

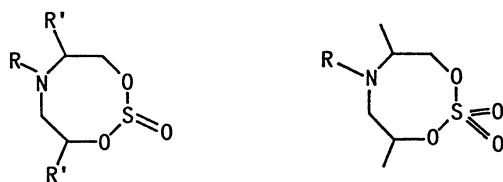
The Stereochemistry of the Sulfur Atom of 4,7-Dimethyl-6-phenyl-5,6,7,8-tetrahydro-4*H*-1,3,2,6-dioxathiazocine 2-Oxides

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Synopsis. The reaction of *N*-(2-hydroxypropyl)-*N*-(2-hydroxy-1-methylethyl)aniline with thionyl chloride afforded four isomers of 4,7-dimethyl-6-phenyl-5,6,7,8-tetrahydro-4*H*-1,3,2,6-dioxathiazocine 2-oxide. Oxidation of the four isomers by the use of KMnO_4 yielded two kinds of sulfates. On the basis of the coupling constants and γ -effects, the stereochemical structures of the dioxathiazocine 2-oxides are discussed.

Cyclic sulfites, mainly 5-^{1,2)} and 6-membered^{3–5)} rings, have been extensively investigated from a conformational viewpoint, while those having large rings have rarely been studied.^{6,7)} The present study was initiated to examine the stereochemical structure in solution of 8-membered ring compounds, 1,3,2,6-dioxathiazocine 2-oxides, in which one of the methylene groups of carbocyclic sulfite has been replaced by an *N*-Ph group.



- 1, $R = \text{C}_6\text{H}_5$, $R' = \text{CH}_3$
2, $R = 4\text{-CH}_3\text{-C}_6\text{H}_4$, $R' = \text{CH}_3$
3, $R = \text{C}_6\text{H}_5$, $R' = \text{H}$

- 4, $R = \text{C}_6\text{H}_5$

The reaction of *N*-(2-hydroxypropyl)-*N*-(2-hydroxy-1-methylethyl)anilines with thionyl chloride afforded 4,7-dimethyl-6-phenyl- (1), and 4,7-dimethyl-6-(*p*-tolyl)-5,6,7,8-tetrahydro-4*H*-1,3,2,6-dioxathiazocine 2-oxides (2). VPC analyses of 1 and 2 showed that each of them consisted of four diastereomers with the following components: 12%(1a), 26%(1b), 11%(1c), and 16%(1d); 25%(2a), 20%(2b), 14%(2c), and 25%(2d). The diastereomeric mixtures were chromatographed on silica gel to give the pure isomers **a–d**.

To determine the configurational relationship between isomers **a–d**, oxidation of the S=O bond was performed by the reported methods for cyclic sulfite.⁸⁾ Treatment of 1a with RuO_4 generated in situ from NaIO_4 and RuO_2 or $\text{RuCl}_3/\text{NaIO}_4$ systems did not provide the corresponding sulfate 4. Similarly, oxidation of 1a with *m*CPBA gave 4 in a poor yield. However, oxidation of 1a with permanganate in acetone provided the sulfate 4a in a 65% yield. Similar oxidation of 1c with permanganate gave the same sulfate 4a in a 77% yield. In a similar experiment, oxidation of 1b and/or 1d with permanganate gave 4b in 66% and 35% yields. From these results, isomers **c** and **d** were proposed to be epimeric forms of isomers **a** and **b**, respec-

tively, about the sulfur atom.

Before embarking on a detailed discussion of the diastereomers of **a–d**, the following information for 4,6-dimethyl-1,3,2-dioxathiane 2-oxide is provided.⁹⁾ In essence, the γ -shift is a useful indicator of the interaction of an axial S=O bond with a *syn*-axial H, resulting in a shielding of the γ carbon by about 9 ppm relative to the case where S=O is equatorial. Replacement of a *syn*-axial H by a carbon results in the loss of a major part of the γ -shift.

On this basis, it is interesting to compare the chemical shifts of the diastereomers **a–d**. The ^{13}C NMR chemical shifts of the heterocyclic and methyl carbons are shown in Table 1. Striking differences between **a** and/or **b** and **c** and/or **d** are recognizable in the chemical shifts of C-4. The C-4 signals of 1a and/or 1b appeared at a higher field by ca. 5.5 ppm (mean value) than those of 1c and/or 1d. This large upfield shift is a consequence of the γ -*sc* relationship between the C-4 and the S=O bond. Furthermore, the C-4 of 1a and 1b bears a *syn*-H to the S=O bond. Similarly, C-4 of 2a and/or 2b also showed a marked high field shift by ca. 5.6 ppm. In contrast, the chemical shift differences of C-8 among **a–d** are almost negligible compared with those of C-4. Furthermore, the C-8 signals of **a–d** appeared downfield by ca. 5.0 ppm than those of the parent compound 3; that is, the geometrical relationship between the C-8 and the exocyclic oxygen is γ -*ap* in **a–d**.

A similar phenomenon is also observed in the ^1H NMR spectra of the title compounds. The ^1H NMR spectra of compounds 1 and 2 are shown in Table 2. The H-4 of 1a, 1b, 2a, and 2b appeared at $\delta = 5.02\text{--}5.05$, $5.12\text{--}5.19$, $4.96\text{--}4.99$, and $5.11\text{--}5.16$, respectively. In contrast, the H-4 of 1c, 1d, 2c, and 2d appeared at $\delta = 4.59\text{--}4.63$, $4.58\text{--}4.65$, $4.57\text{--}4.61$, and $4.58\text{--}4.62$, respectively. The downfield shift of **a** and **b** relative to **c** and **d** may suggest that the S=O bond and the H-4 of **a**

Table 1. The ^{13}C NMR and IR Spectral Data of 1–3

Compd No.	^{13}C NMR, δ in CDCl_3						IR, ν/cm^{-1}
	C-4	C-5	C-7	C-8	4,7- CH_3	S=O	
1a	66.7	49.2	50.3	63.4	19.0	14.0	1186
1b	67.6	52.7	54.6	64.9	20.0	14.9	1202
1c	73.3	50.4	51.3	64.9	18.8	12.8	1199
1d	71.9	56.2	57.6	62.4	19.3	15.9	1205
2a	66.8	49.3	50.4	63.4	19.0	14.1	1194
2b	68.1	53.2	54.9	65.3	19.9	14.9	1206
2c	73.5	50.4	51.7	65.7	18.6	12.6	1199
2d	72.5	57.0	57.8	63.5	19.1	15.9	1201
3	59.2	51.4	51.4	59.2	—	—	1201

Table 2. ^1H NMR Chemical Shifts of the Heterocyclic Protons of **1** and **2**

Compd. No.	Chemical shifts (δ) and coupling constants (Hz)				
	H-5	H-8	H-4	H-7	
1a	3.38dd 3.44dd (16.8, 1.6) (7.3)	3.62dd 4.44dd (11.9, 7.1) (3.2)	5.02- 5.05m	4.21- 4.25m	
1b	3.31dd 3.70dd (15.8, 8.3) (3.7)	4.09dd 4.21dd (12.5, 3.9) (7.6)	5.12- 5.19m	4.06- 4.15m	
1c	3.36dd 3.37dd (16.3, 1.1) (7.9)	3.96dd 4.47dd (12.4, 4.9) (10.3)	4.59- 4.63m	4.29- 4.32m	
1d	3.23dd 3.65dd (15.8, 8.6) (2.5)	4.01dd 4.72dd (12.1, 9.0) (4.5)	4.58- 4.65m	4.08- 4.15m	
2a	3.29dd 3.52dd (16.6, 1.1) (7.3)	3.53dd 4.34dd (12.1, 7.0) (2.5)	4.96- 4.99m	4.08- 4.12m	
2b	3.27dd 3.56dd (15.8, 8.3) (3.4)	4.07dd 4.16dd (12.7, 3.9) (8.0)	5.11- 5.16m	4.01- 4.07m	
2c	3.23—3.34m	3.94dd 4.39dd (12.5, 4.4) (10.3)	4.57- 4.61m	4.17- 4.23m	
2d	3.20dd 3.71dd (15.7, 8.5) (2.4)	3.99dd 4.69dd (11.2, 8.8) (3.4)	4.58- 4.62m	3.98- 4.05m	

and **b** are *cis* to each other because of the anisotropic effects of the S=O bond.¹⁰⁾

In the chair form of cyclohexane, typical vicinal coupling constants¹¹⁾ span the following ranges: $J_{aa}=9.5$ — 12.5 Hz; $J_{ca}=3.0$ — 4.5 Hz; $J_{cc}=2$ — 3 Hz. Albrittsen²⁾ has also reported that J_{4a5a} and J_{4a5c} for 4e-methyl-1,3,2-dioxathiane 2-oxide in the chair form are 11.6 and 2.4 Hz, respectively. The observed vicinal coupling constants for the H-4,5 protons of **1a**—**1d** are as follows: (**1a**) 7.3, 1.6; (**1b**) 8.3, 3.7; (**1c**) 7.9, 1.1; (**1d**) 8.6, 2.5 Hz, whereas the observed coupling constants for the H-7,8 protons are as follows: (**1a**) 7.1, 3.2; (**1b**) 7.6, 3.9, (**1c**) 10.3, 4.9; (**1d**) 9.0, 4.5 Hz. These coupling constants are small compared to the J_{aa} values obtained for 6-membered ring systems such as cyclohexane and 1,3,2-dioxathiane 2-oxide. The intermediate values obtained in the present study for the vicinal couplings can be interpreted in terms of a boat(B)chair(C) $\rightleftharpoons$ BC equilibrium or a twist form. The conformations in the crown family are the crown itself, the CC, and the twist CC. These crown family members do not fit the experimental NMR data, that is, a γ -effect from the S=O bond is not observed at C-8 in **a**—**d**.

To suggest a preferred conformation, MM2 calculations were carried out to obtain a steric energy.¹²⁾ The BC conformation of 4e,6,7a-trimethyl-1,3,6-dioxazocine, which has a structure similar to that of **1** and **2**, is 26.1 and 5.7 kJ mol⁻¹ lower in steric energy compared with those of the TBC and CC forms, respectively. Moreover, it has already been reported that 8-membered ring molecules cyclooctanes,¹³⁾ 1,3-dioxocanes,¹⁴⁾ and azocines¹⁵⁾ exist in the BC form as the favored conformation. Judging from the above results, we have therefore suggested that the preferred conformation of **1** and **2** is the BC form. In the BC conformation for the 5,6,7,8-tetrahydro-4*H*-1,3,2,6-dioxathiazocine 2-oxide skeleton, the sulfur atom has a choice of eight positions. These BC forms are distinguished as BC-1 to BC-8, where the sulfur atom is situated at 1 to 8. Equatorial S=O types are indicated by a prime.

From the ^{13}C NMR data and the arguments presented above, it can be considered that isomers **a** and **b** have BC-2', BC-3, or BC-8 type conformations as shown in Fig. 1, because the geometrical relationships of C-4 and C-8 against the S=O bond are γ -*sc* and γ -*ap*, respectively. However, conformation BC-2 or BC-8' for isomers **c** and **d** are not in accord with the ^{13}C NMR chemical shifts of C-8, because the geometrical relationship between the C-8 and the S=O group is γ -*sc*. It follows that isomers **a** and **b** have conformation BC-3 and those of ring inversion form (BC-7'), and therefore that isomers **c** and **d** have conformation BC-3' (BC-7). One question remains however; which isomer **a** or **b** (**c** or **d**) has which configuration of *cis*- and *trans*-dimethyl forms as shown in Fig. 2? If the equilibrium between the axial and equatorial S=O forms in the *cis* **I** and the *trans* **II** isomers lies on the side of the axial S=O form, to be discussed below, there will be a *syn*-1,3 interaction between the C-7 methyl group and one of the C-5 hydrogen atoms in **I**. The C-5 and C-7 signals of isomer **a** (or **c**) appeared at a higher field than those of **b** (or **d**) as a result of *syn*-1,3 steric interactions between

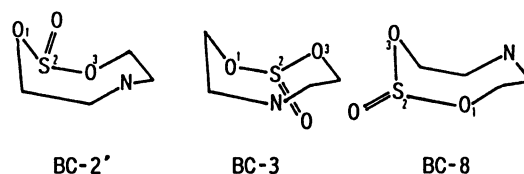


Fig. 1. Possible conformations of the BC form of the 1,3,2,6-dioxathiazocine 2-oxide skeleton. The (conformational) labeling refers to the S=O group.

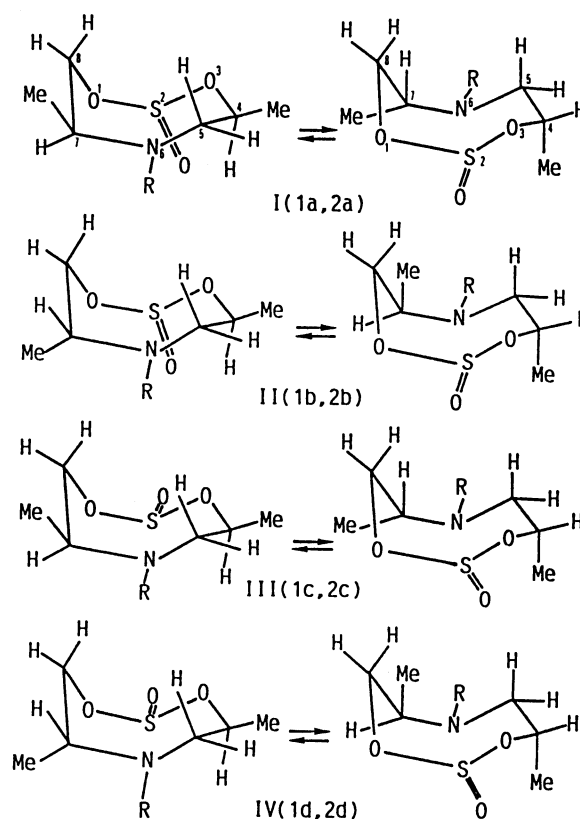


Fig. 2. Possible stereoisomers of **1** and **2**.

the methyl group on C-7 and the hydrogen on C-5.^{16,17)}

It is now well established that the most stable conformation of the 1,3,2-dioxathiane 2-oxides is a chair form with an axial S=O bond. The axial S=O group experiences a minimum number of *sc* interactions between the S=O group and the lone pair electron orbitals of the adjacent oxygen atoms. This conformational preference over the equatorial orientation has been estimated to involve about 8.4 kJ mol⁻¹ in CCl₄.¹⁸⁾ If accepting the value of 8.4 kJ mol⁻¹, an axial S=O conformation in **I** and **II** should be more stable than an equatorial S=O form. On the other hand, as to an axial S=O conformer of **III** and **IV**, there is a 1,3-diaxial interaction between the methyl group on C-4 and the S=O group.

Consequently, we believe that isomers **a** and **c** exist as the stereostructures **I** and **III**, respectively. Similarly, isomers **b** and **d** exist as **II** and **IV**, respectively.

Experimental

All melting points are uncorrected. IR spectra were measured on a Perkin-Elmer 1600 FT spectrometer. ¹H and ¹³C NMR spectra were recorded on a JEOL GSX-400 spectrometer in CDCl₃ solution, using (CH₃)₄Si as an internal standard. Mass spectra were recorded on a Shimadzu QP-2000 spectrometer. Gas chromatography was performed on a Hewlett-Packard 5890A instrument fitted with an OV101 capillary column. *N*-(2-Hydroxypropyl)-*N*-(2-hydroxy-1-methylethyl)anilines were prepared as described previously.¹⁹⁾

4,7-Dimethyl-6-phenyl-5,6,7,8-tetrahydro-4H-1,3,2,6-dioxathiazocine 2-Oxides (1a–1d). A solution of thionyl chloride (1.78 g, 15.0 mmol) in benzene was added to a stirred solution of *N*-(2-hydroxypropyl)-*N*-(2-hydroxy-1-methylethyl)aniline (2.09 g, 10.0 mmol) in benzene (50 ml) and triethylamine (2.5 ml) at 5°C. After stirring for 1 h at 5°C and at room temperature for an additional hour, the mixture was washed with brine and then with H₂O. After drying over Na₂SO₄, the solvent was removed in vacuo to give 2.77 g of **1**. Column chromatography (silica gel, 14% CH₂Cl₂ in hexane) provided 0.31 g (12%) of **1a**, 0.66 g (26%) of **1b**, 0.28 g (11%) of **1c**, and 0.41 g (16%) of **1d**.

1a: Mp 100.0–100.5°C. Calcd for C₁₂H₁₇O₃NS: C, 56.45, H, 6.71, N, 5.49%. Found: C, 56.34; H, 6.67; N, 5.32%.

1b: Found: C, 56.75, H, 6.79, N, 5.22%.

1c: Mp 114.0–115.0°C. Found: C, 56.18; H, 6.65; N, 5.47%.

1d: Mp 105.0–105.5°C. Found: C, 56.53; H, 6.66; N, 5.43%.

4,7-Dimethyl-6-(*p*-tolyl)-5,6,7,8-tetrahydro-4H-1,3,2,6-dioxathiazocine 2-Oxides (2a–2d). The products **2a–2d** were obtained by the reaction of *N*-(2-hydroxypropyl)-*N*-(2-hydroxy-1-methylethyl)-*p*-toluidine with thionyl chloride in a similar manner to that for **1**. Column chromatography (silica gel, 14% CH₂Cl₂ in hexane) provided 0.43 g (25%) of **2a**, 0.35 g (20%) of **2b**, 0.24 g (14%) of **2c**, and 0.43 g (25%) of **2d**.

2a: Calcd for C₁₃H₁₉O₃NS: C, 57.97, H, 7.11, N, 5.12%. Found: C, 58.68, H, 7.25, N, 5.18%.

2b: Mp 151.5–152.0°C. Found: C, 57.96; H, 6.76; N, 4.95%.

2c: Mp 155.5–156.0°C. Found: C, 58.06; H, 7.09; N, 5.14%.

2d: Mp 93.0–94.0°C. Found: C, 57.96; H, 6.76; N, 4.95%.

Oxidation of 1 with KMnO₄. A solution of **1a** (0.16 g, 0.63 mmol) in acetone (10 ml) was added to a stirred solution of KMnO₄ (0.26 g, 1.72 mmol) in acetone (50 ml) at 0°C and the

mixture was stirred overnight. The reaction mixture was poured into saturated NaHCO₃, and the liquid was extracted twice with CH₂Cl₂. The organic layers were combined, washed with H₂O, and then dried over Na₂SO₄. Evaporation of the solvent gave a yellow oil which was chromatographed on silica gel (33% CH₂Cl₂ in hexane) to give 0.11 g (65%) of 4,7-dimethyl-6-phenyl-5,6,7,8-tetrahydro-4H-1,3,2,6-dioxathiazocine 2,2-dioxide **4a** as a yellow oil. A similar treatment of **1c** gave **4a** (77%).

4a: ¹H NMR δ=1.27 (d, 3H, *J*=6.6 Hz), 1.50 (d, 3H, *J*=6.6 Hz), 3.49 (d, 1H, *J*=16.9 Hz), 3.61 (dd, 1H, *J*=16.9 and 8.1 Hz), 4.25 (d, 1H, *J*=11.4 Hz), 4.24–4.29 (m, 1H), 4.54 (dd, 1H, *J*=11.4 and 3.2 Hz), 4.96–5.01 (m, 1H), and 6.60–7.29 (m, 5H); ¹³C NMR δ=13.6, 18.7, 49.5, 50.3, 73.8, 82.7, 112.2, 118.0, 129.8, and 147.2; EIMS *m/z* 271 (M⁺, 35), 207 (27), 134 (24), 133 (100), 132 (40), 105 (24), 104 (49), 92 (24), 91 (85), and 77 (94). Similar treatment of **1b** and **1d** with KMnO₄ yielded **4b** in 66 and 35% yields, respectively.

4b: ¹H NMR δ=1.32 (d, 3H, *J*=6.9 Hz), 1.40 (d, 3H, *J*=6.2 Hz), 3.39 (dd, 1H, *J*=16.2 and 7.7 Hz), 3.83 (dd, 1H, *J*=16.2 and 2.3 Hz), 4.16–4.25 (m, 1H), 4.41 (dd, 1H, *J*=12.2 and 8.8 Hz), 4.58 (dd, 1H, *J*=12.2 and 4.4 Hz), 4.93–5.02 (m, 1H), and 6.81–7.28 (m, 5H); ¹³C NMR δ=15.3, 18.6, 55.1, 55.4, 73.8, 82.2, 117.6, 119.9, 127.5, and 147.2; EIMS *m/z* 271 (M⁺, 37), 162 (21), 134 (24), 133 (100), 132 (34), 105 (20), 104 (44), 92 (26), 91 (87), and 77 (88).

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