molecular modeling.

Supplementary Material Available: X-ray data for compound 5 and 6 (5 pages); listing of structure factors for 5 and 6 (23 pages). Ordering information is given on any current masthead page.