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THE STEREOCHEMISTRY OF OXIDATION AT SULFUR
OXIDATION OF 2-THIABICYCLO[2.2.1]HEPTANE[1]

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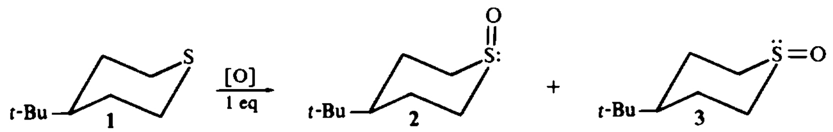
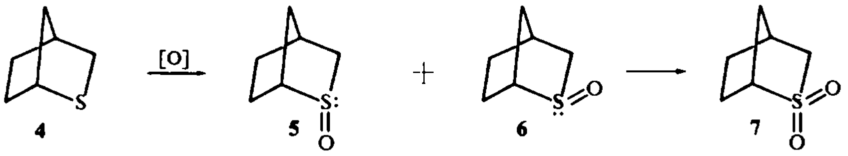
Abstract—Oxidation of 2-thiabicyclo[2.2.1]heptane by a variety of oxidizing agents provided both *endo* and *exo* sulfoxides. The ratio of these sulfoxide isomers is a function of the relative stability of the sulfoxides and/or the mechanism of the oxidation reaction. It has been demonstrated that the *exo* oxide of 2-thiabicyclo[2.2.1]heptane is thermodynamically more stable than the corresponding *endo* oxide, a result not to be predicted from referenced researches in the field.

Johnson and McCants[2] have systematically studied the stereochemistry of oxidation of 4-substituted thianes (e.g. **1**) to the sulfoxides. The isomeric distribution of axial *vs* equational sulfoxides was interpreted as being a function or a combination of the functions of thermodynamic control, steric-approach control, and product-development control. Of particular interest in that study was the remarkable stereoselectivity of several reagents and the greater stability of the axial oxide **2** compared to the equatorial oxide **3**.



In a recent paper[3] we described the synthesis of 2-thiabicyclo[2.2.1]-heptane (**4**). Here we present results of the oxidation of 2-thiabicyclo[2.2.1]-heptane (**4**) by a a variety of reagents and relate the stereochemistry of oxidation to the relative stability of the isomeric sulfoxides and the mechanism of oxidation.

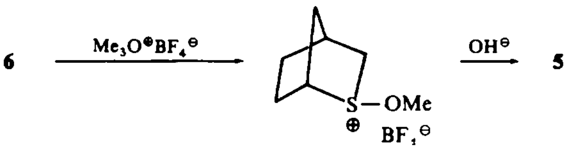


Assignment of configuration. The assignment of structure to the *endo* and *exo* oxides were based on chromatographic behavior and stereoselectivity of oxidations by selected reagents. Retention times on chromatography appear to be directly correlated with the accessibility of the oxygen of the sulfoxide for interaction with the stationary phase. Thus in the thiane system, compounds bearing an axial oxide elute prior to the equatorial isomer. In the more nearly planar 3-substituted thietane 1-oxides,[4] the *cis* isomers elute prior to the *trans*. Of the two isomers (**5** and **6**), the oxide of the *endo* isomer is clearly less accessible. The order of elution of isomers

(**5** and **6**) is the same during thin layer, column (silica gel), and GLC; we assign structure **5** to the isomer of shorter retention time.

The second line of evidence for configurational assignments follows again from our observations in the 4-substituted thiane system; for example, peroxy reagents afford sulfoxides of stereochemistry predicted on the basis of steric accessibility to approach by the reagent. Thus in anchored thianes, a predominance of equatorial oxides result from oxidation by peroxy reagents (e.g. hydrogen peroxide). In the present system such reagents would be expected to approach from the *exo* side. Other examples are discussed below.

Pure *exo*-2-thiabicyclo[2.2.1]heptane oxide (**6**) was obtained on separation from a mixture of *endo* and *exo* sulfoxides by preparative vapor phase chromatography. Pure *endo*-2-thiabicyclo[2.2.1]heptane oxide (**5**) was prepared from *exo* sulfoxide **6** by inversion of configuration of the sulfoxide by O-alkylation and hydrolysis.



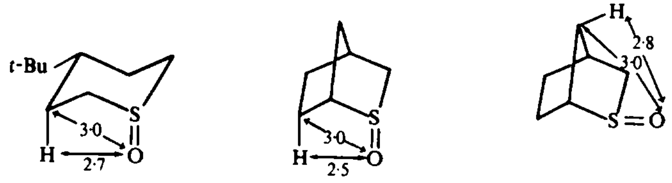
The IR and UV spectra of sulfoxides **5** and **6** exhibited considerable similarity (Table 1), whereas the NMR spectra are complex and quite dissimilar.

Table 1. Physical data on *endo* and *exo* sulfoxides

Isomer	5	6
Mp	169·5–171°	175–176°
Ir (S=O)	1051, 1007 cm^{-1}	1042, 1009 cm^{-1}
Uv (λ_{max})		
cyclohexane	196 mμ	200 mμ
acetanitrile	215 mμ	217 mμ
ethanol	202 mμ	203 mμ

Equilibration studies. The interpretation of stereochemical results of oxidation of sulfides to sulfoxides demands a knowledge of the relative thermodynamic stabilities of the possible isomers. Equilibration of mixtures of 2-thiabicyclo[2.2.1]heptane 2-oxides (**5** and **6**) at 25° with hydrogen chloride in dioxane resulted in a predominance (72%) of the *exo* isomer (ΔG for the reaction *exo* ⇄ *endo* = 0·56 kcal/mole). Treatment of mixtures of the sulfoxides with dinitrogen tetroxide provided a mixture consisting of 18% *endo* and 82% *exo* sulfoxides (ΔG = 0·82 kcal/mole). The equilibrium actually involved in the latter reaction is most likely between complexes of the reagent and the sulfoxide isomers. Thermally induced equilibration of mixtures of sulfoxides **5** and **6** in decalin at 190° resulted in the formation of pure *exo* isomer as far as could be determined by VPC. At elevated temperatures in a gas chromatograph equilibration also occurs. At column temperature of 180° or above, only *exo* isomer can be detected. At 135° and below thermal isomerization does not significantly occur during the residence time in the instrument.

These equilibration studies reveal that the 2-thiabicyclo[2.2.1]heptane 2-oxide bearing *exo* oxygen is, in each case, more stable. This result, although in line with *a priori* prediction that might be made based on analogy to exclusively carbocyclic norbornanes, is not in harmony with that which might be predicted based on the fact that axial oxides are more stable in thiane systems.



2 5 6

FIG. 1 Comparison of nonbonded distances (Å) in sulfoxide isomers. Measurements taken from Dreiding models (the sulfoxide model was made from the available sulfone).

In an earlier paper[2] we suggested that in the axial thiane oxide the possibility "that London attractive terms outweigh van der Waals repulsion and create a favourable interaction between the oxygen and the ring". Recent theoretical calculations by Allinger[5] suggest that this is indeed the case. Note from Fig. 1 that the interatomic distances between the sulfoxide oxygen and near nonbonded neighbors are very similar in axial thiane oxide **2** and the *exo*-isomer **6**. Note also that the nonbonded distance between the *endo* oxygen in **5** and the diametric *endo* hydrogen is shorter than that observed in the thiane—a situation that could possibly create considerable nonbonded repulsion.

Oxidation studies. Oxidation of 2-thiabicyclo[2.2.1]heptane (**4**) was accomplished by a variety of methods outlined in the literature for the sulfide-sulfoxide transformation. Conditions were chosen to prevent any oxidation to the sulfone stage. Analytical data and separation of the resulting sulfoxide mixtures were obtained by GLC employing conditions which were chosen to eliminate any equilibration of the

TABLE 2. A COMPARISON OF THE OXIDATION OF 2-THIABICYCLO[2.2.1]HEPTANE AND 4-t-BUTYLTHIANE TO SULFOXIDES

Oxidizing Reagent		Sulfoxide (%) **5** (*endo*)	 **6** (*exo*)	 **2** (*cis*)	 **3** (*trans*)
t-Butyl hypochlorite	MeOH (− 78)	65	35	100	0
Nitric acid (fuming)	Ac_2O (0)	25	75	67	33
Sodium metaperiodate	H_2O (0)	24	76	75	25
m-Chloroperbenzoic acid	CH_2Cl_2 (0)	23	77	36	64
Dinitrogen tetroxide	.... (0)	18	82	81	19
Hydrogen peroxide	AcOH (25)	18	82	35	65
Iodosobenzene	C_6H_6(80)	16	84	46	54
Hydrogen peroxide	Me_2CO(25)	15	85	37	63
t-Butyl hydroperoxide	C_6H_6 (50)	14	86	36	64
Chromic acid	C_6H_5N (25)	12	88	27	73
t-Butyl hydroperoxide	MeOH (50)	11	89	27	73
Ozone	CH_2Cl_2 (25)	8	92	10	90

sulfoxide isomers. Table 2 presents the relative percentages of *endo* and *exo* sulfoxides formed in each reaction, and for comparison purposes presents the similar data obtained previously on 4-t-butylthiane.[2]

For the moment we refer the reader to our previous mechanistic interpretations of stereochemical results of such oxidations.[2] In the present system it should be kept in mind that the product of stereochemical approach control and that of thermodynamic factors is the same—namely the *exo* isomer. Of particular interest is the fact that t-butyl hypochlorite oxidation was the only method found by us to give a predominance of the *endo* sulfoxide. We shall defer discussion of stereochemistry and its relation to mechanism until data on other ring systems is available to us, at which time such discussion should be more meaningful.

EXPERIMENTAL

M. pts are uncorrected. IR spectra were measured with a Perkin–Elmer Model 621 grating spectrometer. NMR spectra were obtained on a Varian A-60A and a JEOL 100 MHz spectrometer. The UV spectra were recorded on a Cary Model 14 spectrometer. TLC was performed on microscope slides with V-shaped coating on Silica Gel G, developing with EtOAc:acetone (20:80).

2-*Thiabicyclo*[2.2.1]*heptane* (4). This was prepared by the procedure described by Johnson *et al.*[3]

General methods of oxidation. The procedures employed for the oxidation of 4 to sulfoxide are those reported[2] for the oxidations of 4-t-butylthiane. The sulfoxides were found to be extremely hygroscopic, and much caution was exercised in handling the samples.

Equilibration Studies

A. *Hydrochloric acid-dioxan.*[6] A sulfoxide mixture (50 mg) consisting of 26·9% *endo* sulfoxide 5 and 73·1% *exo* sulfoxide 6 was added to 1 ml of a 2:1 mixture of dioxan:conc HCl. The resulting soln was stirred at 25° for 20 min, diluted with 10 ml water, and extracted with three 10 ml portions of CH_2Cl_2. The combined extracts were dried over $MgSO_4$, concentrated, and subjected to GLC analysis.

B. *Dinitrogen tetroxide.* Excess liquid dinitrogen tetroxide was added to 4 at 0°. The mixture was stirred at 0° for 150 min (only 30 min is required for the sulfide oxidation); the ice bath was removed and the excess dinitrogen tetroxide allowed to evaporate. The products were analyzed by GLC.

C. *Thermal.*[7] A sulfoxide mixture consisting of 26·9% *endo* sulfoxide 5 and 73·1% *exo* sulfoxide 6 was heated in freshly distilled decalin at 190° under N_2 for 1 hr. The products remaining on evaporation of the decalin at 30°/0·5 mm Hg, were dissolved in a minimum CH_2Cl_2 and analyzed by GLC.

Analysis of mixtures. Percentage composition of the sulfoxide isomers were ascertained by planimetric integration of charts obtained from an F and M Model 720 chromatograph equipped with a 6 ft × ¼ in column of 10% FFAP on Chromosorb W. An injection port temp of 190°, an oven temp of 135°, and a carrier gas flow rate of 60 ml/min proved to be ideal conditions for a clean separation of the isomeric sulfoxides without thermal isomerization. Retention times of 42 min and 52 min were observed for *endo* sulfoxide 5 and *exo* sulfoxide 6, respectively.

exo-2-*Thiabicyclo*[2.2.1]*heptane oxide* (6). A sulfoxide mixture (26·9% *endo* and 73·1% *exo*) was separated by GLC and the second peak, identified as *exo* sulfoxide 6, was collected as a white solid. This solid was dissolved in CH_2Cl_2. The soln was dried over $MgSO_4$ and evaporated affording a white solid which was sublimed at 150°/760 mm Hg yielding a white hygroscopic solid, m.p. 175–176°.

endo-2-*Thiabicyclo*[2.2.1]*heptane oxide* (5). A mixture of 117 mg (0·9 mmole) of 6 and 148 mg (1·0 mmole) trimethyloxonium tetrafluoroborate in CH_2Cl_2 was stirred for 90 min at 25° and was then filtered. To the cooled filtrate, ether was added to the cloud point; white crystals of *exo*-2-methoxy-2-thiabicyclo-[2.2.1]heptane tetrafluoroborate, m.p. 109–111° (recrystallized) precipitated. Titration of an aqueous soln of this methoxy-sulfonium salt with 0·05N NaOH to the phenophthalein end point followed by saturation with NaCl and extraction with CH_2Cl_2 afforded, after drying over $MgSO_4$, and evaporation, the white hydroscopic solid of *endo* 5, m.p. 169–171°.

2-*Thiabicyclo*[2.2.1]*heptane*-2,2-*dioxide* (7). To a soln of 2 mmoles of 4 in 2 ml AcOH was added 1 ml (≈ 4 mmoles) 40% peracetic acid in AcOH at such a rate to keep the reaction temp near 50°. The reaction mixture was stirred for 24 hr at 25°, diluted with 5 ml water, neutralized with a Na_2CO_3aq, and extracted with three 10 ml portions of CH_2Cl_2. The dried extracts ($MgSO_4$) were evaporated affording a white solid. Sublimation at 110°/0·5 mm Hg yielded sulfone **7**, a white solid (75·9%) m.p. 206–207° (lit.[3] m.p. 203–205°). The same material was obtained by the oxidation of sulfoxides **5** and **6**.

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