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The S_2 Oxygen Atoms Are Essential for the Pronounced Fungitoxicity of the Sulfur-Rich Natural Product, Dysoxysulfone

Sharon A. Bewick,[A] *Stephen Duffy*,[A] *Stephen P. Fletcher*,[A] *Richard F. Langler*,[A,C] *Heather G. Morrison*,[A] *Erin M. O'Brien*,[A] *Charles Ross*,[B,D] *and Vanessa C. Stephenson*[A]

[A] Department of Chemistry, Mount Allison University, Sackville, New Brunswick E4L 1G8, Canada.
[B] Department of Structural Biology, St. Jude Children's Research Hospital, Memphis, TN 38105, USA.
[C] Corresponding author (organic chemistry). Email: rlangler@mta.ca
[D] Corresponding author (crystallography). Email: charles.ross@stjude.org

Synthesis and antifungal testing of 2,4,5,7,9-pentathiadecane 9,9-dioxide has established that the absence of oxygen atoms on S2 significantly attenuates fungitoxicity in accord with our earlier proposal. Attempts to convert that compound into dysoxysulfone led to the discovery of a novel oxidative conversion of unsymmetrical γ-sulfonyl disulfides into the corresponding symmetrical γ-sulfonyl disulfides.

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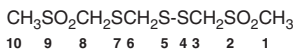
Introduction

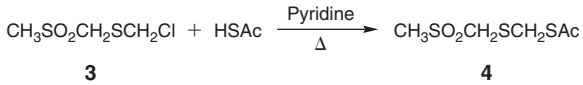
Some time ago, dysoxysulfone (**1**, Scheme 1) was isolated from Fijian mahogany plants.[1] Subsequently, Block et al.[2] synthesized **1** and demonstrated that it has, among others, antifungal and anticancer properties. Thereafter, we disclosed structure–activity results supporting the conclusion that α-sulfone disulfides are effective fungitoxins.[3–5] Furthermore, we have shown that our α-sulfone disulfides exhibit significant antileukemic behaviour *and* that they are toxic to non-transformed (i.e. normal) human cells.[6]



1

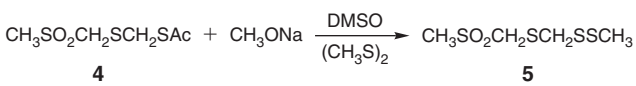
2

Scheme 1.



3 **4**

Scheme 2.



4 **5**

Scheme 3.

More recently, we have undertaken the synthesis of **2** with two goals in mind: (*a*) to establish that, in the absence of oxygen atoms at S2, the dysoxysulfone framework would have sharply diminished antifungal activity in accord with our earlier conclusions[3] and (*b*) to examine selected oxidation reactions of **2**.

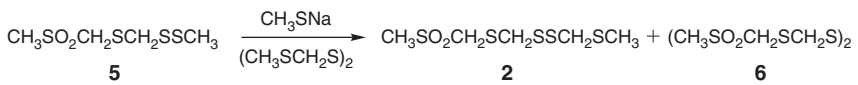
Results and Discussion

Our synthesis of **2** began with the α-chlorosulfone **3** (Scheme 2). Earlier, a successful synthesis of **3**[7] followed by a significant improvement in the regiochemistry of the step that introduces the first oxygen atom[8] were reported. The first step in the conversion of **3** into **2** introduces S5.

Deacylation of **4** proved to be problematic because the resultant mercaptide anion extrudes/adds thioformaldehyde, leading to a mixture of alternating carbon/sulfur frameworks of different lengths. Related behaviour is known in the chemistry of α-mercaptosulfones and α-mercaptosulfide anions.[2,9] The mercaptide anion formed by deacylation of **4** was successfully trapped when the solvent was changed to dimethyl disulfide/dimethyl sulfoxide (DMSO; see Scheme 3).

Compound **5** was smoothly converted to **2** by disproportionation in the appropriate solvent (see Scheme 4).

Biological testing of **5** and **2** showed substantially diminished antifungal activity relative to that of typical α-sulfone



5 **2** **6**

Scheme 4.

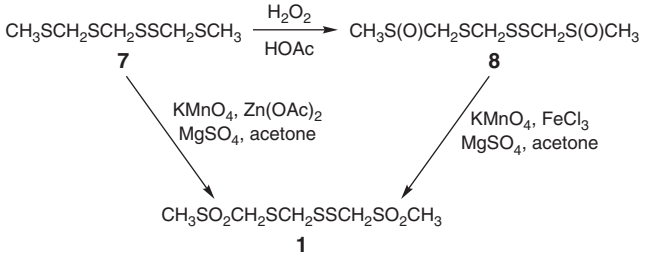
10.1071/CH03253 0004-9425/05/030218

Table 1. Disulfides as antifungal agents

Each compound was introduced (in acetone) onto a small paper disk, which was placed in a culture medium. The diameter of the clear zone (the area where the fungus, *Aspergillus niger* and *Aspergillus flavus* did not grow) around each disk indicated antifungal activity.

Sulfur compound tested	Dose [μg per disk]	Diameter of clear zone [mm][A]	
		A. niger	*A. flavus*
$CH_3SO_2CH_2SCH_2SSCH_3$ **5**	25	1.4	1.5
$CH_3SO_2CH_2SCH_2SSCH_2SCH_3$ **2**	25	1.9	2.7
$CH_3SO_2CH_2SSCH_2CH_3$ [3]	25	4.8	3.3
$CH_3SO_2CH_2SS(CH_2)_4CH_3$ [5]	25	13.8	11.7
$CH_3SO_2(CH_2)_3SSCH_2SCH_3$ **11**	100	0	0

[A] For each test, four replicates were done.



Scheme 5. Block's syntheses of dysoxysulfone **1**.

$CH_3SO_2CH_2SCH_2SSCH_2S(O)CH_3$

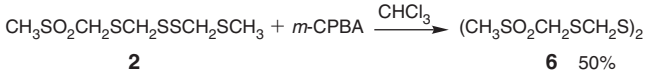
9

Scheme 6.

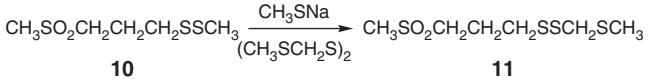
disulfides (see Table 1). Note that simple α-sulfide disulfides show little or no antifungal activity at 100 μg per disk (see results for 2,3,5-trithiahexane and 2,4,5,7-tetrathiaoctane in ref. [3]). Hence, results reported in Table 1 support the conclusion that dysoxysulfone **1**, itself, is an effective antifungal agent[2] because it is an α-sulfone disulfide.

Given that Block's syntheses[2] proceed by oxidation of the pre-assembled skeleton of **1** (see Scheme 5), it seemed that our synthesis of **2** should constitute a formal synthesis of dysoxysulfone **1**. When we attempted to oxidize **2** with hydrogen peroxide, we were unable to isolate significant amounts of the target sulfoxide (**9**, Scheme 6). Attempts to convert **2** into **1** with permanganate in the presence of Block's Lewis acids[2] were unsuccessful. Since Block et al. assumed that their initial difficulties arose from reactions with base, generated during the oxidation reactions, we initiated exploratory work on the oxidation of **2** with *meta*-chloroperoxybenzoic acid (*m*-CPBA)/chloroform. It came as something of a surprise to find that the principal organic product from the oxidation of **2** was the symmetrical disulfide **6**[2] (see Scheme 7). It was, in fact, the presence of **6** in product mixtures obtained from $KMnO_4/MgSO_4$ oxidations of **7** that led Block et al.[2] to postulate a base-induced elimination reaction which would partially degrade **1** to furnish **7**. Our conditions would not permit application of their rationale to the Scheme 7 reaction.

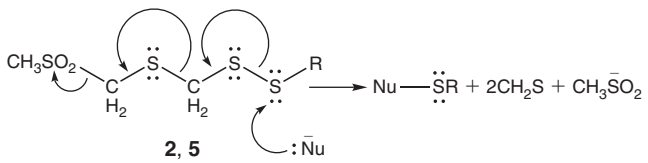
In order to gain more insight into the reaction shown in Scheme 7, we have replaced S7 in compound **2** with a methylene group. Our synthesis is outlined in Scheme 8.



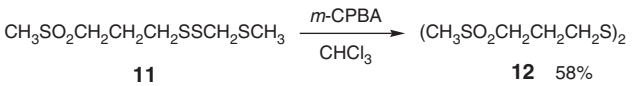
Scheme 7.



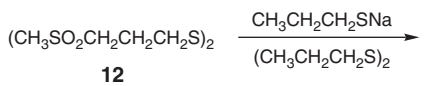
Scheme 8.



Scheme 9.



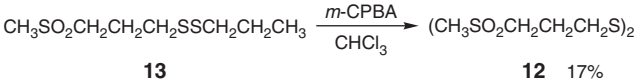
Scheme 10.



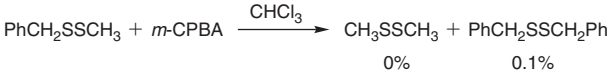
$CH_3SO_2CH_2CH_2CH_2SSCH_2CH_2CH_3$

13

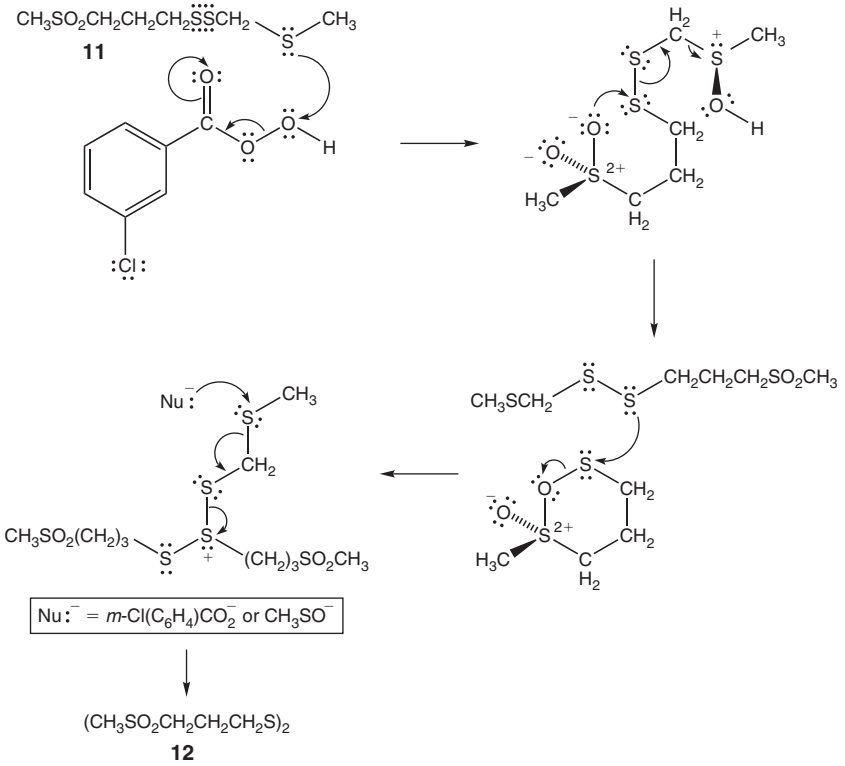
Scheme 11.



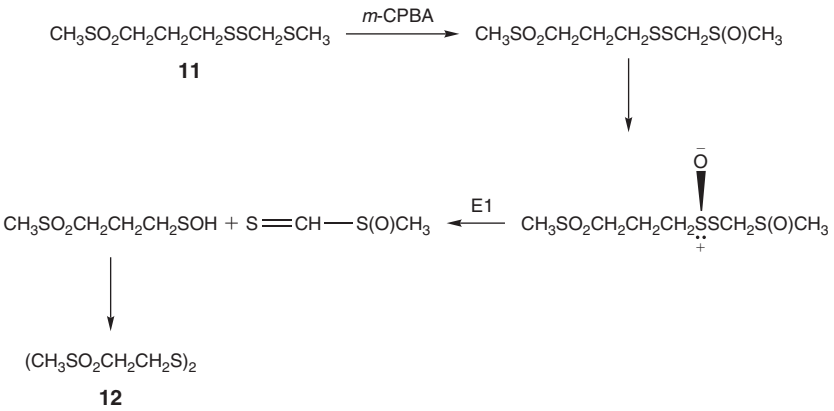
Scheme 12.



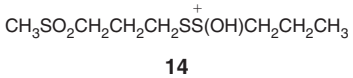
Scheme 13.



Scheme 14.



Scheme 15. Alternative to the Scheme 14 proposal.



Scheme 16.

Note that **11** has no fungitoxicity at 100 μg per disk (see Table 1), in accord with the earlier assertion that simple α-sulfide disulfides show little or no fungitoxicity. The difference in fungitoxicities for **2**, **5**, and **11** may be ascribed to mild activation of the disulfide linkage by the remote sulfonyl group in **2** and **5** which is not available to **11** (see Scheme 9). The reaction shown in Scheme 9 conforms to our earlier suggestion,[3] which rationalizes fungitoxicity for simple α-sulfone disulfides. Oxidation of **11** with *m*-CPBA furnished the symmetrical disulfone disulfide **12** in good yield (see Scheme 10). In addition to full spectroscopic characterization, the structure of **12** was established by X-ray crystallography (see Fig. 1 and Table 2).

Next we prepared compound **13** in which both S7 and S2 (compare **2**) have been replaced by methylenes (see Scheme 11). Peroxidation of **13** furnished a modest amount of symmetrical disulfide **12** (see Scheme 12).

Finally, peroxidation of a simple unsymmetrical disulfide furnished essentially no symmetrical disulfides (see Scheme 13).

The results disclosed in Schemes 7, 10, 12, and 13 suggest (*a*) that the, initially unexpected, efficient conversion of dysoxysulfone relatives into symmetrical disulfides, requires sulfenyl sulfur at S2 and sulfonyl sulfur at S9 and (*b*) that no step in the mechanism for these reactions involves strong

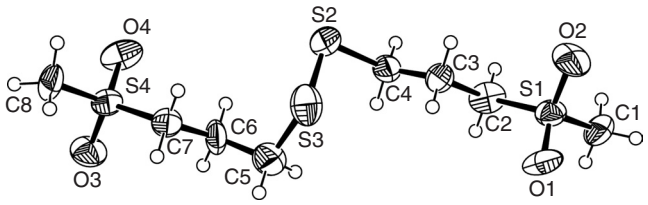


Fig. 1. A perspective drawing of compound **12**.

Table 2. Non-hydrogen atom bond lengths [Å][A] for compound 12

Bond	Distance	Bond	Distance
C(1)–S(1)	1.78(2)	C(8)–S(4)	1.77(2)
S(1)–O(1)	1.423(18)	S(4)–O(4)	1.438(18)
S(1)–O(2)	1.444(17)	S(4)–O(3)	1.440(16)
S(1)–C(2)	1.77(2)	S(4)–C(7)	1.78(2)
C(2)–C(3)	1.53(2)	C(7)–C(6)	1.53(2)
C(3)–C(4)	1.50(2)	C(6)–C(5)	1.52(2)
C(4)–S(2)	1.82(2)	C(5)–S(3)	1.82(2)
S(2)–S(3)	2.04(2)		

[A] Corresponding bond lengths were constrained to be equal in left and right halves of the molecule.

base. A mechanism, consistent with the foregoing results is presented in Scheme 14. There have been some reports[10–12] suggesting that sulfonyl oxygen can coordinate electrophilic sites in accord with the heart of the mechanism shown in Scheme 14.

A referee has suggested an alternative mechanism for the results disclosed in Schemes 7, 10, 12, and 13. In that proposal, oxidation would furnish a sulfoxide thiosulfinate with the regiochemistry shown in Scheme 15. Both Scheme 14 and Scheme 15 can account for the results in Schemes 7, 10, and 13. However, Scheme 12 shows significant symmetrical disulfide formation (17%) for a substrate which lacks the α-sulfide disulfide functionality. Absent the α-sulfide linkage, the Scheme 15 mechanism doesn't apply to Scheme 12. The expected regiochemistry for oxidation of **13** would produce the cationic intermediate **14** (Scheme 16) which could be cleaved by the neighbouring sulfonyl group in a manner analogous to that pictured in Scheme 14.

Conclusions

1. Synthesis and biological testing of dideoxydysoxysulfone **2** shows it to be a weak antifungal agent. Compound **2** is an order of magnitude less fungitoxic than the pentyl disulfide (Table 1) which is an α-sulfone disulfide that has the same skeletal length as **2**.
2. Peroxidations (*m*-CPBA) of **2** and **11** led to unexpectedly high yields of symmetrical disulfone disulfides. The proposed mechanism (Scheme 14) involves participation of S2 and a sulfonyl oxygen on S9.

Experimental

IR spectra were recorded on a Perkin–Elmer 710B grating spectrophotometer. ^{1}H NMR spectra (60 MHz) were obtained on a Varian EM360L instrument. ^{1}H NMR (270 MHz) and ^{13}C NMR spectra were obtained on a JEOL JNM-GSX 270 Fourier-transform NMR system. Unless otherwise specified, all NMR spectra were obtained for the compounds in deuterated chloroform solutions using tetramethyl silane as an internal standard. Routine mass spectra (MS) were obtained on a Hewlett–Packard 5988A gas-liquid chromatography mass spectrometer (GLC/MS) system. Operating conditions for the GLC/MS were as follows: column packing Supelco SPB-1; column dimensions 0.2 mm × 12 m; carrier gas He (flow 1 mL min^{-1}) with a split ratio of 100:1; solvent delay 1.5 min; temperature program heated from 50 to 225°C at +15°C min^{-1}; ion source temperature 225°C. Melting point analyses were determined on a Gallenkamp MFB-595 capillary melting point apparatus and are uncorrected.

Yield Determinations for Reactions with m-*CPBA*

Samples were weighed analytically and diluted to the low ppm range before analysis. Samples (1 μL) were analyzed using a Varian CP-3800 gas chromatograph (GC) equipped with a CP-8410 autoinjector, connected to a Saturn 2000 mass selective detector. The GC oven contained a Varian 30 m × 0.25 mm i.d. × 0.25 μm film thickness CP-Sil 8 CB low bleed/MS column. The GC temperature program was as follows, injection temperature 250°C, initial temperature 50°C, hold for 2 min, ramp to 220°C at +20°C min^{-1} and hold for 2 min, ramp to 260°C at +5°C min^{-1} and hold for 21.5 min for a total analysis time of 42 min. Helium gas was used as the carrier and the column flow rate was held constant at 1.0 mL min^{-1}. On occasion, the GC run was terminated before the final time was reached provided that the analyte had eluted from the column. The mass selective detector was operated in both the electron impact (EI) and the chemical (CH_4) ionization (CI) modes. The mass range selected was typically 50 to 500 amu. A minimum of three microscans were averaged to produce each scan, resulting in a data accumulation rate of 0.5 s per scan for EI and 0.62 s per scan for CI. The emission current was set at 30 μA. Percent yields were calculated based on response factors for each of the identified compounds, by comparing the integrated peak areas of standards to the peak areas obtained from reaction products through the use of the *Saturn* GC/MS workstation software.

Biological Testing

Details have been provided earlier.[3]

Preparation of 2,4-Dithiapentane 2,2-Dioxide-5-thiolacetate ***4***

The chlorosulfide sulfone **3**[7] (0.30 g, 1.72 mmol) and thioacetic *S*-acid (0.127 g) were added to dry pyridine (3 mL). The reaction mixture was immersed in a constant temperature bath (82°C) for 1.5 h.

Chloroform (100 mL) was added and the resultant mixture washed with 5% hydrochloric acid (100 mL). The organic layer was then extracted with 2.5% w/v sodium hydroxide solution (100 mL), dried ($MgSO_4$), filtered, and the solvent evaporated.

Crude **4** was recrystallized from methanol affording sulfone sulfide thiolacetate **4** (0.135 g, 0.63 mmol, 37%). An analytical sample was prepared by sublimation (60°C, 1.7 Torr). After 18 h, the cold finger was cleaned and the sublimation resumed for 3.5 h. Crystalline, sublimed thiolacetate (mp 77.8–80.5°C) was obtained (Found: C 27.8, H 4.5. $C_5H_{10}O_3S_3$ requires C 28.0, H 4.7%). ν_{max}/cm^{-1} 1700, 1320, 1140. δ_H (60 MHz; $CDCl_3$; Me_4Si) 2.36 (3H, s, CH_3CO), 3.03 (3H, s, CH_3SO_2), 3.93 (2H, s, CH_2), 4.30 (2H, s, CH_2). δ_C (68 MHz; $CDCl_3$; Me_4Si) 30.55, 31.87, 38.26, 53.08, 193.78. *m/z* (GLC/MS, R_t 26.2 min) 135 (54%, $M^{+\bullet} - CH_3SO_2$), 89 (36), 43 (100).

Preparation of 2,4,6,7-Tetrathiaoctane 2,2-Dioxide ***5***

Sodium metal (34 mg, 1.47 mmol) was dissolved in methanol (10 mL) and the solvent evaporated. The residue was dried in vacuo. DMSO (3 mL) was added and the resultant mixture stirred vigorously (mechanical stirrer) for 5 h. During this period, the reaction mixture was open to the atmosphere. Thereafter, **4** (0.30 g, 1.37 mmol) was dissolved in DMSO (1 mL) and the resultant solution added to the reaction mixture. Dimethyl disulfide (6 mL) was added, the flask stoppered and the reaction gently stirred at ambient temperature for 50 h. The reaction mixture, initially yellow, turned orange by the time the reaction was completed.

2.5% Hydrochloric acid (100 mL) was added and the resultant mixture extracted with diethyl ether (3 × 100 mL portions). The organic layer was concentrated, 2.5% hydrochloric acid (100 mL) added and the resultant mixture extracted with diethyl ether (3 × 100 mL aliquots). The combined organic layers were dried ($MgSO_4$), filtered, and the solvent evaporated.

Crude product was chromatographed on silica gel (30 g) employing chloroform for elution (30 mL fractions). Fraction 5 was concentrated affording the sulfone sulfide disulfide **5** (0.17 g, 8.0 mmol, 58%) as an oil. ν_{max}/cm^{-1} (liquid film) 1300, 1140. δ_H (270 MHz; $CDCl_3$; Me_4Si) 2.51 (3H, s, CH_3SS), 3.07 (3H, s, CH_3SO_2), 4.05 (2H, s, CH_2), 4.19 (2H, s, CH_2). δ_C (68 MHz; $CDCl_3$; Me_4Si) 23.26, 38.45, 41.22, 51.49. *m/z* (GLC/MS, R_t 9.8 min) 218 (19%, $M^{+\bullet}$), 139 (100), 93 (73).

Preparation of 2,4,6,7,9-Pentathiadecane 2,2-Dioxide ***2***

Sodium metal (0.016 g) was dissolved in methanol (5 mL). Methanethiol (20 mL) was slowly bubbled through the solution. The solvent was evaporated and the residual sodium methanethiolate dried in vacuo. DMSO (10 mL) was added and the resultant solution stirred for 0.5 h.

A portion (0.3 mL) of the sodium thiolate solution was added to a solution of **5** (0.50 g, 2.29 mmol) in $(CH_3SCH_2S)_2$[13] (3 mL) and the reaction stirred at ambient temperature for 7 d.

The entire reaction mixture was poured onto a chromatography column (50 g silica gel in light petroleum). The column was eluted with light petroleum (10 × 50 mL fractions). Thereafter, chloroform (50 mL fractions) were collected. Fractions 5–14 were combined affording unchanged $(CH_3SCH_2S)_2$ (3 g). Fractions 15–17 were combined and concentrated, furnishing dideoxydysoxysulfone **2** (0.531 g, 2.01 mmol, 87%). The bulk of minor contaminants were trapped on the cold finger of a sublimator (bath, 60°C, 1.3 Torr; 192 h). Recrystallization from chloroform furnished **2** (mp 68–70°C) (Found: C 22.9, H 4.3. $C_5H_{12}O_2S_5$ requires C 22.7, H 4.6%). ν_{max}/cm^{-1} (KBr) 1300, 1100. δ_H (270 MHz; $CDCl_3$; Me_4Si) 2.53 (3H, s, CH_3SS), 3.06 (3H, s, CH_3SO_2), 3.94 (2H, s, CH_2), 4.08 (2H, s, CH_2), 4.27 (2H, s, CH_2). δ_C (68 MHz; $CDCl_3$; Me_4Si) 15.21, 38.55, 42.04, 44.94, 51.44. *m/z* (GLC/MS, R_t 12.5 min) 264 (5%, $M^{+\bullet}$), 93 (11), 61 (100).

Fractions 18–20 were combined and concentrated affording the bissulfide disulfide disulfone **6**[2] (0.021 g, 0.061 mmol, 5%). After recrystallization from methanol, **6** had mp 125.3–125.6°C. ν_{max}/cm^{-1} (KBr) 1228, 1126. δ_H (270 MHz; $CDCl_3$; Me_4Si) 3.04 (6H, s, CH_3SO_2), 4.05 (4H, s, CH_2), 4.26 (4H, s, CH_2). δ_C (68 MHz; $CDCl_3$; Me_4Si) 38.64, 41.74, 51.37.

Preparation of 2,6,7,9-Tetrathiadecane 2,2-Dioxide ***11***

A sodium methanthiolate/DMSO solution was prepared as described for the preparation of **2**. A portion of the sodium methanethiolate solution (0.4 mL) was added to a solution of the sulfone disulfide **10**[3] (0.50 g, 2.50 mmol) in $(CH_3SCH_2S)_2$[13] (3 mL) and the reaction stirred at ambient temperature for 21 d.

The entire reaction mixture was poured onto a chromatography column (50 g silica gel in light petroleum). The column was eluted with light petroleum (15 × 50 mL fractions), followed by chloroform (50 mL fractions). The light petroleum fractions furnished unchanged $(CH_3SCH_2S)_2$. Fractions 22–27 were combined and concentrated affording the sulfone sulfide disulfide **11** (0.62 g, 2.50 mmol, 100%). Recrystallization from methanol gave **11** (mp 56–58°C). (Found: C 29.5, H 6.0. $C_6H_{14}O_2S_4$ requires C 29.2, H 5.7%). ν_{max}/cm^{-1} (KBr) 1317, 1214, 1141. δ_H (270 MHz; $CDCl_3$; Me_4Si) 2.23 (3H, s, CH_3S), 2.30 (2H, quintet, CH_2), 2.93 (2H, t, CH_2), 2.95 (3H, s, CH_3SO_2), 3.18 (2H, t, CH_2), 3.84 (2H, s, CH_2). δ_C (68 MHz; $CDCl_3$; Me_4Si) 15.30, 21.72, 36.80, 40.90, 44.84, 52.81. *m/z* (GLC/MS, R_t 12.0 min) 246 (5%, $M^{+\bullet}$), 79 (5), 61 (100).

Preparation of 2,6,7,11-Tetrathiadodecane 2,2,11,11-Tetroxide ***12***

Sodium metal (0.12 g) was dissolved in methanol (10 mL), the solvent evaporated and the residue dried in vacuuo. DMSO (3.5 mL) was added and the resultant mixture stirred vigorously with a mechanical stirrer for 5 h. During this time, the reaction mixture was open to the atmosphere. Dimethyl disulfide (10 mL) and $CH_3SO_2(CH_2)_3SAc$[3] (1.0 g, 5.1 mmol) were added and the reaction mixture stirred at ambient temperature for 2 d.

2.5% Hydrochloric acid (100 mL) was added and the resultant mixture extracted with diethyl ether (3 × 100 mL aliquots). The combined organic layers were evaporated. 2.5% Hydrochloric acid (100 mL) was added to the residue and the resultant mixture extracted with diethyl ether (3 × 100 mL aliquots). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The residue was recrystallized from methanol (4 mL) affording the disulfone disulfide **12** (0.488 g, 1.24 mmol, 50%). After a second recrystallization, **12** had mp 107.1–108.3°C. The X-ray crystal structure is determined below. ν_{max}/cm^{-1} (KBr) 1317, 1216, 1141. δ_H (270 MHz; $CDCl_3$; Me_4Si) 2.30 (4H, quintet, CH_2), 2.85 (4H, t, CH_2), 2.96 (6H, s, CH_3SO_2), 3.18 (4H, t, CH_2). δ_C (68 MHz; $CDCl_3$; Me_4Si) 21.63, 36.42, 41.05, 52.81. *m/z* (GLC/MS) 306 (17%, $M^{+\bullet}$), 121 (100).

Preparation of 2,6,7-Trithiadecane 2,2-Dioxide ***13***

Sodium metal (20 mg) was dissolved in methanol (10 mL) and 1-propanethiol (73 mg) added. The solvent was evaporated and the residue dried in vacuuo for 1 h. DMSO (1 mL) and di-*n*-propyl disulfide (5 mL) were added. The reaction mixture was stirred at ambient temperature for 1 h. The disulfone disulfide **12** (0.265 g, 0.86 mmol) was added and the reaction mixture stirred at ambient temperature for 7 d.

2.5% Hydrochloric acid (100 mL) was added, the resultant mixture extracted with diethyl ether (2 × 100 mL aliquots) and the solvent evaporated. 2.5% Hydrochloric acid (100 mL) was added and the resultant mixture extracted with diethyl ether (2 × 100 mL portions). The combined organic layers were dried ($MgSO_4$), filtered, and the solvent evaporated.

The crude product was chromatographed on silica gel (35 g) employing chloroform for elution (25 mL fractions). Fractions 9–12 were combined and concentrated affording **13** as a reddish oil (78 mg, 0.34 mmol, 20%). Bulb-to-bulb distillation (0.25 Torr) furnished **13** as a pale yellow oil (43 mg). δ_H (270 MHz; $CDCl_3$; Me_4Si) 1.00 (3H, t, CH_3C), 1.70 (2H, sextet, CH_2), 2.30 (2H, quintet, CH_2), 2.68 (2H, t, CH_2), 2.81 (2H, t, CH_2), 2.94 (3H, s, CH_3SO_2), 3.17 (2H, t, CH_2). δ_C (68 MHz; $CDCl_3$; Me_4Si) 13.12, 21.65, 22.52, 36.43, 40.87, 40.93, 52.96. *m/z* (GLC/MS) 228 (18%, $M^{+\bullet}$), 121 (100), 105 (42).

Preparation of Benzyl Methyl Disulfide

Sodium metal (20 mg) was dissolved in methanol (1 mL). Benzyl thiol (0.1 mL) was added, the solvent evaporated and the residue dried in vacuuo for 45 min. DMSO (6 mL), dibenzyl disulfide (2.01 g, 8.17 mmol), and dimethyl disulfide (12 mL) were added and the reaction mixture stirred at ambient temperature for 48 h.

2.5% Hydrochloric acid (70 mL) was added and the resultant mixture extracted with diethyl ether (3 × 50 mL portions). The combined organic layers were concentrated. 2.5% Hydrochloric acid (70 mL) was added and the resultant mixture washed with diethyl ether (3 × 50 mL aliquots). The combined organic layers were dried ($MgSO_4$), filtered, and the solvent evaporated. The residue was rectified at reduced pressure affording benzyl methyl disulfide (2.29 g, 13.5 mmol, 83%, bp 105–110°C/2.5 Torr). δ_H (270 MHz; $CDCl_3$; Me_4Si) 2.09 (3H, s, CH_3SS), 3.89 (2H, CH_2), 7.32 (5H, m, Ph). *m/z* (GLC/MS) 170 (19%, $M^{+\bullet}$), 91 (100).

Reaction of Unsymmetrical Disulfides with m-*CPBA*

Unsymmetrical disulfides **2**, **11**, **13**, and benzyl methyl disulfide were separately treated with *m*-CPBA as outlined below for **11**.

50% *m*-CPBA (0.255 g) was covered with THF (8 mL) and water (2 mL) and the reaction mixture stirred briefly. The sulfone sulfide disulfide **11** (99 mg, 0.4 mmol) was added and the reaction mixture stirred at ambient temperature for 7 d.

The THF was evaporated and chloroform (200 mL) added. The resultant mixture was extracted with 2.5% w/v sodium hydroxide (2 × 50 mL aliquots). The combined aqueous layers were back-extracted with chloroform (50 mL). The combined organic layers were dried ($MgSO_4$),

filtered, and concentrated, affording crude product (62 mg). Both ^{1}H and ^{13}C NMR showed that dominant peaks matched appropriate chemical shifts for the disulfone disulfide **12**. GLC/MS established that the crude contained **12** (0.036 g, 58%). Recrystallization furnished **12** with mp 107.0–108.2°C.

Oxidation of the unsymmetrical disulfides gave symmetrical disulfides (% yield): **2** furnished **6** (50%); **11** furnished **12** (58%); **13** furnished **12** (17%); benzyl methyl disulfide furnished dimethyl disulfide (0%) and dibenzyl disulfide (0.1%).

Crystallography

A small single crystal was selected and mounted on a Bruker Proteum-R single-crystal diffractometer (SMART 6000 CCD area detector on a MacScience rotating-anode generator). Data were collected at 25°C using $Cu_{K\alpha}$ radiation generated 50 kV, 90 mA, and monochromated by Osmic 'blue' optics. Data were collected using the *Proteum* program suite; images were processed using *SAINT* and scaled and absorption-corrected using *SADABS*.

The data consisted of four sets of 600 images, the crystal being reoriented between sets to maximize coverage of reciprocal space. Each image is a 0.3° ω-scan. Sets 1 and 2 (detector setting 90° 2θ) were collected for 20 s per image, set 3 (35° 2θ) for 15 s per image, and set 4 (0° 2θ) for 10 s.

Examination of the diffraction pattern revealed that the lattice was monoclinic, with systematic absences consistent with the space group $P2_1$ or $P2_1/m$. Refinement of the unit cell resulted in the parameters: a 4.85(8), b 29.97(45), c 5.38(7) Å; β 112.7(5)°. The relatively large uncertainty in the cell parameters is ascribed to the poor crystallinity of the sample. The reflections were integrated from the scaled set of images, resulting in a dataset consisting of 1685 reflections in the range $-3 < h < 4$, $-23 < k < 29$, $-5 < l < 5$, corresponding to a resolution limit of ~1 Å. $R_{int} = 0.031$ for the 1067 unique reflections.

Examination of intensity statistics strongly suggested that $P2_1$ was the proper choice of space group and the structure was solved in that space group using *SHELXS*. Due to the relatively small number of data, the structural refinement (using *SHELXL*) was highly restrained. All hydrogen atoms were forced to adopt ideal geometry and corresponding bond lengths and bond angles in the two halves of the molecule were restrained to the same value. The crystal was found to be twinned and the twin proportion was refined to 0.27(9). The final refinement statistics were: *wR*2 0.19, *R*1 0.071, *S* 1.11. The maximum residual electron density was 0.86 e Å^{-3}. This and several other peaks in the residual map appear to correspond to the S atoms in an alternative orientation of the molecule in the unit cell.

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