Anal. Calcd for $C_{18}H_{24}N_2O_4S_4$: C, 46.93; H, 5.25; N, 6.08; S, 27.84. Found: C, 47.23; H, 5.40; N, 6.15; S, 27.79.

Registry No.—**6**, 25906-63-2; **10**, 25906-64-3; **11**, 25906-65-4; **12**, 25906-66-5; **13**, 25906-67-6; **14**, 25906-68-7; **15**, 25906-69-8; **16**, 25906-70-1; **18**, 25906-71-2; **19**, 25906-72-3; **21**, 25906-73-4; **22**, 25906-74-5; **23**, 25906-75-6; **24**, 25906-76-7; **25**, 25906-77-8; **26**, 25902-98-1; **27**, 25902-99-2; **28**, 25957-59-9; **30**, 25903-00-8.

The Stereochemistry of Oxidation at Sulfur. Oxidation of 2-Methylthiolane[1,2]

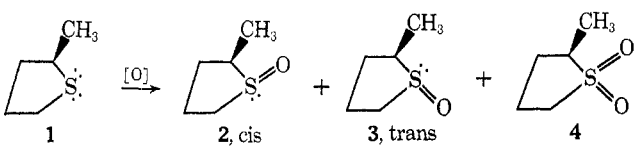
JUAN J. RIGAU,[3a] CONLEY C. BACON,[3b] AND CARL R. JOHNSON*

Department of Chemistry, Wayne State University, Detroit, Michigan 48202

Received March 14, 1970

Pure samples of the diastereomeric 2-methylthiolane 1-oxides were isolated and characterized by chromatographic retention time and nmr spectroscopy. The cis isomer exhibits the shorter retention times on chromatography. The methyl resonance of the trans isomer shows the greater benzene-induced shift. The stereochemistry of oxidation of 2-methylthiolane by a variety of reagents is recorded.

Oxidation of sulfides is likely to remain the foremost method for the preparation of sulfoxides. The availability of stereochemical data on this transformation is useful from both mechanistic and synthetic standpoints. In earlier papers we have examined the details of the conversion of 4-substituted thianes[4] and 2-thiabicyclo-[2.2.1]heptane[5] to the diastereomeric S-oxides. We now record a related study on the oxidation of 2-methylthiolane (2-methyltetrahydrothiophene) (1).



1 2, cis 3, trans 4

Assignment of Configuration.—Pure samples of the isomeric sulfoxides **2** and **3** were obtained by careful elution chromatography on acid-washed alumina beginning, most conveniently, with mixtures in which one isomer was significantly more abundant. The structural assignments were based on three main lines of evidence: chromatographic retention times, nmr studies, and oxidation studies. The sulfoxides are highly hygroscopic liquids.

The isomer which exhibited the higher retention time on both column and vapor phase chromatography was assigned the trans structure **3**. Experience in our laboratories and others has shown that in the absence of complicating effects the isomer with the more sterically accessible sulfoxide oxygen has the higher retention time. Perhaps the most rigorous proof of structure comes from nmr studies summarized in Table I.

It is obvious from an inspection of the data of Table I that arguments based on the magnitude of chemical shifts would be ineffective for structural assignments. It has been assumed for some time that the anistropy of the S=O bond approximates that of the carbon–carbon triple bond. This assumption is probably a valid one, but the utility is limited by the less well understood screening by the free electron pair. The most effective data is provided by the benzene-induced shifts.[6,7] Ledaal[8] has recently proposed that benzene–polar solute collision complexes are best represented by a model with the positive end of the dipole of the polar functional group located along the sixfold axis of the benzene molecule. In the case of the sulfoxides in question, the deshielding of the methyl by the aromatic solvent should be more dramatic in the trans sulfoxide than in the cis (Figure 1). The interested reader is referred to an excellent group of recent articles dealing with penicillin sulfoxides.[9] The stereochemical assignment made here is entirely in line with arguments presented in detail in these papers concerning the steroechemistry of penicillin sulfoxides.

TABLE I

SOLVENT EFFECTS IN THE NMR SPECTRA OF 2-METHYLTHIOLANE AND DERIVATIVES[a]

Compd	Concn, mmol/ml	Solvent	δ_{CH_3}	J (Hz)	$(\delta' - \delta_{C_6H_6})$
1 (sulfide)	1.70	CCl_4	1.27	7.0	+0.11
		C_6H_6	1.16	7.0	
2 (cis sulfoxide)	1.70	DMSO-d_6	1.22	6.7	+0.04
		CCl_4	1.28	7.0	+0.10
		$CDCl_3$	1.40	6.5	+0.22
		C_6H_6	1.18	6.2	
3 (trans sulfoxide)	1.70	DMSO-d_6	1.13	7.3	+0.39
		CCl_4	1.19	7.0	+0.45
		$CDCl_3$	1.23	7.1	+0.49
		C_6H_6	0.74	7.2	
4 (sulfone)		CCl_4	1.27	7.0	+0.23
		C_6H_6	1.04	7.0	

[a] The spectra were run at ambient temperature using TMS as standard.

Infrared analysis of the 2-methylthiolane 1-oxides showed very minor differences outside the sulfoxide

* Author to whom correspondence should be addressed.

(1) Part XXII in the series Chemistry of Sulfoxides and Related Compounds.

(2) We gratefully acknowledge support by the National Science Foundation (Grant No. GP 8648).

(3) (a) Fellow of the Economic Development Administration, Commonwealth of Puerto Rico; (b) National Science Foundation Undergraduate Research Participant.

(4) C. R. Johnson and D. McCants, Jr., *J. Amer. Chem. Soc.*, **87**, 1109 (1965).

(5) C. R. Johnson, H. Diefenbach, J. E. Keiser, and J. C. Sharp, *Tetrahedron*, **25**, 5649 (1969).

(6) W. Amann and G. Kresge, *Tetrahedron Lett.*, 4909 (1968).

(7) E. J. Strom, B. S. Snowden, Jr., and P. A. Toldan, *Chem. Commun.*, 50 (1969); M. Nishio, *ibid.*, 51 (1969).

(8) T. Ledaal, *Tetrahedron Lett.*, 1683 (1968).

(9) R. D. G. Copper, P. V. DeMarco, J. C. Cheng, and N. D. Jones, *J. Amer. Chem. Soc.*, **91**, 1408 (1969); R. D. G. Cooper, P. V. DeMarco, and D. D. Spry, *ibid.*, **91**, 1528 (1969).

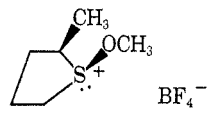
TABLE II

EQUILIBRATION OF 2-METHYLTHIOLANE 1-OXIDES[a]

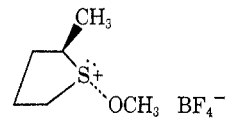
Sulfoxides before reaction, cis:trans	Reaction conditions	Sulfoxides after reaction, cis:trans
19:81	HCl–dioxane, 20 min, 25°	76:24
64:36	HCl–dioxane, 2–3 min, 25°	78:22
62:38	Sulfuric acid–water, 2 min, 25°	79:21
75:25	N_2O_4, 30 min, 0°	62:38

[a] All reactions gave trace amounts of unidentified products.

promoted hydrolysis of these salts occurred with complete inversion of configuration at the sulfonium sulfur.[12] Hydrolysis of **5** led to pure **3** and hydrolysis of **6** gave pure **2**.



5, cis



6, trans

TABLE III

OXIDATION OF 2-METHYLTHIOLANE

Reagent	Conditions, °C	2-Methylthiolane 1-oxides, cis:trans	4-*t*-Butylthiane 1-oxides,[b] cis:trans
Dinitrogen tetroxide	0	62:38	81:19
Sodium metaperiodate	H_2O, 0	43:57	75:25
Hydrogen peroxide	CH_3COCH_3, 0	56:44	37:63[a]
m-Chloroperbenzoic acid	CH_2Cl_2, 0	54:46	36:64
m-Chloroperbenzoic acid	H_2O–dioxane pH 12, 0	30:70[b]	
Chromic acid	C_5H_5N, 0–25[c]	16:84	27:73
Iodosobenzene	C_6H_6, 68	58:38[d]	46:54[e]
Iodobenzene dichloride	C_5H_5N, H_2O, 0	26:74[b]	...[f]
Ozone	CH_2Cl_2, −78	22:70[g]	10:90[h]
Ozone	CH_2Cl_2, 25	23:77	
tert-Butyl hypochlorite	$(CH_3)_2CHON$, −78	65:35	100:0[i]
Isopropyl hypochlorite	CH_2Cl_2, −78	6:94	

[a] Reaction run at 25°. [b] Traces of sulfone. [c] Run at 0° for 1 hr, then 1 hr at 25°. [d] Sulfone, 4%. [e] Run at 80°. [f] Oxidation of 4-*p*-chlorophenylthiane at room temperature afforded 10% cis:90% trans sulfoxides; at −40°, 5% cis:95% trans (ref 17). [g] Sulfone, 8%. [h] Run at −40°. [i] Run in ethanol at −78°.

region. No unambiguous way of correlating solvent effects on sulfoxide band shapes and positions with geometry appeared possible. Infrared data in several solvents are reported in the experimental section. The mass spectra of the diastereomeric sulfoxides did not reveal significant differences.

Equilibration of Sulfoxides.—The stereomutation of sulfoxides can be achieved by numerous methods.[10] The equilibration methods used and results obtained in the present system are given in Table II.

The result that cis oxides are more stable than the trans is not out of line with our earlier observation that cis axial oxides are more stable than equatorial in the 4-substituted thianes.[4] In the latter case we suggested that attractive interaction between the oxygen and the ring accounts for this result. Recent theoretical studies substantiate this suggestion.[11] Along these same lines it is interesting to note the similarities in nonbonded distances labeled in Figure 1.

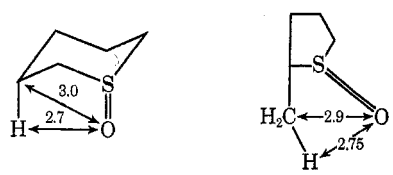


Figure 1. Comparison of nonbonded distances (Å) in cyclic sulfoxides. Distances estimated from Drieding models.

The sulfoxides were characterized additionally by the preparation of crystalline salts by O-alkylation with trimethyloxonium fluoroborate. As anticipated, base-Chloride ion is known to equilibrate alkoxysulfonium salts.[13] When a sample of the pure trans salt **6** was exposed to hydrogen chloride, equilibration was complete in less than 1 min. The equilibrium composition was 70% cis and 30% trans based on integration of the nmr resonances of the methoxy groups. Note from Table II that this value is very close to that observed for the hydrogen chloride catalyzed equilibration[14] of the free sulfoxides.

Oxidation Studies.—Table III shows the percentages of cis and trans sulfoxides produced under a variety of oxidation conditions; previous results obtained for 4-*tert*-butylthiane are included for comparison.[4] Due care was exercised to prevent or minimize oxidation to the sulfone state. In general, less stereoselectivity of oxidation was found in the case of 2-methylthiolane than in the 4-substituted thianes. This is somewhat surprising in view of the close proximity of the methyl substituent on the thiolane to the sulfur reaction site.

In an earlier paper[4] the stereochemical results of oxidations of cyclic sulfides were considered to be the outcome of thermodynamic control, steric approach control, or product development control. Since the present results are not significantly out of line with earlier discussions, additional commentary on the relationship of stereochemistry and mechanism is not in order at this time.

In connection with these oxidation studies, it was noted that in competitive reactions the cis sulfoxide **2** was oxidized to the sulfone by *m*-chloroperbenzoic acid somewhat faster than the trans sulfoxide **3**. It seems logical that the electron pair trans to the methyl group

(10) For a review, see K. Mislow, *Rec. Chem. Progr.*, **28**, 217 (1967).
(11) N. L. Allinger, J. A. Hirsch, M. A. Miller, and I. J. Tyminski, *J. Amer. Chem. Soc.*, **91**, 337 (1969).
(12) C. R. Johnson and D. McCants, Jr., *ibid.*, **87**, 5404 (1965).
(13) C. R. Johnson and J. J. Rigau, *ibid.*, **91**, 5398 (1969).
(14) J. Jacobus and K. Mislow, *ibid.*, **89**, 5228 (1967).

would be more accessible to electrophilic attack by the peracid.

Experimental Section

Melting points are uncorrected. Infrared spectra were measured on a Perkin-Elmer Model 621 spectrometer. Nuclear magnetic resonance spectra were obtained on a Varian A-60A spectrometer. Microanalyses were performed by Midwest Microlab, Inc., Indianapolis, Ind.

2-Methylthiolane was prepared in 60% yield by reaction of 1,4-dibromopentane with sodium sulfide nonahydrate in aqueous ethanol, bp 132° (lit.[15] 132°).

General Methods of Oxidation.—The procedures employed for the oxidations summarized in Table III are generally those previously reported for the oxidation of thianes.[4] Exceptions are noted below. In this work, where necessary, the sulfoxides were extracted from aqueous solutions with chloroform. The aqueous phase was then saturated with sodium chloride and the chloroform extraction repeated. The ratio of sulfoxide extracted by this procedure was identical with that present in water as shown by extracting known mixtures from water.

A. *m*-Chloroperbenzoic Acid (pH 12).[16]—The peracid (0.85 mmol) was added to 21 ml of a potassium chloride–sodium hydroxide buffer solution (pH 12) in water–dioxane (60:40). This solution was added over a 5-min period to 1 mmol of the sulfide in 10 ml water–dioxane cooled in an ice bath. The mixture was stirred at ice-bath temperature for 5 hr prior to work-up.

B. Iodobenzene Dichloride.[17]—A solution of iodobenzene dichloride (1 mmol) in anhydrous pyridine (3 ml) was added dropwise during 5 min to a stirred solution of the sulfide (1 mmol) in 3 ml of pyridine–water (20:80) and cooled in an ice bath. After 30 min at 0° the mixture was allowed to warm to 25°. The mixture was diluted with water prior to extraction.

C. *tert*-Butyl Hypochlorite.—To 1 mmol of the 1-methylthiolane in 10 ml of isopropyl alcohol at −78° was added 1 mmol of *tert*-butyl hypochlorite. After 30 min at that temperature 100 ml of 0.1 *N* aqueous sodium hydroxide was added and the mixture was shaken vigorously prior to extraction.

D. Isopropyl Hypochlorite.—A methylene chloride solution of isopropyl hypochlorite (1 equiv) was cooled to −78° and rapidly added to 1 equiv of the sulfide dissolved in methylene chloride and cooled to −78°. The reaction was worked up as described above for *tert*-butyl hypochlorite.

Analysis of Mixtures.—Percentage composition of mixtures were ascertained by planimetric integration of curves obtained from an F & M Model 720 chromatograph employing an 8 ft × 1/4 in. 20% Carbowax 20M on Chromosorb W column at 170°, a flow rate near 60 ml/min; retention times were 17 min for **2** and 21 min for **3**.

Separation of *cis*- and *trans*-1-Methylthiolane 1-Oxide.—Mixtures of sulfoxides were chromatographed on a 14 in. × 3/8 in. column of Fisher Scientific Co. alumina acid, activity I, employing ether, methylene chloride, and methanol as eluents. The fractions were monitored by vapor phase chromatography.

Registry No.—**1**, 1795-09-1; **2**, 25859-44-3; **3**, 25859-45-4; **4**, 1003-46-9.

(15) E. W. Whitehead, R. A. Dean, and F. A. Fidler, *J. Amer. Chem. Soc.*, **73**, 3632 (1951).

(16) For other examples of oxidations by peracids at high pH, see R. Curci, A. Giovini, and G. Modina, *Tetrahedron*, **4**, 1227 (1966).

(17) G. Barbieri, M. Cinquini, S. Colonna, and F. Montanari, *J. Chem. Soc. C*, 659 (1968).

3-Substituted Thietanes. Synthesis and Oxidation to Sulfoxides[1,2]

WALTER O. SIEGL[3] AND CARL R. JOHNSON*

Department of Chemistry, Wayne State University, Detroit, Michigan 48202

Received March 13, 1970

A method is reported which appears to be general for the synthesis of 3-aryl and 3-alkylthietanes from the readily available aryl methyl and alkyl methyl ketones. The cycloaddition product of sulfene and the appropriate enamine is reduced to the desired 3-aryl- or 3-alkylthietane in three steps. Thietanes deuterated in the α position could be prepared by exchange under mild conditions at the sulfone stage. The oxidation of 3-alkylthietanes to the isomeric sulfoxides was examined with a variety of oxidants; the thietane system appears to be less sensitive to the nature of the oxidant than the previously examined thiane system. Isomeric cis and trans sulfoxides could be separated by chromatography on silica gel; the cis isomer was eluted prior to trans in each of six 3-substituted thietane systems examined.

With the increasing sophistication of the organic chemistry of sulfur has come the postulation of tetracovalent sulfur reaction intermediates of trigonal bipyramid geometry.[4] For intermediates of such geometry the ligands about sulfur must subtend an angle of either 90 or 120 degrees; thus the thietane ring system, in which the C-S-C angle is close to 90°, becomes an important model. Substituted thietane 1-oxides are also pertinent models for studying the intramolecular neighboring group effect of sulfinyl oxygen,[5] and for studying the competitive stereochemical requirements of sulfinyl oxygen and the nonbonded electron pair on trigonal sulfur.[6,7] It was our interest in the latter of these which established our need for a 3-substituted thietane system the isomeric sulfoxides of which could be identified stereochemically.

To simplify a study of the conformational preference of sulfinyl oxygen it was necessary to "anchor" the conformation of the thietane ring. The puckering of thietane rings is well documented.[8] By analogy to examples in cyclobutane chemistry, it is reasonable to hypothesize that a thietane molecule with a relatively bulky substituent at the 3 position would exist predominantly in a puckered conformation with the bulky substituent equatorial.[9] Thus, if the substituent at C_3 exerts a decided equatorial preference, a substituent

* Author to whom correspondence should be addressed.

(1) (a) Part XXIII in the series Chemistry of Sulfoxides and Related Compounds.

(2) We gratefully acknowledge support by the National Science Foundation (Grant No. GP-8648).

(3) National Aeronautics and Space Administration Trainee, 1966–1969.

(4) (a) S. Oae, M. Yokoyama, M. Kise, and N. Furukawa, *Tetrahedron Lett.*, 4131 (1968); (b) B. M. Trost, W. L. Schinski, and I. B. Mantz, *J. Amer. Chem. Soc.*, **91**, 4320 (1969); (c) R. Tang and K. Mislow, *ibid.*, **91**, 5644 (1969); (d) C. R. Johnson and J. J. Rigau, *ibid.*, 5398 (1969); (e) C. R. Johnson and D. McCants, Jr., *ibid.*, **87**, 5404 (1965).

(5) (a) S. M. Kotin, Ph.D. Dissertation, University of Pennsylvania, 1962; (b) J. J. Ubel, Ph.D. Dissertation, University of Illinois, 1964.

(6) C. R. Johnson and D. McCants, Jr., *J. Amer. Chem. Soc.*, **87**, 1109 (1965).

(7) (a) C. R. Johnson and W. O. Siegl, *ibid.*, **91**, 2796 (1969); (b) *Tetrahedron Lett.*, 1879 (1969).

(8) (a) B. Z. Zrbuzov, O. N. Nuretdinova, and A. N. Vereshchagin, *Dokl. Akad. Nauk SSSR*, **172**, 591 (1967); (b) W. D. Keller, T. R. Lusebrink, and C. H. Sederholm, *J. Chem. Phys.*, **44**, 782 (1966); (c) S. Allenmark, *Ark. Kemi*, **26**, 73 (1966); (d) D. O. Harris, H. W. Harrington, A. C. Luntz, and W. D. Gwinn, *J. Chem. Phys.*, **44**, 3467 (1966).

(9) J. Lillien and R. A. Doughty, *J. Amer. Chem. Soc.*, **89**, 155 (1967).