1,3-Dimethylalloxazine 5-Oxide (11). Crude product of the above separation (30 mg) was recrystallized from 5 mL of water/ethanol (1:1) yielding 12 mg of yellow needles with mp 216 °C (lit. mp 237 °C)[9,14] (authentic sample mp 218 °C, no depression).

Anal. Calcd for $C_{12}H_{10}N_4O_3$: C, 55.81; H, 3.90; N, 21.70. Found: C, 55.79; H, 3.88; N, 21.39. Mol wt 258.2.

2,3-Dimethylalloxazine 5,10-Dioxide (12). Orange colored eluate (40 mg) was purified by recrystallization from 10 mL of ethanol to give 20 mg of orange crystals with mp 236–238 °C.

Anal. Calcd for $C_{12}H_{10}N_4O_4$: C, 52.55; H, 3.68; N, 20.43; OCH_3, 11.3. Found: C, 52.85; H, 3.67; N, 20.20; OCH_3, 9.8.

1,3-Dimethylalloxazine 5,10-Dioxide (13). Crude reaction product (0.1 g) was recrystallized from a mixture of 5 mL of water and 2 mL of ethanol to give 0.076 g of shiny crystals, mp 194 °C.

Anal. Calcd for $C_{12}H_{10}N_4O_4$: C, 52.55; H, 3.68; N, 20.43. Found: C, 52.81; H, 3.67; N, 20.10. Mol wt 274.2.

3-Methyl-10-methoxyalloxazine 5-Oxide (14). Crude material (40 mg) was recrystallized from 10 mL of ethanol to give 20 mg of orange crystals with mp 196–198 °C.

Anal. Calcd for $C_{12}H_{10}N_4O_4$: C, 52.55; H, 3.68; N, 20.43; OCH_3, 11.3. Found: C, 52.39; H, 3.71; N, 20.22; OCH_3, 11.7.

Biological Activity of Alloxazine Di-*N*-oxide. Assays were performed under the supervision of the Drug Research and Development Section, Division of Cancer Treatment, National Cancer Institute, U.S. Public Health Services by the procedures described in Geran et al.[16] A compound is considered to show significant in vivo activity against the Walker 256 tumor system if it causes reduction of tumor weight in the treated rats to 42% or less of the tumor weight in the control animals. In this test system the alloxazine di-*N*-oxide at 60 mg/kg showed an 80% reduction in tumor weight. In other tests using mouse leukemia L-1210 no life prolongation was noted. The alloxazine di-*N*-oxide inhibited the growth of *Lactobacillus casei* (ATCC 7469) growing in folic acid limited medium at 20 mcg/mL, and this inhibition was not reversed by citrovorum factor, thymidine, or riboflavin.

Registry No.—**1**, 490-59-5; **2**, 2891-59-0; **3**, 1086-80-2; **5**, 22525-79-7; **7**, 50628-74-5; **8**, 54011-43-7; **9**, 39132-80-4; **10**, 4897-17-0; **11**, 2962-89-2; **12**, 62015-56-9; **13**, 32706-14-2; **14**, 62015-57-0.

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(17) We thank Mrs. M. Bischler and Mr. E. Krienitz, Department of Chemistry, University of Konstanz, for the determination of the physical data, and Professor D. Perlman, School of Pharmacy, for assistance with the bioassay determinations.

Structural Studies of Organosulfur Compounds.[1] 3. Stereochemistry and Conformational Distortions in *trans*-Hexahydro-1,4-benzoxathiane *S*-Oxides

Donna M. Frieze, Philip F. Hughes, Robert L. Merrill, and Slayton A. Evans, Jr.*

William Rand Kenan, Jr., Laboratories of Chemistry, University of North Carolina, Chapel Hill, North Carolina 27514

Received October 25, 1976

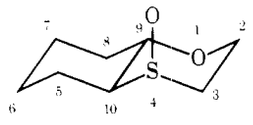
trans-Hexahydro-1,4-benzoxanthiane and the 4-oxides have been prepared and the stereochemistry of the sulfinyl derivatives determined. Acid-catalyzed equilibration of the sulfoxides indicate that the axial sulfoxide is more stable than the equatorial by 0.85 ± 0.07 kcal/mol. Application of the *R*-value method indicates that the axial sulfoxide is severely flattened when compared to the equatorial diastereomer.

In a recent report[1] we had established the preferred conformation of the sulfinyl oxygen atom in the 1,4-oxathiane system **1** in the absence of other substituents[2] as predominantly *axial* by low temperature ^{13}C NMR techniques. This result was found to be in keeping with a number of previous reports describing sulfinyl oxygen conformations with other heteroatoms within the six-membered ring or as substituents,[3] but yet contrary to a number of other studies describing the conformational characteristics of sulfoxides.[4] We reasoned that the calculated conformational free energy difference, $\Delta\Delta G^\circ \simeq 0.4$ kcal/mol, for the sulfinyl oxygen atom in thiane 1-oxide (**2**) and 1,4-oxathiane 4-oxide (eq $\rightleftharpoons$ ax; $\Delta G^\circ = -0.17$ kcal/mol for thiane 1-oxide[3b] and $\Delta G^\circ = -0.68$ kcal/mol for 1,4-oxathiane 4-oxide[1]) results, in part, from the presence of an attractive intramolecular electrostatic interaction in 1,4-oxathiane 4-oxide which is absent in the pentamethylene sulfoxide, **2**. This may be viewed as a 1,4-attractive interaction between the negatively charged oxygen of the sulfoxide and the positive carbon atoms (and perhaps hydrogens) at C2 and C6.[5] Intramolecular dipole–dipole interactions appear to be dominant features in a number of heterosubstituted sulfoxides. In fact, a recent report describing the results of empirical force field (molecular mechanics[6]) calculations on six-membered ring sulfoxides[7] suggests that the conformations of the sulfinyl oxygen atom are controlled largely by dipolar considerations which exist between a ring heteroatom and the sulfinyl oxygen atom.

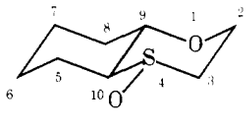
An attractive or repulsive interaction, which might result in a decrease or increase in the distance between the axial sulfinyl oxygen and the C2, C6 carbons and hydrogens, would be expected to induce either mild puckering or flattening of the central ring of **1** when compared to a system without an axial sulfinyl oxygen.[8] This distortion could be identified from precise determinations of vicinal coupling constants which could ultimately be translated into torsional angles.[9,10]

In this report, we have examined the conformational distortions caused by the sulfinyl and sulfonyl oxygens in the 4-oxides of *trans*-hexahydro-1,4-benzoxathiane (**6**). We view

6 and its 4-oxides as excellent choices since the trans ring-fused decalin analogues would ensure conformational rigidity of the chair conformation of the basic 1,4-oxathiane ring thus preventing conversion to boat or twist-boat conformations but providing allowances for minor conformational distortions. We, of course, recognize that the sulfoxides, **13** and **14**, do not exactly simulate the chair conformations of sulfoxide **1** because there is one additional 1,3-syn-axial sulfinyl oxygen–carbon hydrogen interaction in **13** involving C5.[11] However, we have assumed that this interaction is effectively neutralized by an essentially equivalent interaction involving the equatorial sulfinyl oxygen atom and the C5 carbon and hydrogen in **14**.



13



14

Results and Discussion

Syntheses. We prepared the model systems, **6**, **13**, **14**, and **15**, by the series of reactions described in Chart I. As reported in previous studies,[12] *trans*-2-mercaptocyclohexanol (**3**) was obtained from the reaction of cyclohexene oxide with thiourea in acidic media. This mercapto alcohol **3** was reacted with bromoacetaldehyde diethyl acetal and potassium hydroxide to give the open-chain acetal[13] which spontaneously cyclized on standing or could be condensed with boron trifluoride etherate to afford a ca. 1:1 mixture of the cyclic acetals, **4** and **5**. Attempted reductive cleavage of the ethoxyl group in the mixture of **4** and **5** with lithium aluminum hydride–aluminum chloride[14] gave essentially starting material and small quantities of saturated and unsaturated oxathianes, **6** and **7**, respectively. *trans*-Hexahydro-1,4-benzoxathiin (**7**) was easily hydrogenated with hydrogen over palladium on carbon in ethanol[15] to give pure **6** after sublimation. The yields of **7** and eventually **6** could be significantly improved by converting the acetals **4** and **5** into lactols (**9** and **10**) with 4–6% sulfuric acid at reflux for 48 h.[16] The lactols, **9** and **10**, were acylated with acetic anhydride in pyridine[17] to give a mixture of acetates (**11**, **12**) which was pyrolyzed[17] (180 °C) to give **7** in nearly quantitative yield. Oxidation of **6** with *m*-chloroperoxybenzoic acid (MCPBA)[3h] or sodium metaperiodate ($NaIO_4$)[3h] gave good yields of the sulfoxides **13** and **14** but significantly different isomeric distributions (see Experimental Section). Sulfone **15** was prepared by oxidation of **6** with excess hydrogen peroxide in acetic acid at reflux or with 2 equiv of MCPBA at ambient temperature. The sulfone was also prepared by oxidation of **7** with H_2O_2–HOAc[16] followed by reduction with hydrogen over palladium on carbon in ethanol.[16]

Stereochemical Assignments. The stereochemistry of sulfoxides **13** and **14** was determined by ^1H and ^{13}C NMR spectroscopy and from the degree of stereoselectivity resulting from oxidation of **6** to **13** and **14**.

Recently, considerable interest has centered on the application of ^{13}C NMR as a tool for stereochemical assignments of cyclic organosulfur compounds. A useful feature of ^{13}C NMR is the substantial upfield shifts observed for carbons which are syn-clinal[1,3a,f,18,19] and anti-periplanar[20] to a substituent on sulfur. In the syn-clinal arrangement, the upfield shifts are thought to arise from steric interactions resulting from congestion of atoms involving carbon,[21,22] while the upfield shifts in the anti-periplanar array may be best viewed as a hyperconjugative transfer of charge from the free-electron pairs on a second-row heteroatom (e.g., N, O, or F) to the anti-periplanar carbon[20] or a σ-inductive effect when ammonium and sulfonium ion substituents are γ-anti to the carbon.[20,23]

The initial assignments of the C2, C3, C9, and C10 atoms in **6** were based on the expected electronegative influence of the heteroatoms (oxygen and sulfur)[24] α to the carbons and off-resonance decoupling which served to unequivocally assign the bridgehead carbons (C9, C10).[25] The C2 atom in sulfoxide **13** (δ 57.14 ppm) is 5.96 ppm to higher field than C2 of sulfoxide **14** and C9 of **13** (δ 70.12 ppm) also experiences an upfield shift of 7.16 ppm relative to C9 in **14** (δ 77.28 ppm). See Table I for the relevant ^{13}C NMR data. Similar observations describing this upfield shift effect of carbon when proximal (syn-clinal) to the sulfinyl oxygen have been reported for a number of conformationally homogeneous systems[26] and

Chart I

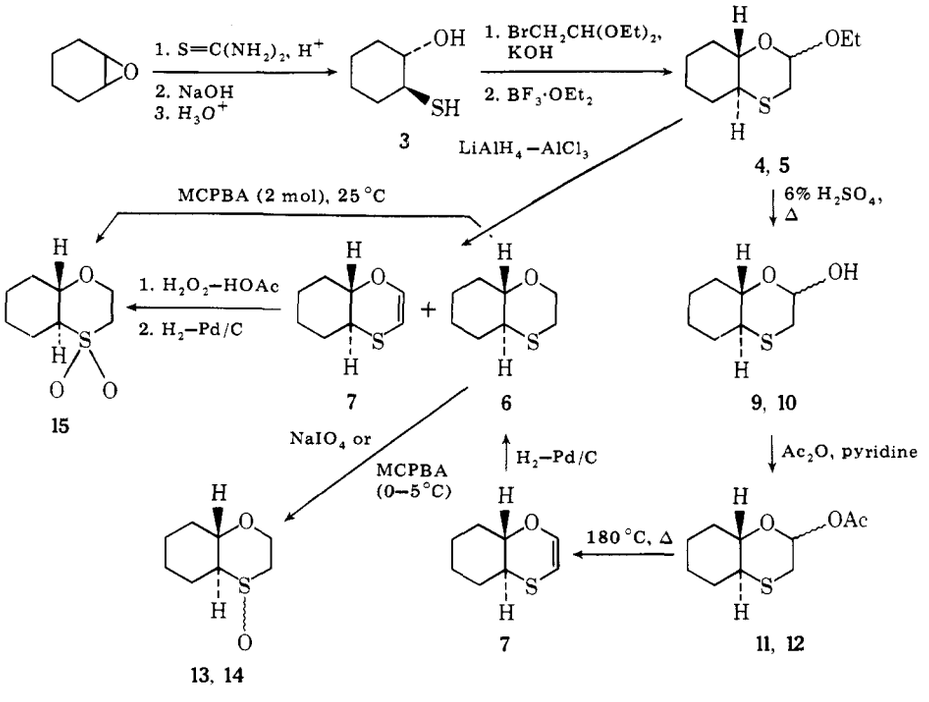
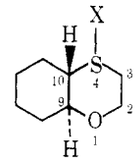


Table I. Carbon Chemical Shifts of *trans*-Hexahydro-1,4-benzoxathiane and *S*-Oxides[a]



Carbon atom	Sulfide 6 (X = lone pair)	Axial sulfoxide 13 (X = oxygen atom)	Sulfone 15 ($X = O_2$)	Equatorial sulfoxide 14 (X = oxygen atom)
2	68.78	57.14	65.03	63.10
3	32.74	45.99	52.61	51.77
10	43.96	57.30	65.75	66.58
9	82.57	70.12	78.94	77.28

[a] ^{13}C NMR shifts are reported in parts per million (δ) downfield from internal tetramethylsilane and are considered accurate to ±0.01 ppm. See Experimental Section for details.

Table II. ^1H NMR Data of *trans*-Hexahydro-1,4-benzoxathiane and 4-Oxides[a]

NMR parameter[b,c]	Axial sulfoxide (13)	Sulfone (15)	Sulfide (6)	Equatorial sulfoxide (14)
$^3J_{2e,3a}$	4.0	5.30	3.43	4.08
$^3J_{2e,3e}$	2.50	2.60	2.10	3.00
$^3J_{2a,3a}$	9.0	10.90	11.55	12.20
$^3J_{2a,3e}$	5.00	2.83	2.20	1.30
$^2J_{2ae}$	12.70	12.80	11.60	13.30
$^2J_{3ae}$	11.0	13.60	13.60	12.15
δ_{2e}	3.98	4.28	4.18	4.20
δ_{2a}	4.43	4.12	3.74	3.71
δ_{3e}	2.87	3.07	2.35	3.38
δ_{3a}	2.82	3.28	3.05	2.96

[a] See Experimental Section for additional NMR data. [b] Coupling constants are given as hertz. [c] Proton chemical shifts are given in parts per million (δ) downfield from tetramethylsilane (Me_4Si).

based on comparison with these observations we assign sulfoxide **13** as the one possessing the axial sulfinyl oxygen and **14** with the equatorial one.

It is noteworthy that the C2 and C9 atoms in **6** are deshielded relative to the same atoms in **14** by 5.68 and 5.29 ppm, respectively. These are among the largest γ-anti-periplanar shifts currently known[19b] and their magnitudes indicate that they are comparable to the γ-gauche or syn-clinal effect in other systems. The relatively large differences between the two sets of carbons in **6** and **14** may arise from a composite effect involving hyperconjugative transfer of charge[20] and a σ-inductive effect[23] to the γ-anti carbons since the sulfur atom has both residual positive character and an oxygen substituent with electron pairs.

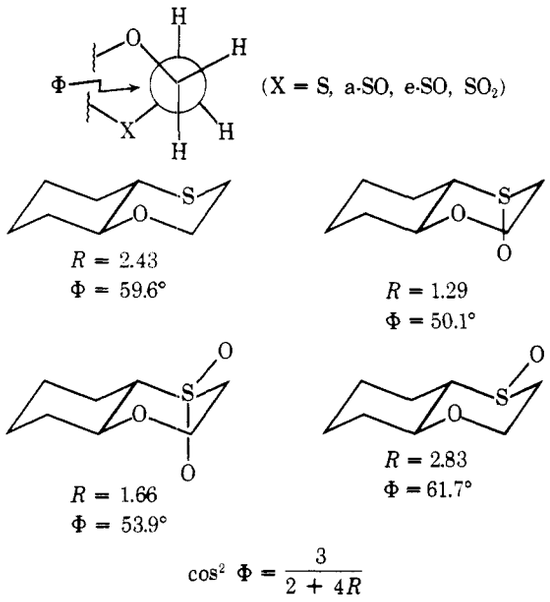
The configurational assignments are further corroborated by the observed downfield shifts of the axial C2 and C9 protons on the introduction of an axial oxygen at sulfur (e.g., **6** → **13**). See Table II for the appropriate proton chemical shifts.[28] This paramagnetic shift is presumably due to an anisotropic deshielding effect,[28] van der Waals steric effect, and/or an electric field effect[29] of the S–O group on the C2 and C9 protons in the 1,3-diaxial conformation.

Oxidation of 4-*tert*-butylthiane with a number of oxidants including $NaIO_4$ and MCPBA has been extensively investigated[3h] and a useful degree of selectivity per oxidant has been established.[3h,30a] For instance, oxidation of 4-*tert*-butylthiane with $NaIO_4$ give 75% cis (axial sulfoxide) and 25% trans while oxidation with MCPBA affords only 36% cis and 64% trans isomer. For *trans*-hexahydro-1,4-benzoxathiane (**6**), we have assumed that the ring oxygen is sufficiently removed from the immediate environment of the sulfur so as not to influence the mode of oxidation and the subsequent product distribution. Oxidation of **6** with $NaIO_4$ gives a mixture of sulfoxides containing 65% of **13** (axial sulfoxide) and 35% of **14** while oxidation with MCPBA gives 26% of **13** and 74% of **14** (equatorial sulfinyl oxygoen). These results are in good agreement with those previously reported for 4-*tert*-butylthiane[3h,30a] and serve to confirm by extrapolation the stereochemistry of sulfoxides **13** and **14**.

Conformational Distortions. All of the ^1H NMR parameters have been determined for all of the *trans*-hexahydro-1,4-benzoxathiane derivatives by comparison of computer simulations with experimental spectra. Thus, excellent use could be made of the *R*-value method[9] with proper extensions to torsional angle determinations[10] to assess the relative magnitude(s) of any conformational distortions. It has been previously demonstrated that the ratio, *R*, of the average $^3J_{trans}$ to $^3J_{cis}$ couplings in six-membered rings is a direct function of conformational distortions within the ring,[9] but relatively independent of the electronegativities of the substituents.[31] Thus, for molecules in the perfect chair conformation, $R \cong 2.0$, while *R* values greater than 2.75 characterize puckered chair forms and those values approximating 1.2 describe molecules in the flexible or flattened conformation.[9] The qualitative nature of the *R*-value method has largely been removed by the demonstration of a satisfactory correlation between dihedral angles determined by x-ray methods[10] and those calculated from *R* values. The calculated *R* values and torsional angles are given in Chart II. From the data it is apparent that the torsional angles for sulfide **6** and equatorial sulfoxide **14** are quite similar, suggesting (as perhaps expected) that the 1,4-oxathiane ring in both systems is not appreciably distorted. The relatively large torsional angle about O–C2–C3–S in **6** is virtually equivalent to that found in 1,4-oxathiane, $\phi = 60°$.[9] However, in the axial sulfoxide **13** and the sulfone **15** the relatively smaller torsional angles indicate that these molecules are slightly flattened about O–C2–C3–S with **13** experiencing the greatest perturbation. This distortion may be viewed as an attempt to relieve repulsive 1,3-syn-axial (nonbonding) interactions between the sulfinyl oxygen (or sulfonyl oxygen) and the C2, C9 carbons and hydrogens. The difference in torsional angles between the sulfone and the axial sulfoxide (ca. 5°) is due, at least in part, to different degrees of hybridization and the effective steric demands of the S→O bond in each compound while the difference in the diastereoisomeric sulfoxides (ca. 10°) is largely due to their respective steric environments.

The conformational free energy of the sulfinyl group ($\Delta G_{S\rightarrow O}$) was determined from acid-catalyzed (HCl–dioxane–water) equilibration[32,33] of both the axial and equatorial isomers. The equilibrium composition obtained from at least

Chart II. *R* Values and Calculated Torsional Angles of *trans*-Hexahydro-1,4-benzoxathiane Derivatives



$$\cos^2 \Phi = \frac{3}{2 + 4R}$$

five determinations from each side gave $\Delta G°_{30.0} = 0.85 \pm 0.07$ kcal/mol for the axial $\rightleftharpoons$ equatorial sulfinyl oxygen equilibrium *favoring the axial S → O group* which is in good agreement with the low temperature determination ($\Delta G°_{-80} = 0.68$ kcal/mol)[1] involving 1,4-oxathiane 4-oxide considering the slight differences in the system and the solvent media. From this it is clear that energy minimization in the axial sulfoxide is accompanied by flattening; however, **13** still assumes a ground-state energy considerably lower than that of **14**. These observations, in some respects, support the recent conclusions drawn from molecular mechanics calculations[7] where the suggestion is made that there is only minor repulsion in the axial form of thiane 1-oxide when compared to the major repulsive nonbonding interactions between the equatorial sulfinyl oxygen and the four vicinal hydrogens. The design and results of our experiments do not allow for an assessment of steric perturbations which might be evident in **14**. It is conceivable that severe flattening of the ring in **13** is partially attenuated by an intramolecular electrostatic attraction without which one might expect an even larger perturbation in the form of ring deformation.

Experimental Section

Melting points were obtained in a Mel-Temp melting point apparatus with an open capillary tube and are uncorrected.

Microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn., and Integral Microanalytical Laboratories, Inc., Raleigh, N.C.

^{1}H NMR spectra were recorded on JEOL Model C-60 HL and Varian Model XL-100-12 NMR spectrometers. ^{13}C NMR FT spectra were recorded on a Varian Model XL-100-12 NMR spectrometer controlled by a 620/f computer. All FT spectra were obtained at ambient temperature (ca. 30 °C) and Fourier transforms were based upon 8K data points with off-resonance and noise decoupling. The proton and carbon chemical shifts of samples as 5–15 (w/w %) deuteriochloroform ($CDCl_3$) solutions are presented in parts per million (δ) downfield from internal tetramethylsilane (Me_4Si) and these values are considered accurate to ±0.01 ppm unless otherwise indicated. The coupling constants are given in hertz and are accurate to ±0.1–0.2 Hz unless otherwise specified. All relevant experimental proton signals were simulated with an in-house modification of LAOCOON III capable of handling eight spins. ^{1}H NMR coupling patterns are designated as s = singlet, d = doublet, m = multiplet, q = quartet, and t = triplet.

Infrared spectra were obtained from samples as neat films and solutions and were recorded on Perkin-Elmer Models 257 and 421 spectrophometers with polystyrene (1601.4 cm^{-1}) as reference. Absorption intensities are shown as s = strong, w = weak, m = medium, vs = very strong, and vw = very weak.

Gas–liquid partition chromatography (GLC) analyses were performed on Hewlett-Packard Models 5750 and 5754 research gas chromatographs. A Varian Aerograph Series 2700 instrument was used for preparative separations. *trans*-2-Mercaptocyclohexanol (**3**) was prepared from the procedure described by Bordwell and Andersen.[12]

***trans*-2-(Thioacetaldehyde diethyl acetal)cyclohexanol.** A solution of *trans*-2-mercaptocyclohexanol (11.75 g, 90.0 mmol) in 30 mL of 95% ethanol was added to a solution of potassium hydroxide (7.0 g, 125 mmol, assuming 85% purity) in 100 mL of 95% ethanol and stirred at ambient temperature for 15 min. A solution of bromoacetaldehyde diethyl acetal (18.0 g, 90.0 mmol) in 30 mL of ethanol was added to the mercaptide solution and the resulting orange solution was refluxed for 22 h. Potassium bromide was removed by filtration and the resulting ethanolic solution was concentrated to dryness (rotary evaporator) to afford a red residue. This material was dissolved in 100 mL of ether and the ethereal solution was washed with water (100 mL), dried (anhydrous magnesium sulfate), and concentrated (rotary evaporator) to give a yellow oil. Distillation under reduced pressure gave 12.9 g (58%) of a colorless oil: bp 113–117 °C (0.125 Torr); IR (neat film) 3442 (broad band, OH), 2990 (m), 2940 (s), 2860 (m), 1450 (m), 1351 (w), 1128 (s), 1068 (vs), 1018 (m), and 917 cm^{-1} (w). This material slowly cyclized to give a mixture consisting of a 1:1 ratio of **4** and **5**.

2-Ethoxy-*trans*-hexahydro-1,4-benzoxathianes (4 and 5). A solution of *trans*-2-(thioacetaldehyde diethyl acetal)cyclohexanol (12.9 g, 52.0 mmol) in 100 mL of dry ether was treated with 1 mL of boron trifluoride etherate at room temperature for 48 h. The resulting solution was washed with water (100 mL) and twice with a saturated solution of sodium carbonate (100 mL). The ethereal solution was dried (anhydrous magnesium sulfate) and concentrated to dryness (rotary evaporator) to afford an oil. Distillation under reduced pressure gave 5.95 g (57%) of a clear oil of two components which was otherwise homogeneous by GLC: bp 65–72 °C (0.02 Torr); IR (neat film) 2979 (m), 2940 (s), 2870 (m), 1456 (m), 1378 (w), 1343 (m), 1210 (m), 1160 (m), 1132 (s), 1076 (s), 1018 (m), 990 (m), and 856 cm^{-1} (w). Anal. Calcd for $C_{10}H_{18}O_2S$: C, 59.37; H, 8.97. Found: C, 58.90; H, 9.07.

***trans*-Hexahydro-1,4-benzoxathiane (6).** *trans*-Hexahydro-1,4-benzoxathiin (**7**, 10.0 g, 64 mmol) in 50 mL of absolute ethanol was reduced with hydrogen (50 psi) over 10% palladium on carbon (10.0 g) for 13 h. The catalyst was removed by filtration and the ethanol solution was concentrated to dryness (rotary evaporator) to give an oily material which gave after sublimation (37 °C, 0.25 Torr) 8.7 g (71%) of an oily, crystalline substance. Recrystallization of this material from petroleum ether (bp 30–60 °C) gave 5.7 g (47%) of a colorless, crystalline solid: mp 40.5–41.5 °C; IR (CCl_4) 2940 (s), 2860 (m), 1450 (m), 1302 (m), 1196 (m), 1109 (s), 1062 (m), and 1018 cm^{-1} (m); ^{1}H NMR ($CDCl_3$) δ 0.93–2.08 (m, 8 H, CH_2). 2.35 (d of t, J_{gem} = 13.6, J_{ea} = 2.2, J_{ee} = 2.1 Hz, 1 H, SCH_e), 2.65 (m, 1 H, SCH), 3.05 (t of d, J_{gem} = 13.6, J_{aa} = 11.55, J_{ae} = 3.43 Hz, 1 H, SCH_a), 3.28 (m, 1 H, OCH), 3.74 (t of d, J_{gem} = 11.6, J_{aa} = 11.55, J_{ae} = 2.2 Hz, 1 H, OCH_e), and 4.18 ppm (d of q, J_{gem} = 11.6, J_{ea} = 3.43, J_{ee} = 2.1 Hz, 1 H, OCH_e). Anal. Calcd for $C_8H_{14}SO$: C, 60.71; H, 8.92. Found: C, 60.94; H, 8.84.

2-Hydroxy-*trans*-hexahydro-1,4-benzoxathianes (9 and 10). The 2-ethoxy-*trans*-hexahydro-1,4-benzoxathiane mixture of **4** and **5** (41.6 g, 200 mmol) was poured into a solution of 4–6% sulfuric acid (300 mL) and refluxed for 40 h, cooled to ambient temperature, and neutralized with sodium bicarbonate. The solid material was dissolved in ether and the solution dried (magnesium sulfate), then concentrated to dryness (rotary evaporator) to afford a solid. Recrystallization from a methylene chloride–hexane solution gave 12.5 g (36%) of colorless crystals, mp 97–100 °C. Anal. Calcd for $C_8H_{14}SO_2$: C, 55.14; H, 8.09. Found: C, 55.25; H, 8.88. The mother liquor from the recrystallization contained unreacted starting material (**4** and **5**).

2-Acetyl-*trans*-hexahydro-1,4-benzoxathianes (11 and 12). The mixture of acetols **9** and **10** (18.0 g, 103 mmol), 75 mL of acetic anhydride, and 75 mL of pyridine was heated to reflux for ca. 20 min and then reduced in volume to about 30 mL (rotary evaporator). The remaining solution was cooled to ambient temperature and 150 mL of water was added to hydrolyze the residual anhydride. The mixture was neutralized with a saturated solution of sodium bicarbonate and extracted with ether (2 × 100 mL) and the ethereal solution was dried (magnesium sulfate) and concentrated to dryness (rotary evaporator). The product was distilled under reduced pressure to afford a colorless oil (20.1 g, 90%), bp 75–76 °C (0.04 Torr). Anal. Calcd for $C_{10}H_{16}SO_3$: C, 55.57; H, 7.40. Found: C, 55.49; H, 7.76.

***trans*-Hexahydro-1,4-benzoxathiin (7).** The mixture of **11** and **12** (19.2 g, 128 mmol) was heated in an oil bath to 180 °C at atmospheric pressure. The heating was continued until acetic acid had ceased distilling over. The resulting oil was distilled under reduced pressure (0.04 Torr) to afford essentially quantitative yield of the olefin **7** (14.0 g, 99.2%): bp 36–37 °C (0.04 Torr); ^{13}C NMR δ 139.31 (=CHO) and 93.52 ppm (=CHS); ^1H NMR δ 5.06 (d, 1 H, J = 6.3 Hz, =CHS) and 6.56 ppm (d, 1 H, J = 6.3 Hz, =CHO).

***trans*-Hexahydro-1,4-benzoxathiane 4,4-Dioxide (15).** A solution of *trans*-hexahydro-1,4-benzoxathiane (300 mg, 2.84 mmol) in 5 mL of glacial acetic acid and 3 mL of hydrogen peroxide (excess) was heated to reflux for 20 min, then cooled to ambient temperature. The cooled solution was diluted with water (30 mL) and extracted with chloroform (2 × 20 mL). The chloroform solution was washed with a saturated solution of sodium bicarbonate (2 × 20 mL), water (20 mL), and finally with a saturated sodium chloride solution (20 mL). The resulting solution was dried (magnesium sulfate) and concentrated to dryness (rotary evaporator) to give 308 mg (86%) of a colorless, crystalline powder which was recrystallized from hexane: mp 120–121 °C; IR ($CHCl_3$) 2946 (s), 2865 (m), 1444 (m), 1308 (s), 1292 (m), 1278 (m), 1270 (m), 1172 (m), 1126 (vs), 1110 (s), 1024 (m), 1008 (m), and 960 cm^{-1} (w); ^1H NMR ($CDCl_3$) δ 0.97–2.45 (m, 8 H, CH_2), 2.85 (m, 1 H, SCH), 3.07 (d of t, J_{gem} = 13.6, J_{ea} = 2.83, J_{ee} = 2.6 Hz, 1 H, SCH_e), 3.28 (d of q, J_{gem} = 13.6, J_{aa} = 10.9, J_{ae} = 5.3 Hz, 1 H, SCH_a), 3.67 (m, 1 H, OCH), 4.12 (d of t, J_{gem} = 12.8, J_{aa} = 10.9, J_{ae} = 2.83 Hz, 1 H, OCH_a), and 4.28 ppm (d of q, J_{gem} = 12.8, J_{ee} = 2.6, J_{ea} = 5.3, 1 H, OCH_e). Anal. Calcd for $C_8H_{14}O_3S$: C, 50.43; H, 7.45. Found: C, 50.50; H, 7.42.

***trans*-Hexahydro-1,4-benzoxathiane 4-Oxides (13 and 14) from $NaIO_4$.** A solution of *trans*-hexahydro-1,4-benzoxathiane (3.0 g, 19 mmol) in 50% methanol (200 mL) and dioxane (3 mL) was reacted with sodium metaperiodate (4.0 g, 19.0 mmol) at 0–5 °C (ice bath) for 6 h and at room temperature overnight (14 h). Sodium iodate was removed by filtration and the resulting aqueous layer was extracted with chloroform (3 × 100 mL). The organic layer was dried (anhydrous magnesium sulfate) and concentrated to dryness (rotary evaporator) to afford 2.96 g (90%) of a colorless, crystalline solid: mp 89–92 °C; IR ($CHCl_3$) 1448 (m), 1092 (s), 1038 (s), 1012 (vs), and 997 cm^{-1} (s). TLC (silica gel, chloroform–petroleum ether as eluent) indicated the presence of starting sulfide **6** and two other components. The crude mixture was separated by column chromatography (silica gel with chloroform–petroleum ether as eluent) to give a pure mixture of sulfoxides (2.46 g, 75%) with the axial sulfoxide **13** predominating in the mixture (axial, 65%; equatorial 35%) as determined by GLC.

***trans*-Hexahydro-1,4-benzoxathiane 4-Oxides (13 and 14) from MCPBA.** A solution of mCPBA (400 mg, 2.0 mmol) in 25 mL of anhydrous methylene chloride was added dropwise over a period of 1 h to a solution of *trans*-tetrahydro-1,4-benzoxathiane (330 mg, 2.10 mmol) in anhydrous methylene chloride (25 mL) at 0–5 °C (ice bath). The solution was stirred for 12 h, then allowed to come to ambient temperature overnight (ca. 15 h). The solution was cooled (ice water), filtered to remove the chlorobenzoic acid, washed with a saturated solution of sodium bicarbonate (3 × 25 mL), and finally dried (magnesium sulfate). Removal of the solvent (rotary evaporator) gave 296 mg (82%) of a colorless product, mp 74–76 °C. GLC indicated the presence of **6** and the sulfoxides **13** and **14**. The mixture of sulfoxides contained 74% equatorial isomer and 26% axial.

Separation of the Diastereoisomeric Sulfoxides. Separation of **13** and **14** was accomplished on a silica gel column (1 × 18 in., 70–325 mesh, EM Reagents) eluting with a 60:40 (v/v %) chloroform–petroleum ether solution and collecting 40-mL fractions. The diastereoisomeric sulfoxides were obtained analytically pure by this procedure.

4a-*trans*-Hexahydro-1,4-benzoxathiane 4-Oxide (13): mp 105.5–107.0 °C; ^1H NMR ($CDCl_3$) δ 1.04–2.2 (m, 8 H, CH_2), ca. 2.28 (m, 1 H, SCH), 2.82 (m, J_{gem} = 11.0, J_{aa} = 9.0, J_{ae} = 4.0 Hz, 1 H, SCH_a), 2.87 (m, J_{gem} = 11.0, J_{ea} = 5.0, J_{ee} = 2.5 Hz, 1 H, SCH_e), 3.98 (m, J_{gem} = 12.70, J_{ea} = 3.5, J_{ee} = 2.9 Hz, 1 H, OCH_e), 4.03 (m, 1 H, OCH), and 4.43 ppm (d of q, J_{gem} = 12.70, J_{aa} = 9.0, J_{ae} = 5.0 Hz, 1 H, OCH_a). Anal. Calcd for $C_8H_{14}O_2S$: C, 55.14; H, 8.09. Found: C, 54.99; H, 8.25.

4e-*trans*-Hexahydro-1,4-benzoxathiane 4-Oxide (14): mp 116.0–117.0 °C; ^1H NMR ($CDCl_3$) δ 1.04–2.25 (m, 8 H, CH_2), 2.53 (m, 1 H, SCH), 2.96 (t of q, J_{gem} = 12.15, J_{aa} = 12.2, J_{ae} = 4.08 Hz, 1 H, SCH_a), 3.27 (m, 1 H, OCH), 3.38 (d of q, J_{gem} = 12.15, J_{ea} = 1.3, J_{ee} = 3.0 Hz, 1 H, SCH_e), 3.71 (t of d, J_{gem} = 13.3, J_{aa} = 12.2, J_{ae} = 1.3 Hz, 1 H, OCH_a), and 4.20 ppm (d of q, J_{gem} = 13.3, J_{ea} = 4.08, J_{ee} = 3.0 Hz, 1 H, OCH_e). Found: C, 55.00; H, 8.20.

Equilibrations. Equilibrium concentrations of **13** and **14** were obtained by equilibrating weighted mixtures of **13** and **14** from both sides at 300 K in a hydrochloric acid–dioxane–water solution.[33] The reaction mixtures were diluted with water and extracted with methylene chloride and the methylene chloride solutions were neutralized with a saturated solution of sodium bicarbonate, dried (sodium sulfate), and concentrated to dryness (rotary evapoartor) to give crystalline material. Gas–liquid partition chromatographic analyses were performed on samples of the solid material dissolved in chloroform on 6 and 12 ft × 0.125 in. (i.d.) stainless steel columns with 10% XE-60 nitrile on Chromosorb W-HP-AW-DMCS (100–120 mesh) at 200–210 °C. Response ratios were measured from the areas obtained from weighed samples. Equilibrium compositions were usually attained after 2 h and after 8–22 h major decomposition (or rearrangement) products were observed by GLC.

Acknowledgments. Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, the North Carolina Board of Science and Technology, the University Research Council, and a grant from the Merck Co. for support of this research. We also thank Dr. Dwight W. Chasar for his early thoughts regarding the factors affecting the axial–equatorial preferences of sulfinyl oxygen atoms in six-membered rings. We thank Dr. David L. Harris for recording numerous ^1H and ^{13}C NMR spectra.

Registry No.—**3,** 60861-06-5; **4,** 62015-70-7; **5,** 62057-83-4; **6,** 62015-71-8; **7,** 62015-72-9; **9,** 62015-73-0; **10,** 62057-84-5; **11,** 62015-74-1; **12,** 62057-85-6; **13,** 62015-75-2; **14,** 62057-86-7; **15,** 62015-76-3; *trans*-2-(thioacetaldehyde, diethyl acetal)cyclohexanol, 62015-77-4; bromoacetaldehyde diethyl acetal, 2032-35-1.

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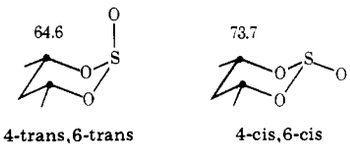
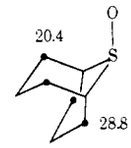


4-trans,6-trans 4-cis,6-cis

the carbons shown as darkened circles.) The chemical shift difference between the γ-gauche (δ 20.4 ppm) and γ-anti (δ 28.8 ppm) carbons in 9-thiabicyclo[3.3.1]nonane *S*-oxide compares favorably with previous reports.[18b]



(27) On tabulating the C2 and C3 proton chemical shifts (Table II), we noted that a comparison of these shifts lends support to the suggestion of Khan et al.[4c] in that the bond anisotropies of the C–S and C–S(O_2) bonds are opposite in sign to those of C–C, C–O, and C–S(O).[4c] If we use the $+\Delta\delta$ representation for cases where the C3 axial proton resonates at higher field than the C3 equatorial and $-\Delta\delta$ for examples where the C3 equatorial proton comes to higher field than C3 H_a (following the scheme introduced by Khan et al.[4c] for convenience), it is clear that sulfone **15** ($\Delta\delta = -0.21$ ppm) and sulfide **6** ($\Delta\delta = -0.70$ ppm) show the same overall pattern of shifts supporting, at least in principle, the identify of sign for C–S and C–S(O_2) bond anisotropies. On the other hand, the sign of the chemical shift difference between the axial and equatorial protons α to the sulfinyl group in **13** ($\Delta\delta = +0.05$ ppm) and **14** ($\Delta\delta = +0.42$ ppm) and the ones α to the ring oxygen in **6** ($\Delta\delta = +0.44$ ppm), **15** ($\Delta\delta = +0.16$ ppm), and **14** ($\Delta\delta = +0.49$ ppm) suggest that the C–O and C–S(O) bond anisotropies are also of the same sign. As expected the positive sign of $\Delta\delta$ was not observed for the C2 methylene group of **13** because the axial sulfinyl group exerts a substantial deshielding effect on the 1,3-syn-axial C2 proton.[29]
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