BULLETIN OF THE CHEMICAL SOCIETY OF JAPAN, VOL. 44, 3073—3077 (1971)

The Stereochemistry of 5-Substituted 2-Oxo-3-aryl-1,2,3-oxathiazolidines

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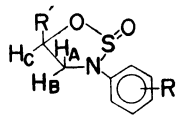
(Received February 4, 1971)

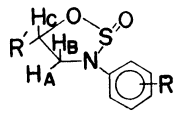
New six 2-oxo-3-aryl-5-methyl-1,2,3-oxathiazolidines and six 2-oxo-3-aryl-5-chloromethyl-1,2,3-oxathiazolidines have been prepared in good yields by the reactions of *N*-sulfinylanilines with propylene oxide and epichlorohydrin respectively in the presence of catalysts. The compounds obtained exist in isomeric *cis* and *trans* forms at the S=O bond. The configurations of their stereoisomers were discussed by means of NMR.

Recently, a few studies have been reported on the preparations of some oxathiazolidines. For example, Etlis *et al.*[1] reported that, in the presence of NEt_4Br, *N*-sulfinylanilines (**1**) reacted with alkene oxides at 95—100°C to give 2-oxo-3-aryl-1,2,3-oxathiazolidines. On the other hand, Deyrup and Moyer[2] have prepared oxathiazolidines by the reactions of β-amino alcohols with thionyl chloride in the presence of a base; the stereochemical structures of the compounds thus obtained have also been determined by means of their NMR spectra. In a previous paper, we reported that, in the absence of a catalyst, **1** reacted with ethylene oxide at a low temperature to form the corresponding oxathiazolidines.[3] The studies have now been extended to some substituted oxathiazolidines with a view to obtain a clearer picture of the stereoisomers.

In this paper, we wish to describe the reaction of **1** with propylene oxide (**2**) or epichlorohydrin (**3**) in the presence of catalysts and the configurations of the reaction products, oxathiazolidines (**4**), by means of a study of their NMR spectra.



4 *cis*
R=H, CH_3, Cl



4 *trans*
R′=CH_3, CH_2Cl

Experimental

Measurements. All the melting and boiling points are uncorrected. All the NMR spectra were recorded at 60 MHz with a Japan Electron Optics Model JNM-3H-60 spectrometer. The chemical shifts were described in parts per million downfield from the internal TMS (δ). The IR spectra were recorded on a Hitachi Model EPI-2 grating spectrophotometer. GLC analysis was carried out on a Yanagimoto Gas Chromatograph, Model GCG-550-T, using a 2.15-m column packed with Silicone SE-30 (10 wt%). The percentage composition of the products was estimated by means of the relative peak areas (uncorrected).

Materials. *N*-Sulfinylanilines, *N*-sulfinylaniline (R=H), *N*-sulfinyltoluidines (R=*o*-CH_3, *m*-CH_3, and *p*-CH_3), and *N*-sulfinylchloroanilines (R=*o*-Cl, *m*-Cl, and *p*-Cl) were prepared as has been described in the literatute.[4] **2** and **3** were commercially-available and were of pure in grade. All the reagents used were of an analytical grade.

General Procedure for the Reaction of 1 with 2 or 3. To a vigorously-stirred mixture of **1** with **2** or **3**, a solution of the catalyst in dimethylformamide (DMF) was added. After the mixture had been stirred for an appropriate time at a constant temperature, the residual catalyst was either filtered off or was washed off with water. The removal of DMF left a red-brown colored oily product which, on distillation *in vacuo*, gave oxathiazolidine. The progress of the reaction was periodically checked by measuring the NMR spectrum and glc of the reaction mixture.

Acid Hydrolysis of 2-Oxo-3-phenyl-5-methyl-1,2,3-oxathiazolidine (5). A mixture of 2.9 g of oxathiazolidine (**5**) in 10 m*l* of ethylalcohol and hydrochloric acid (60 mg, 1.64 mmol in 10 m*l* of water) was refluxed for 4 hr. The reaction mixture was extracted in methylene chloride, and then the solution was washed with water. The organic layer was dried; the subsequent removal of methylene chloride left a pale yellow product which, on distillation *in vacuo*, gave a clear pale yellow liquid (122—123°C/3 mmHg, 1.9 g, 83%) and which was identified as *N*-(β-hydroxypropyl)aniline by comparing its infrared spectrum with that of an authentic sample.[5] IR spectrum: 3375, 2970, 1603, 1501, 745, 688 cm^{-1}

1) V. S. Etlis, A. P. Sineokov, and M. E. Sergeeva, *Khim. Geterotskil. Soedin*, 682 (1966); *Chem. Abstr.*, **66**, 55150s (1967).
2) J. A. Deyrup and C. L. Moyer, *J. Org. Chem.*, **34**, 175 (1969).
3) F. Yamada, T. Nishiyama, M. Kinugasa, and M. Nakatani, This Bulletin, **43**, 3611 (1970).
4) A. Michaelis and R. Herz, *Ber.*, **23**, 3480 (1890).
5) K. D. Petrov, *Sbornik Statei Khim., Akad. Nauk S. S. S. R.*, **1**, 374 (1953); *Chem. Abstr.*, **49**, 997g (1955).

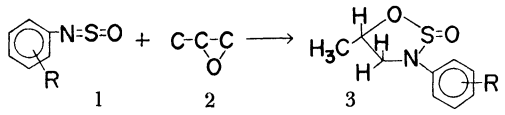
Results and Discussion

The Reaction. The products of these reactions and their physical properties are summarized in Tables 1 and 2. The conversion rate of each reaction can be determined by means of the data of the integrated ring protons in its NMR spectrum. These results indicate that the rate is influenced by the composition of the catalyst and by the reaction temperature. The rate of the reaction in the presence of lithium chloride (LiCl) is almost the same as that in the presence of lithium bromide (LiBr), but the rate in the presence of tetraethylammonium bromide (NEt_4Br) is slower than that in the presence of LiCl. This is also brought out clearly by a comparison of the values of the yields (Tables 1 and 2).

General Structure and Assignment of the Configuration. Let us now discuss how the general structure of the reaction products was determined. For example, the compound **5** (Table 1) can be converted to *N*-(β-hydroxypropyl)-aniline by acid-catalyzed hydrolysis. *N*-(β-hydroxypropyl)-aniline was further identified by comparing its infrared spectrum with that of an authentic sample, prepared by another route,[5] and by the results of the elemental analysis. All of the above facts, the results of the elemental analyses, and the spectral data (Tables 1 and 2) support the idea that the products have the structure of **4**.

The structure of **4** indicates the possibility that the reaction product consists of a pair of isomers, namely, the *cis* and *trans* configurations between the S=O group and the substituent, R'. After the reaction had been completed, the NMR spectrum of the reaction mixture always indicated the presence of the two isomers in the product. Therefore, we considered that the two isomers in the reaction product coincide with the *cis* and *trans*

TABLE 1. REACTIONS OF **1** WITH **2**

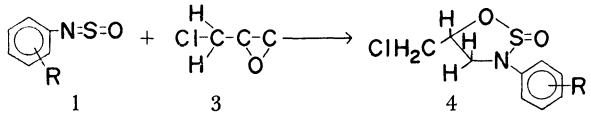


1 2 3

Compd. no.	R	2/1 mol. ratio	Cat.[a] mol	Temp. °C	Time hr	Yield %	Mp °C or Bp (mmHg)	*trans/cis*	% C	% H	% N	% Cl
5	H	1.49	—	25	300	0						
5	H	1.40	0.02	40	6.5	83	59.3—59.8[c,d]	1.44	54.68	5.58	7.12	
5	H	1.40	0.03	40	5.5	70			(54.82)	(5.58)	(7.11)[e]	
6	*o*-CH_3	1.40	0.02	40	13.3	85	129—130(3)[c]	3.00	56.79	6.17	6.72	
									(56.88)	(6.16)	(6.64)	
7	*m*-CH_3	1.40	0.03	35	12.0	78	42.2—45.7[c]	2.62	56.77	6.17	6.73	
8	*p*-CH_3	1.40	0.02	40	13.0	80	83.2—85.0[b]	2.22	56.87	6.22	6.62	
9	*o*-Cl	1.40	0.01	40	7.2	75	76.8—78.0[b]	2.14	46.72	4.38	6.05	15.30
									(46.65)	(4.32)	(6.05)	(15.33)
10	*m*-Cl	1.40	0.015	40	3.9	76	69.0—70.4[c]	2.22	46.69	4.32	6.03	15.30
10	*m*-Cl	1.40	0.036	40	2.5	80						
11	*p*-Cl	1.40	0.01	40	7.1	85	91.8—92.6[c]	2.57	46.54	4.45	6.05	15.30

a) LiCl. b) Mp of *cis* isomer. c) Mp of *trans* isomer.
d) lit[1] mp 57°C. e) Calcd value.

TABLE 2. REACTIONS OF **1** WITH **3**



1 3 4

Compd. no.	R	3/1 mol. ratio	Cat mol	Temp. °C	Time hr	Yield %	Mp °C	*trans/cis*	% C	% H	% N	% Cl
12	H	4.0	—	40	450	0		—				
12	H	1.40	0.01[a]	50	3.8	55	98.6—99.1[d,f]	—	46.62	4.22	6.05	15.27
12	H	1.40	0.01[b]	50	3.8	61			(46.75)	(4.35)	(6.17)	(15.06)[g]
13	*o*-CH_3	1.51	0.01[c]	65	9.2	78	76.5—77.1[d]	0.75	48.95	4.86	5.94	14.58
									(49.02)	(4.93)	(6.48)	(14.45)
14	*m*-CH_3	1.40	0.02[a]	40	6.0	76	59.8—60.6[e]	0.68	48.90	4.88	6.23	14.50
15	*p*-CH_3	1.51	0.008[c]	62	15.0	62	76.7—77.1[d]	0.67	48.93	4.89	6.38	14.58
16	*o*-Cl	1.51	0.005[c]	62	5.5	77	101.6—102.0[d]	0.68	40.62	3.32	5.32	26.72
									(40.68)	(3.43)	(5.23)	(26.61)
17	*m*-Cl	1.02	0.02[a]	40	2.5	72	88.3—89.3[e]	1.00	40.76	3.27	5.31	26.78
18	*p*-Cl	1.40	0.01[a]	40	2.6	72	79.2—81.5[d]	0.69	40.68	3.43	5.35	26.74
18	*p*-Cl	1.40	0.02[a]	40	2.0	70		0.64				

a) LiCl. b) LiBr. c) NEt_4Br. d) Mp of *cis* isomer. e) Mp of *trans* isomer.
f) lit,[1] mp 95°C, g) Calcd value.

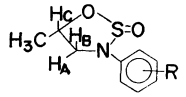
isomers of the oxathiazolidine. The *cis* or *trans* configuration was assigned by means of NMR spectroscopy.

In each reaction product, the *cis* or *trans* isomer can be separated by recrystallization from carbon tetrachloride. As can be seen in Table 1, the *cis* configuration was assigned to the products **8** and **9**, and the *trans* one, to the products **5**, **6**, **7**, **10**, and **11**. On the other hand, in Table 2, the *trans* configuration is assigned to the products **14** and **17**, and the *cis* one, to the products, **12**, **13**, **15**, **16**, and **18**. As is shown by these results, in each case only one of the isomeric pair can be separated; the other could not be isolated in a pure grade.

The ratio of the *cis* to the *trans* isomer in the reaction product can be determined by comparing the data of the integrated signal due to the methyl (in the case of the reaction of **1** with **2**) or methyne protons (in the reaction of **1** with **3**). The results obtained are also listed in Tables 1 and 2. The ratios are dependent mainly upon the substituents R and R′. The electron-releasing nature of R′ seems to be unfavorable to the formation of the *cis* isomer. The ratios are practically unaffected by the amount and the structure of the catalyst.

NMR Spectra of Oxathiazolidines. The chemical shifts of the oxathiazolidines are listed in Tables 3 and 4. The results show that a pair of isomeric 2-oxo-3-aryl-5-methyl (or chloromethyl)-1,2,3-oxathiazolidines was yielded by each reaction of **1** with **2** or **3**. The sulfoxide bond is well known to have acetylenic-like anisotropy.[6] For this reason, the deshielding of oxathiazolidine-ring substituents which are *cis* to the sulfoxide bond results. As can be seen in Table 3, **5a** and **5b** are identified as a pair of isomers. The methyl-proton signal in the *trans* isomer (**5b**) appeared at δ 1.42 ppm, while those in the *cis* isomer (**5a**) were observed at δ 1.59 ppm. On the other hand, the chloromethyl-proton signal in the *trans* isomer (**12b**) appeared at δ 3.65 ppm and, in the *cis* isomer (**12a**), further

Table 3. Spectral properties of 2-oxo-3-aryl-5-methyl-1,2,3-oxathiazolidines

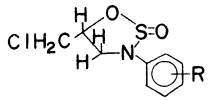


Compd. no.	R	Config	IR(S=O) cm^{-1}	NMR data, δ, ppm in CCl_4	
				H_C	H_A
5a	H	*cis*		4.78—5.15 (m)	3.80 (d, J=10.5)
5b	H	*trnas*	1174	5.19—5.53 (m)	3.24 (t, J *trans*=8.5, J *gem*=8.5)
6a	*o*-CH_3	*cis*		4.58—4.99 (m)	3.74 (d, J=10.0)
6b	*o*-CH_3	*trans*	1168	5.09—5.47 (m)	3.24 (q, J *trans*=7.2, J *gem*=8.8)
7a	*m*-CH_3	*cis*		4.75—5.11 (m)	3.69 (d, J=10.2)
7b	*m*-CH_3	*trans*	1168	5.20—5.52 (m)	3.24 (t, J *trans*=8.8, J *gem*=8.8)
8a	*p*-CH_3	*cis*	1161	4.57—5.08 (m)	3.68 (d, J=6.3)
8b	*p*-CH_3	*trans*		5.08—5.42 (m)	3.13 (t, J *trans*=8.3, J *gem*=8.3)
9a	*o*-Cl	*cis*	1160	4.66—5.05 (m)	3.78 (d, J=6.7)
9b	*o*-Cl	*trans*		5.03—5.53 (m)	3.38 (q, J *trans*=7.0, J *gem*=8.7)
10a	*m*-Cl	*cis*		4.85—5.23 (m)	3.80 (d, J=7.8)
10b	*m*-Cl	*trans*	1163	5.26—5.68 (m)	3.31 (t, J *trans*=8.5, J *gem*= 8.5)
11a	*p*-Cl	*cis*		4.25—4.73 (m)	3.87 (d, J=7.7)
11b	*p*-Cl	*trans*	1171	5.23—5.58 (m)	3.26 (t, J *trans*=8.7, J *gem*=8.7)

	NMR data, δ, ppm in CCl_4			
	H_B	CH_3	R	Ring Proton
5a	3.79 (d, J=8.1)	1.75 (d, J=6.0)	—	6.8 —7.3 (m)
5b	3.85 (q, J *cis*=5.4)	1.58 (d, J=6.0)	—	6.84—7.31 (m)
6a	3.61 (d, J=5.8)	1.60 (d, J=6.2)	2.44 (s)	7.23 (s)
6b	4.09 (q, J *cis*=7.5)	1.50 (d, J=6.2)	2.24 (s)	7.23 (s)
7a	3.66 (d, J=7.8)	1.73 (d, J=5.7)	2.43 (s)	6.6 —7.2 (m)
7b	3.83 (q, J *cis*=5.4)	1.57 (d, J=5.7)	2.43 (s)	6.66—7.22 (m)
8a	3.66 (d, J=8.7)	1.68 (d, J=6.2)	2.40 (s)	7.00 (q)
8b	3.71 (q, J *cis*=6.8)	1.46 (d, J=6.0)	2.40 (s)	7.0 (q)
9a	3.80 (d, J=9.0)	1.72 (d, J=6.0)	—	7.00—7.53 (m)
9b	4.06 (q, J *cis*=7.6)	1.50 (d, J=6.0)	—	7.07—7.48 (m)
10a	3.78 (d, J=6.3)	1.79 (d, J=6.0)	—	6.8 —7.3 (m)
10b	3.93 (q, J *cis*=5.2)	1.65 (d, J=6.0)	—	6.84—7.34 (m)
11a	3.83 (d, J=4.4)	1.77 (d, J=6.0)	—	7.0—
11b	3.86 (q, J *cis*=5.4)	1.63 (d, J=6.0)	—	7.05 (q)

6) J. G. Pritchard and P. C. Lauterbur, *J. Amer. Chem. Soc.*, **83**, 2105 (1961).

TABLE 4. SPECTRAL PROPERTIES OF 2-OXO-3-ARYL-5-CHLOROMETHYL-1,2,3-OXATHIAZOLIDINES



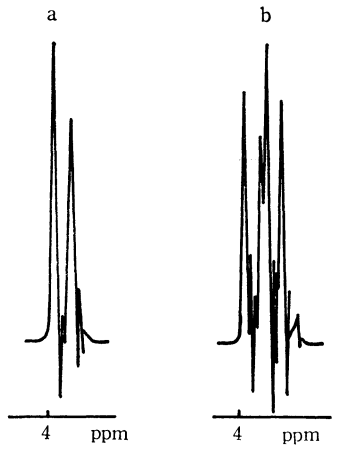
Compd. no.	R	Confign	IR(S=O) cm^{-1}	NMR data, δ, ppm in CCl_4			
				CH	CH_2 and $-CH_2Cl$	R	Ring proton
12a	H	*cis*	1154	4.78—5.22 (m)	3.82 (d, J=6.6) 3.96 (d, J=6.6)	—	6.99—7.48 (m)
12b	H	*trans*		5.15—5.64 (m)	3.80 (d, J=6.0)	—	6.9 —7.4 (m)
13a	*o*-CH_3	*cis*	1156	4.70—5.16 (m)	3.85—4.28 (m)	2.49 (s)	7.21 (s)
13b	*o*-CH_3	*trans*		5.10—5.40 (m)	3.71 (d, J=6.0)	2.49 (s)	7.21 (s)
14a	*m*-CH_3	*cis*		4.72—5.14 (m)	4.13 (d, J=7.2)	2.45 (s)	6.8 —7.3 (m)
14b	*m*-CH_3	*trans*	1177	5.13—5.53 (m)	3.50—4.12 (m)	2.45 (s)	6.84—7.30 (m)
15a	*p*-CH_3	*cis*	1146	4.70—5.17 (m)	3.92 (d, J=6.6)	2.41 (s)	7.02 (q)
15b	*p*-CH_3	*trans*		5.11—5.41 (m)	3.75 (d, J=4.8)	2.41 (s)	7.0 (q)
16a	*o*-Cl	*cis*	1162	4.74—5.21 (m)	4.07 (d, J=6.0)	—	7.12—7.53 (m)
16b	*o*-Cl	*trans*		5.07—5.39 (m)	3.70 (d, J=6.6)	—	7.1—7.5 (m)
17a	*m*-Cl	*cis*		4.88—5.23 (m)	3.76—4.17 (m)	—	6.8—7.2 (m)
17b	*m*-Cl	*trans*	1177	5.25—5.68 (m)	3.55—4.17 (m)	—	6.81—7.26 (m)
18a	*p*-Cl	*cis*	1156	4.81—5.31 (m)	3.96 (d, J=6.0)	—	7.12 (q)
18b	*p*-Cl	*trans*		5.23—5.64 (m)	3.81 (d, J=4.8)	—	7.1 (q)

downfield at δ 3.83 ppm.

Several NMR spectra of oxathiazolidines are first-order spectra and show *cis* and *trans* coupling constants which can be interpreted in terms of the geometry around C–4 and C–5 single bonds. The coupling constants are shown in Tables 3 and 4.

Moyer reported that the coupling constants, J *trans*, J *cis*, and J *gem*, for *trans* 2-oxo-3-*t*-butyl-5-phenyl-1,2,3-oxathiazolidine are 6.5, 6.5, and 8.5 Hz respectively.[7] These values are very close to those of the compounds, as is shown in Table 3.

Solvent Effects. The signal of the methylene protons (C–4) of **18a** appeared as a two-proton doublet in a carbon tetrachloride solution. In a methylene chloride solution, the doublet form was transformed to a quartet form, as is shown in Fig. 1. This phenomenon indicates that the signal of the C–4 methylene protons overlaps that of the C–5 chloromethyl protons. The coupling constant of the C–4 methylene protons was 6.0 Hz in a carbon tetrachloride solution as well as in a methylene chloride solution.



a. CCl_4 solution b. CH_2Cl_2 solution

Fig. 1. NMR spectra for methylene protons of **18a**.

In the carbon tetrachloride solution, the equilibrium composition of the compound **11** was 42% *cis* and 58% *trans*, based on the integration of the NMR spectra of the methyl protons. After this solution had been heated at 80—85°C for 13 hr, the *trans* isomer composition increased from 58% to 72%. The *cis* isomer, however, did not entirely disappear. In the case of the carbon disulfide solution, no change in the composition was observed even upon heating under the same conditions. It is clear that both the solvent and temperature effects may markedly affect the equilibration of the *cis* and *trans* isomers. This suggests that the oxathiazolidine ring interacts with a solvent such as carbon tetrachloride and that then the *cis*-form is turned into the *trans*-form at a suitable temperature.

On the other hand, the NMR spectral data of the *cis* and *trans* isomers of some oxathiazolidines in a benzene solution exhibit benzene-induced shifts, as is shown in Table 5. Figure 2 shows the proposed geometry of the benzene-solute collision complex of the oxathiazolidines. As for the aromatic solvent effect on the sulfoxides, recent papers have described studies con-

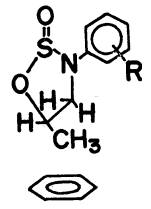


Fig. 2. Proposed geometry of benzene-solute collision complex of the oxathiazolidines.

7) C. L. Moyer, "2-Oxo-1,2,3-oxathiazolidines", Dissertations, II, Harvard University (1968) (Avail. Univ. Microfilms, Ann Arbor, Mich., Order No. 68—16878), p. 95; *Chem. Abstr.* **70**, 77677d(1969).

Table 5. Solvent effects on the NMR spectra of the oxathiazolidines

Compd. no.	R	Confign	Concn, mmol/ml	Δ, ppm=$\delta(CCl_4)-\delta(C_6H_6)$			
				H_A	H_B	H_C	CH_3
5b	H	*trans*	0.75	+0.61	+0.62	+0.31	+0.53
6b	*o*-CH_3	*trans*	0.75	+0.55	+0.39	+0.36	+0.47
7b	*m*-CH_3	*trans*	0.75	+0.59	+0.59	+0.29	+0.51
8a	*p*-CH_3	*cis*	0.75	—	—	+0.38	+0.35
9a	*o*-Cl	*cis*	0.75	+0.75	+0.30	+0.50	+0.45
10b	*m*-Cl	*trans*	0.75	+0.87	+0.89	+0.40	+0.59
11b	*p*-Cl	*trans*	0.75	+0.75	+0.77	+0.38	+0.58

cerning the stereochemistry of the penicillin sulfoxides[8] or the methylthiolane oxides.[9] In these compounds, the situation of the methyl group in question is the α-position relative to the sulfoxide group. In the case of the oxathiazolidines, in spite of the situation of the methyl group in the β-position, it was found that the stereochemical assignment is nearly in line with the arguments presented in the above papers. As can be seen in Table 5, however, the shifts of the protons of the compound **6b** were somewhat different. This difference may be ascribed to some effect of the *o*-methyl substituent.

The authors are grateful to the members of the Laboratory of Analysis, Faculty of Science, of Osaka University and the staff of the Research Laboratories, Fujisawa Pharmaceutical Co., Ltd. for the elementary analyses.

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