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Two isomeric 4-methyl-6-phenyl-5,6,7,8-tetrahydro-4H-1,3,2,6-dioxathiazocine 2-oxides were prepared, and their pmr and cmr spectra were examined. From the aromatic solvent shielding values and the magnitudes of the γ shifts, the title compounds are found to exist in the *trans* and *cis* forms in solution.

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Stereochemical studies on cyclic sulfites have been reported by several workers [1-8]. For example, Buchanan [9] reported that 4-phenyl-1,3,2-dioxathiane 2-oxide exists in two stereochemical isomers and that the assignment of these isomers could be made by the use of nmr and ir spectroscopies. Namely, cmr chemical shift at C-4 and C-6 having the axial S=O bond appears at higher field than that with the equatorial S=O bond because of γ -gauche relationship between the axial S=O and the C-4, 6 ring carbons. Ir spectra of compounds with axial and equatorial S=O types showed characteristic sulfinyl stretching at 1190 and 1210 cm^{-1} respectively.

In a previous paper [10], we reported the reaction of *N,N*-bis(2-hydroxyethyl)anilines with thionyl chloride giving the 6-phenyl-5,6,7,8-tetrahydro-4H-1,3,2,6-dioxathiazocine 2-oxides, which had a structure similar to that of 1,3,2-dioxathiane 2-oxides.

In this paper, we report the detail of the stereochemical assignment of 1,3,2,6-dioxathiazocine 2-oxide system by means of nmr spectroscopy.

EXPERIMENTAL

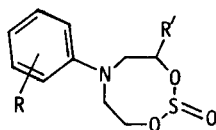
All the melting points are uncorrected. The ir spectra were recorded on a Shimadzu Model-27G spectrometer as a potassium bromide disc. Pmr spectra were determined at 100- and 60-MHz with JEOL JNM-PS-100 and JNM-PMX-60 spectrometers in deuteriochloroform. Cmr spectra were obtained using a JNM-PS-100/EC-100 FT spectrometer in deuteriochloroform operating at 25.15 MHz, with complete proton decoupling. Cmr spectra were measured in the range from room temperature to 90° using a variable temperature controller, JNM-VT-3C, with attachments. The chemical shifts were referred to with the internal tetramethyl silane as the standard. *N*-(2-hydroxypropyl)-*N*-(2-hydroxyethyl)anilines and *N,N*-bis(2-hydroxyethyl)anilines were prepared by the reaction of the corresponding anilines with propylene oxide or ethylene oxide [11].

RESULTS AND DISCUSSION

The 4-methyl-6-phenyl-5,6,7,8-tetrahydro-4H-1,3,2,6-dioxathiazocine 2-oxides (1-4) were prepared by the reactions of *N*-(2-hydroxypropyl)-*N*-(2-hydroxyethyl)anilines with thionyl chloride in the presence of triethylamine [10]. In each reaction, two isomers of types **a** and **b** can be separated by the use of silica gel column with hexane as an eluent. The products of these reactions and their physical properties are summarized in Table 1.

Table 1

Physical Properties of Compounds 1-6

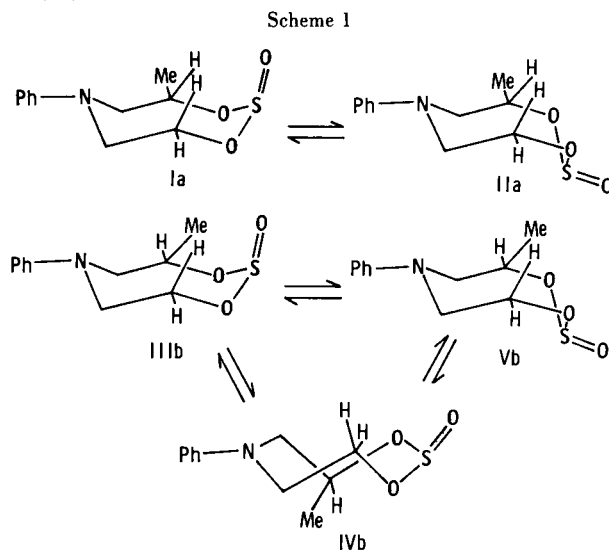


Compound No.	R.	R'	Yield/%	Mp °C	C	Found (Calcd)%		IR, S=O ν/cm^{-1}
						H	N	
1a	<i>m</i> -CH ₃	CH ₃	21	71.8-73.3	56.35 (56.45)	6.68 (6.71)	5.39 (5.49)	1180
1b	<i>m</i> -CH ₃	CH ₃	20	97.5-99.0	56.10	6.59	5.43	1205
2a	<i>p</i> -CH ₃	CH ₃	10	79.1-80.0	56.38	6.76	5.53	1195
2b	<i>p</i> -CH ₃	CH ₃	8	98.0-99.4	56.58	6.81	5.42	1200
3a	<i>m</i> -Cl	CH ₃	15	95.8-96.8	47.85 (47.91)	4.99 (5.12)	5.17 (5.08)	1190
3b	<i>m</i> -Cl	CH ₃	10	104.7-105.0	47.92	4.96	5.02	1200
4a	<i>p</i> -Cl	CH ₃	8	90.0-91.0	47.91	5.21	5.05	1190
4b	<i>p</i> -Cl	CH ₃	9	92.6-93.1	48.19	5.29	5.08	1200
5	<i>m</i> -CH ₃	H	40	64.5-65.2	54.72 (54.74)	6.23 (6.27)	5.84 (5.81)	1173
6	<i>m</i> -Cl	H	25	78.8-79.4	45.77 (45.87)	4.64 (4.63)	5.25 (5.35)	1195

Regarded from the standpoint that these **a** and **b** are conformational isomers, it may be considered that one isomer exists in equilibrium mixture of both isomers at elevated temperature. If this were indeed the case an nmr experiment where the temperature is varied should serve to equilibrate one isomer to a mixture of the two. We first attempted the measurement of cmr spectrum of types **a** and **b** in benzene, respectively, at 90°. Consequently, the peaks of the newly formed isomer were not found in the compounds of types **a** and **b**.

Secondly, we tried the reaction of *N,N*-bis(2-hydroxyethyl)anilines having no 4-substituted methyl group with thionyl chloride by a similar synthetic method to **1** - **4**. These results are shown in Table 1. In this reaction, the sole product was obtained. From the above results, it may be thought that the isomers **a** and **b** are a pair of *cis-trans* configurational isomers, the one compound with equatorial methyl and the other one with axial methyl group.

From the above considerations, some possible stereoisomers of types **a** and **b** are illustrated in Scheme 1. Isomer **Ia** is *trans* form with chair-chair(CC) form. **IIa** is conformational isomer of **Ia**. Similarly, isomer



Possible configurations of types **a** and **b**.

IIIb is *cis* form with CC form. Judging from examination of the molecular model, the isomer **IIIb** will give rise to serve nonbonded interactions between the 4-axial methyl group, lone-pair electrons of the nitrogen and the axial S=O group. Therefore, the isomer **IVb** also can be considered for the 1,3,2,6-dioxathiazocine 2-oxide skeleton. **Vb** is conformational isomer of **IIIb** or **IVb**.

The ir spectra of type **a** showed a characteristic band of the S=O group at 1180 - 1195 cm^{-1} . On the other hand, type **b** appeared at a slightly higher wave number than type **a**. In the case of 1,3,2-dioxathiane 2-oxides, the S=O stretching band at 1190 - 1198 cm^{-1} indicates an axial S=O conformer, while the band at 1233 - 1234 cm^{-1} is an equatorial conformer. Twist forms apparently give intermediate values [12]. Albriktsen [13] has been reported that the S=O group in 1,3,2-dioxathiane 2-oxides is situated between two geminal electron pairs at the adjacent atoms. Therefore, the axial S=O group experiences a minimum number of gauche interactions between the S=O group and the lone-pair electrons which is assumed to be the most stable structure for similar systems (14). If this consideration can be extended to type **a** and **b** of the compounds **1** - **4**, the preferred orientation of the S=O group of type **a** is the axial and type **b** is the pseudo-axial, namely the twist form. The configurations of **IIa** and **Vb** are unlikely because of the equatorial S=O group. We have therefore, suggested that, the preferred configurations of types **a** and **b** are the structures of either **Ia**, **IIIb** or **IVb**.

In the cmr spectra, the marked sensitivity to γ -effects of molecular

geometry is well known, that is, eclipsed or gauche arrangement produces an upfield shift of the signal relative to the shielding of a corresponding carbon in the anti form.

The cmr chemical shift of the heterocyclic and methyl carbons are shown in Table 2. Striking differences between types **a** and **b** are recognizable in the chemical shift of C-4. The chemical shifts of type **a** appeared higher field about 5 - 7 ppm than those of type **b**. Therefore, it

Table 2
 ^{13}C Nmr Chemical Shifts of Compounds **1-6**

Compound No.	Chemical shifts, δ				
	C-4	C-5	C-7	C-8	4-CH ₃
1a	66.3	57.2	51.5	58.7	19.0
1b	73.2	58.2	52.2	61.6	18.6
2a	66.2	57.2	51.4	58.6	18.9
2b	73.1	58.2	52.3	61.7	18.6
3a	65.9	57.2	51.4	58.1	18.8
3b	72.4	57.8	51.9	59.9	18.7
4a	65.8	57.2	51.4	58.1	18.8
4b	72.5	58.1	52.0	60.1	18.7
5	60.2	51.2	51.2	60.2	-
6	59.2	51.4	51.4	59.2	-

can be considered that the geometrical relationship of type **a** between the C-4 and the oxygen attached to the sulfur is γ -gauche, whereas the same relationship in type **b** is anti. On the other hand, chemical shift differences at C-8 between types **a** and **b** are small compared with C-4, that is, geometrical relationship between the C-8 and the oxygen attached to the sulfur is in almost the same situation in types **a** and **b**. These γ -shifts have already been reported for 1,3,2-dioxathiolane 2-oxides and 1,3,2-dioxathiane 2-oxides which had a structure similar to that of 1,3,2,6-dioxathiazocine 2-oxide skeleton. For example, Buchanan et. al. [15] have reported that the C-4 of axial S=O type is shielded by 9.3 ppm relative to the C-4 of equatorial type of 4,6-dimethyl-1,3,2-dioxathiane 2-oxide.

From the above consideration, it suggested that the preferred structure of type **a** exists in the *trans* CC configuration with the axial S=O group (structure **Ia** in Scheme 1), whereas type **b** exists in the *cis* twist-chair (TC) configuration with the pseudo-axial S=O group (structure **IVb** in Scheme 1).

The preferred configurations of compounds **1-4** are further illustrated by means of pmr. For the geometry of solute-solvent collision complexes, Ledall [16] proposed a common model with the dipole axis of the solute molecule located along the six fold-symmetry axis of a benzene nucleus, with the positive end of the dipole nearest, and the negative end farthest away. Assuming that collision complexes of a similar geometry are formed between solvent benzene molecules and the S=O bond in the 1,3,2,6-dioxathiazocine 2-oxide system, then the geometry of the association differs in the three isometric 1,3,2,6-dioxathiazocine 2-oxides (**Ia**, **IIIb** and **IVb**). The following considerations are presented. For the **Ia** configuration, aromatic solvents association should take place from the back side of the negatively polarized oxygen of the S=O bond. Consequently, the H-4 and the H-8 axial protons are only marginally affected, while the remaining protons in the solute molecule are strongly shielded. In the **IIIb** configuration, the H-8 axial proton and the axial methyl protons on C-4 are only marginally affected. Alternatively for the **IVb** configuration, a collision complex should be formed from the benzene ring attached to nitrogen; consequently, it is anticipated that all protons of the heterocyclic ring will experience strong shielding effects in aromatic solvents.

Table 3 shows the benzene-induced shift ($\Delta = \delta$ deuteriochloroform - δ perdeuteriobenzene) of compounds **1-4**. As can be seen in Table 3, the 4,8-axial protons of type **a** are only marginally affected (mean shifts are

Table 3

Benzene-Induced Solvent Shifts
 $\Delta = [\delta \text{ Deuteriochloroform} - \delta \text{ Perdeuteriobenzene}]$
 for Compounds **1-4**

Compound No.	4-CH ₃	Resonance				
		H _{5a} [a]	H _{5a} [b]	H _{6a}	H _{6a}	H _{4a}
1a	0.44	0.47	0.64	0.27	0.67	0.12
1b	0.51	0.53	0.57	0.53	0.63	0.47
2a	0.40	0.45	0.56	0.26	0.55	0.12
2b	0.46	0.47	0.49	0.43	0.59	0.45
3a	0.51	0.60	0.76	0.33	0.78	0.20
3b	0.62	0.67	0.71	0.83	0.83	0.59
4a	0.46	0.58	0.68	0.33	0.81	0.16
4b	0.42	0.53	0.55	0.42	0.50	0.43

[a] Axial. [b] Equatorial

ca. +0.12 and +0.27 ppm, respectively) while the remaining protons and the methyl protons in the heterocyclic ring are strongly shielded (+0.44 ~ +0.67 ppm). Only the structure of **1a** in Scheme 1 is compatible with these observations; therefore, preferred structure of type **a** are considered to take *trans* CC configuration with axial S=O group. In contrast, in the case of type **b**, all protons of the heterocyclic ring are strongly shielded (+0.47 ~ +0.63 ppm). Therefore, it can be considered that the preferred structure of type **b** exists in the *cis* TC configuration with the pseudoaxial S=O group.

REFERENCES AND NOTES

- [1] J. G. Pritchard and P. C. Lauterbur, *J. Am. Chem. Soc.*, **83**, 2105 (1961).
- [2] P. C. Lauterbur, J. G. Pritchard and R. L. Vollmer, *J. Chem. Soc.*, 5307 (1963).
- [3] G. Wood and M. H. Miskow, *Tetrahedron Letters*, 1109 (1969).
- [4] G. W. Buchanan and T. Durst, *ibid.*, 1683 (1975).
- [5] G. Wood, G. W. Buchanan and M. H. Miskow, *Can. J. Chem.*, **50**, 521 (1972).
- [6] G. W. Buchanan, J. B. Stothers and G. Wood, *ibid.*, **51**, 3746 (1973).
- [7] P. Alkbriktsen, *Acta Chem. Scand.*, **26**, 3678 (1972).
- [8] H. Nikander, V. Mukkala, T. Nurmi and K. Pihlaja, *Org. Magn. Reson.*, **18**, 375 (1976).
- [9] G. W. Buchanan, C. M. E. Cousineau and T. C. Mundell, *Tetrahedron Letters*, 2775 (1978).
- [10] T. Nishiyama, K. Ido and F. Yamada, *J. Heterocyclic Chem.*, **16**, 597 (1979).
- [11] K. D. Petrov, *Sb. Statei Khim., Akad. Nauk SSSR*, **1**, 374 (1953); *Chem Abstr.*, **49**, 997g (1955).
- [12] D. G. Hellier and F. J. Webb, *J. Chem. Soc.*, 612 (1977).
- [13] P. Alkbriktsen, *Acta Chem. Scand.*, **26**, 1783 (1972).
- [14] S. Wolfe, A. Rauk, L. M. Tel and J. G. Csizmadia, *J. Chem. Soc., B*, 136 (1971).
- [15] G. W. Buchanan and D. G. Hellier, *Can. J. Chem.*, **54**, 1428 (1976).
- [16] T. Ledal, *Tetrahedron Letters*, 1683 (1968).