chloride was stirred for 5 hr at room temperature. Treatment as described above afforded 2.1 g (73%) of a colorless oil (**11**): bp 132—134° (0.5 mmHg). *Anal.* Calcd for $C_{13}H_{20}O_7$ (**11**): C, 54.16; H, 6.99. Found: C, 54.22; H, 6.83. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1735 (C=O), IR ν_{max}^{neat} cm^{-1}: 1740 (C=O). NMR ($CDCl_3$) δ: 1.13 (3H, d, J=7 Hz, C_6–CH_3), 1.29 (3H, s, C_5–CH_3), 2.72 (1H, q, J=7 Hz, C_6–H), 2.58—3.36 (2H, ABq, J=18 Hz, $2\times C_4$–H), 3.45 (2H, s, $2\times C_2$–H), 3.65 (6H, s, $2\times OCH_3$), 3.72 (3H, s, OCH_3).

Acknowledgement This work was supported in part by a Grant-in-Aid from the Ministry of Education, Science and Culture, Japan. The authors are indebted to the Central Analysis Room of this Institute for elemetal analyses and spectral measurements.

[Chem. Pharm. Bull. 28(1) 330—336 (1980)]

Organic Sulfites containing a 1,2-Oxazine Ring[1)]

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(Received June 30, 1979)

The reaction of 5-hydroxy-2-phenyltetrahydro-2*H*-1,2-oxazin-3-one derivatives (**2**) with thionyl chloride in the presence of pyridine afforded a mixture of stereoisomers of bis(3-oxo-2-phenyltetrahydro-2*H*-1,2-oxazine-5-yl) sulfite derivatives (**3**) in total yields of 75—83%. On high-performance liquid chromatography, two meso-diastereoisomers (3-I and 3-II) and a racemic compound (3-III) were isolated.

Keywords——organic sulfites; bis(2-aryl-3-oxotetrahydro-2*H*-1,2-oxazine-5-yl) sulfite; 1,2-oxazine derivatives; thionyl chloride; esterification; stereoisomer; HPLC; separation

In the previous paper,[1)] we reported syntheses of 2-phenyltetrahydro-2*H*-1,2-oxazine-3,5-dione derivatives (**1**) from γ-bromoacetoacetyl bromide and N-phenylhydroxylamines. As a continuation of our studies on these heterocycles, we have investigated the reduction of the C_5-carbonyl group of **1** to give 2-phenyltetrahydro-2*H*-1,2-oxazin-3-one. In this connection, we have already reported the transformation of 1,2-diphenylhexahydropyridazine-3,5-dione (**4**) to give 1,2-diphenyl-1,2,3,6-tetrahydropyridazin-3-one (**6**) *via* 5-hydroxy-1,2-diphenylhexahydropyridazin-3-one (**5**).[3)] Namely, reduction of the dione (**4**) with sodium borohydride gave the 5-hydroxy derivative (**5**), which, on treatment with phosphorus oxychloride was transformed into the pyridazinone (**6**). Using this procedure, 2-phenyltetrahydro-2*H*-1,2-oxazine-3,5-dione (**1a**, R=H) was reduced with sodium borohydride to give 5-hydroxy-2-phenyltetrahydro-2*H*-1,2-oxazin-3-one (**2a**). Reaction of **2a** with phosphorus oxychloride or phosphorus trichloride in pyridine resulted in recovery of the starting material. However, treatment of **2a** with thionyl chloride in the presence of pyridine did not give the dehydrated compound but a mixture of organic sulfites containing a 1,2-oxazine ring, on which we now report.

Compound **2a** was allowed to react with a half equivalent of thionyl chloride in the presence of one equivalent of pyridine in carbon tetrachloride under reflux to afford a colorless crystalline product (**3a**). The product did not have a sharp melting point and thin-layer

1) This paper forms Part II of "Reaction of γ-Bromoacetoacetyl Bromide with N-Phenylhydroxylamine Derivatives." Part I: K. Tabei, E. Kawashima, and T. Kato, *Chem. Pharm. Bull.*, **27**, 1842 (1979).
2) Location: *a) Horinouchi, 1432–1, Hachioji city, Tokyo, 192-03, Japan*; *b) Aobayama, Sendai, 980, Japan.*
3) T. Kato, M. Sato, and K. Tabei, *J. Org. Chem.*, **39**, 3205 (1974).

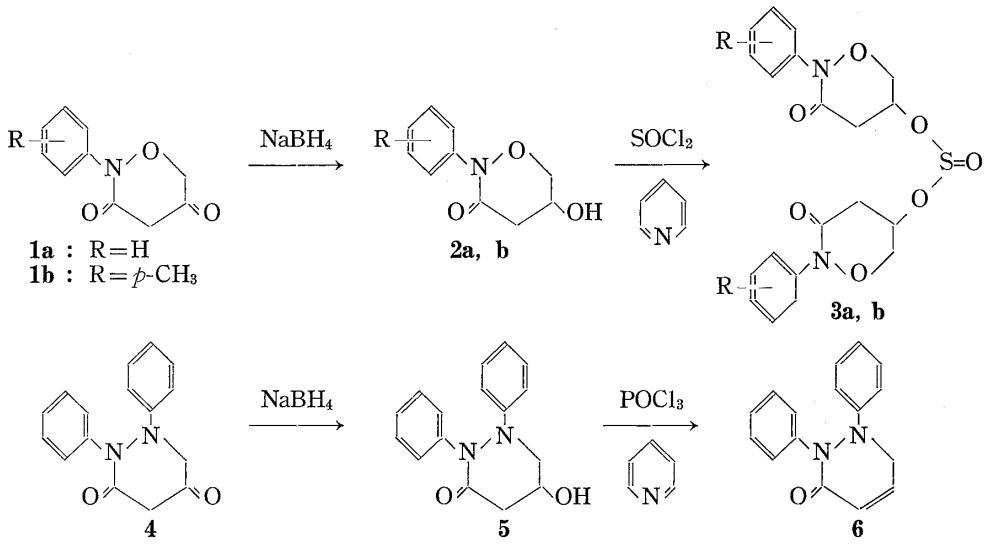


Chart 1

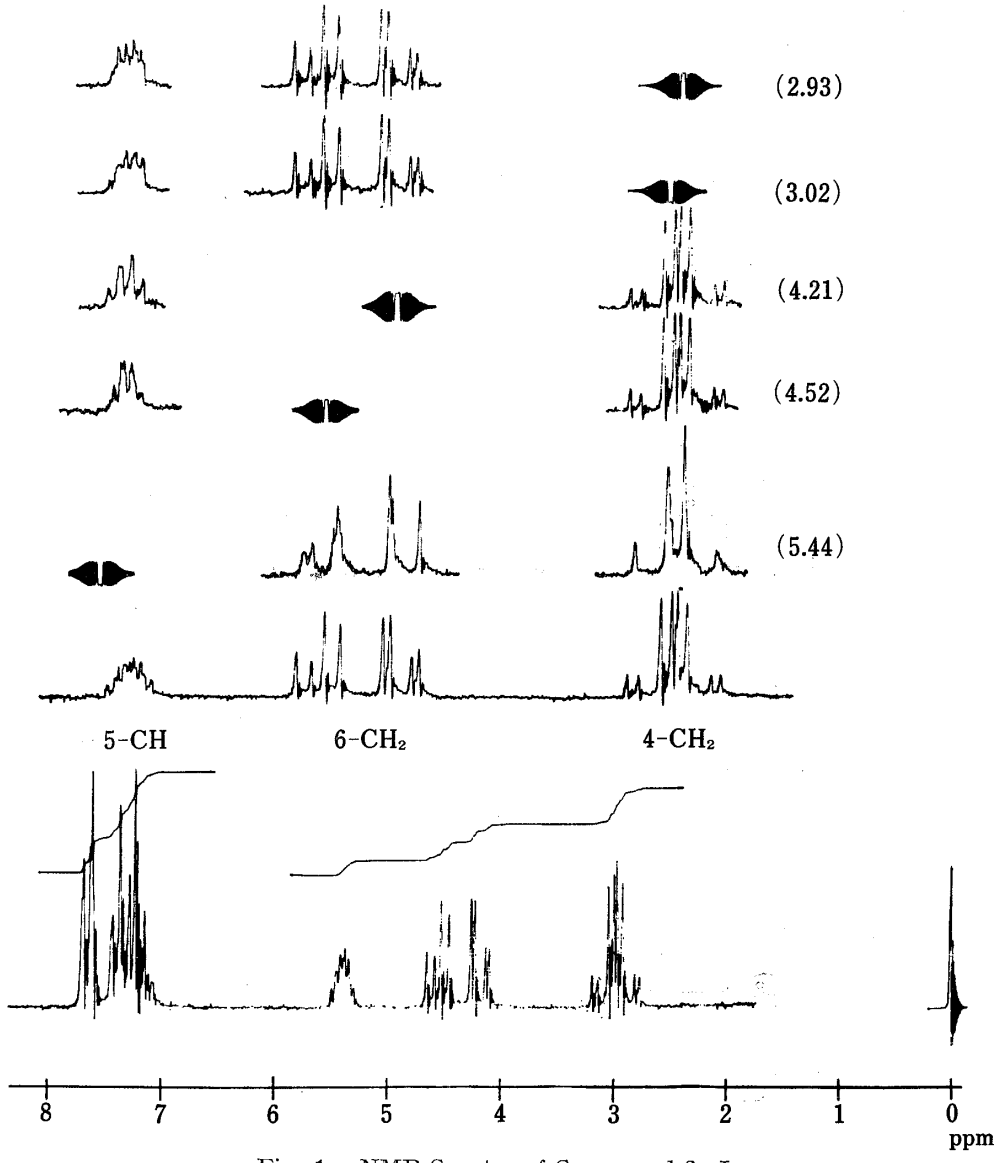


Fig. 1. NMR Spectra of Compound **3a**-I

The top six spectra are expanded (×2) and irradiated at parenthesized δ (ppm).

TABLE I. Bis (2-aryl-3-oxotetrahydro-2*H*-1,2-oxazine-5-yl) Sulfite (3)

3 (R, Total yield %)		3a (R=H, 83%)			3b (R=*p*-CH_3, 75%)		
Isomer (mp °C)		I (135°)	II (83°)	III (154°)	I (111°)	II (123.5°)	III (135°)
Proportion (%)[a]		30.42	16.61	52.97	32.46	18.02	49.52
Retention time (sec)[a]		544	608	761	527	582	764
Molecular formula		$C_{20}H_{20}N_2O_7S$			$C_{22}H_{24}N_2O_7S$		
Anal. Calcd (%)		C, 55.54; H, 4.66; N, 6.48; S, 7.42			C, 57.38; H, 5.25; N, 6.08 S, 6.96		
Anal. Found (%)	C	55.50	55.38	55.71	57.16	57.37	57.57
	H	4.71	4.67	4.93	5.10	5.33	5.30
	N	6.26	6.35	6.20	6.17	5.83	5.85
	S	7.40	7.48	7.55	7.10	7.06	7.16
IR ν_{max}^{KBr} (cm^{-1})	$\nu_{C=O}$[b]	1678	1668 and 1673	1670 and 1690	1685	1660 and 1680	1675 and 1690
	ν_{N-O}	1375	1370	1380	1375	1363	1365
	$\nu_{S=O}$	1190	1210	1210	1195	1203	1205
NMR δ (ppm) ($CDCl_3$)	4-CH_2	2.87, 2.92, 3.06, 3.10 [(2H, ABX_O, J_{AB}=14 Hz)×2]	2.84, 2.89, 3.05, 3.11 [(2H, ABX_O, J_{AB}=15 Hz)×2]	2.80—3.27 (4H, m)	2.85, 2.95, 3.01, 3.08 [(2H, ABX_O, J_{AB}=14 Hz)×2]	2.84, 2.88, 3.03, 3.10 [(2H, ABX_O, J_{AB}=16 Hz)×2]	2.75—3.25 (4H, m)
	6-CH_2	4.16, 4.20, 4.54, 4.56 [(2H, ABX_O, J_{AB}=14 Hz)×2]	4.23, 4.29, 4.51, 4.56 [(2H, ABX_O, J_{AB}=15 Hz)×2]	4.10—4.68 (4H, m)	4.14, 4.19, 4.45, 4.51 [(2H, ABX_O, J_{AB}=14 Hz)×2]	4.27, 4.30, 4.48, 4.52 [(2H, ABX_O, J_{AB}=16 Hz)×2]	4.05—4.62 (4H, m)
	5-CH	5.40 (2H, m)	5.42 (2H, m)	5.40 (2H, m)	5.38 (2H, m)	5.38 (2H, m)	5.40 (2H, m)
NMR on irradiation at 5.40 ppm	4-CH_2	2.85 and 3.06 [(2H, AB_q, J=14 Hz)×2]	2.85 and 3.07 [(2H, AB_q, J=15 Hz)×2]	2.68 and 3.04, 2.92 and 3.07 (2H×2, AB_q×2, J=14 Hz)	2.87 and 3.05 [(2H, AB_q, J=14 Hz)×2]	2.82 and 3.00 [(2H, AB_q, J=16 Hz)×2]	2.87 and 3.06 2.92 and 3.10 (2H×2, AB_q×2, J=14 Hz)
	6-CH_2	4.15 and 4.50 [(2H, AB_q, J=14 Hz)×2]	4.26 and 4.52 [(2H, AB_q, J=15 Hz)×2]	4.10 and 4.41, 4.12 and 4.44 (2H×2, AB_q×2, J=14 Hz)	4.16 and 4.49 [(2H, AB_q, J=14 Hz)×2]	4.18 and 4.46 [(2H, AB_q, J=16 Hz)×2]	4.12 and 4.43, 4.17 and 4.47 (2H×2, AB_q×2, J=14 Hz)
Mass spectra (*m/e*)		432 (M^+), 193, 175, 119	432 (M^+), 193, 175, 119, 107	432 (M^+), 193, 175, 119, 107	460 (M^+), 207, 189, 133, 121, 105	460 (M^+), 207, 189, 133, 121, 105	460 (M^+), 207, 189, 133, 121, 105

a) Determined with a Spectro Physics SP-8000 apparatus (Wako Gel 10 μ column).
b) In $CHCl_3$ solution, a single band appeared in the 1685—1690 cm^{-1} region.

chromatography (TLC) showed several very closely located spots. Thus **3a** was subjected to high-performance liquid chromatography (HPLC) on a silica gel column using chloroform as an eluent. Three kinds of products, **3a**-I (mp 135°), **3a**-II (mp 83°), and **3a**-III (mp 154°), were isolated. Their retention times increased in the order I, II, and III.

Elemental analyses and mass spectra of these products gave the formula $C_{20}H_{20}N_2O_7S$ [*m/e* 432 (M^+)]. The infrared (IR) and nuclear magnetic resonance (NMR) spectra of the isomers were very similar, as shown in Table I. The characteristic absorption bands (IR) in the 1680, 1380, and 1200 cm^{-1} regions were assigned to an amide (C=O), a 1,2-oxazine (N–O), and a sulfite (S=O) group, respectively. Their NMR spectra showed characteristic signals due to 4-CH_2, 6-CH_2, and 5-CH protons of a 1,2-oxazine ring at 2.80—3.25 ppm (4H, ABX octet or multiplet), 4.10—4.65 ppm (4H, ABX octet or multiplet), and about 5.40 ppm (2H, multiplet), respectively. These spectral data show that **3a** was a mixture of stereoisomers of bis(3-oxo-2-phenyltetrahydro-2*H*-1,2-oxazine-5-yl) sulfite.

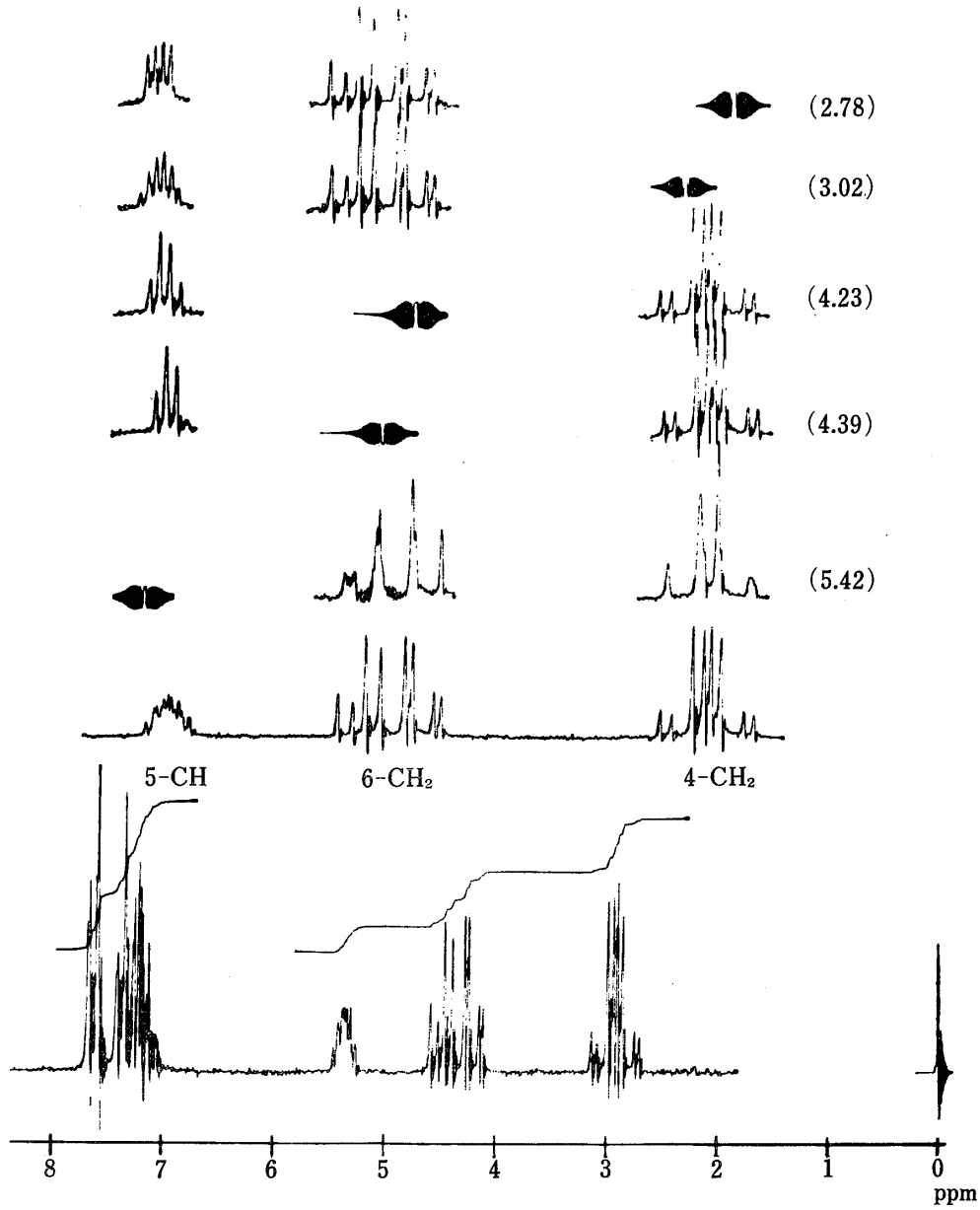


Fig. 2. NMR Spectra of Compound **3a**-II

The top six spectra are expanded (×2) and irradiated at parenthesized δ (ppm).

Quantitative analyses by HPLC showed that the proportions (%) of the isomers, **3a**-I —III, were 30.42, 16.61, and 52.97%, respectively (total yield: 83%). The reaction of **2a** with thionyl chloride was also performed at room temperature and at −20° in almost the same total yield and with the same product ratio as above.

Similar reaction of **2b** (R=*p*-CH_3) with thionyl chloride in the presence of pyridine afforded **3b** in 75% yield. HPLC of **3b** gave three stereoisomers, **3b**-I (mp 111°), **3b**-II (mp 123.5°), and **3b**-III (mp 135°), in proportion (%) of 32.46, 18.02, and 49.52%, respectively. The analytical and spectral data are listed in Table I. In circular dichroism (CD) studies it was also found that all these products, **3a**, **b**-I—III, were optically inactive.

The stereochemistry of the product (**3a**, **b**-I—III) was elucidated by NMR decoupling experiments. Namely, the characteristic ABX octet signals of **3a**-I and II in the 2.80—3.25 and 4.10—4.65 ppm regions changed to quartet signals on irradiation at 5.40 ppm, as shown in Fig. 1 and 2. On the other hand, the diffused multiplet of **3a**-III in the 2.80—3.27 and

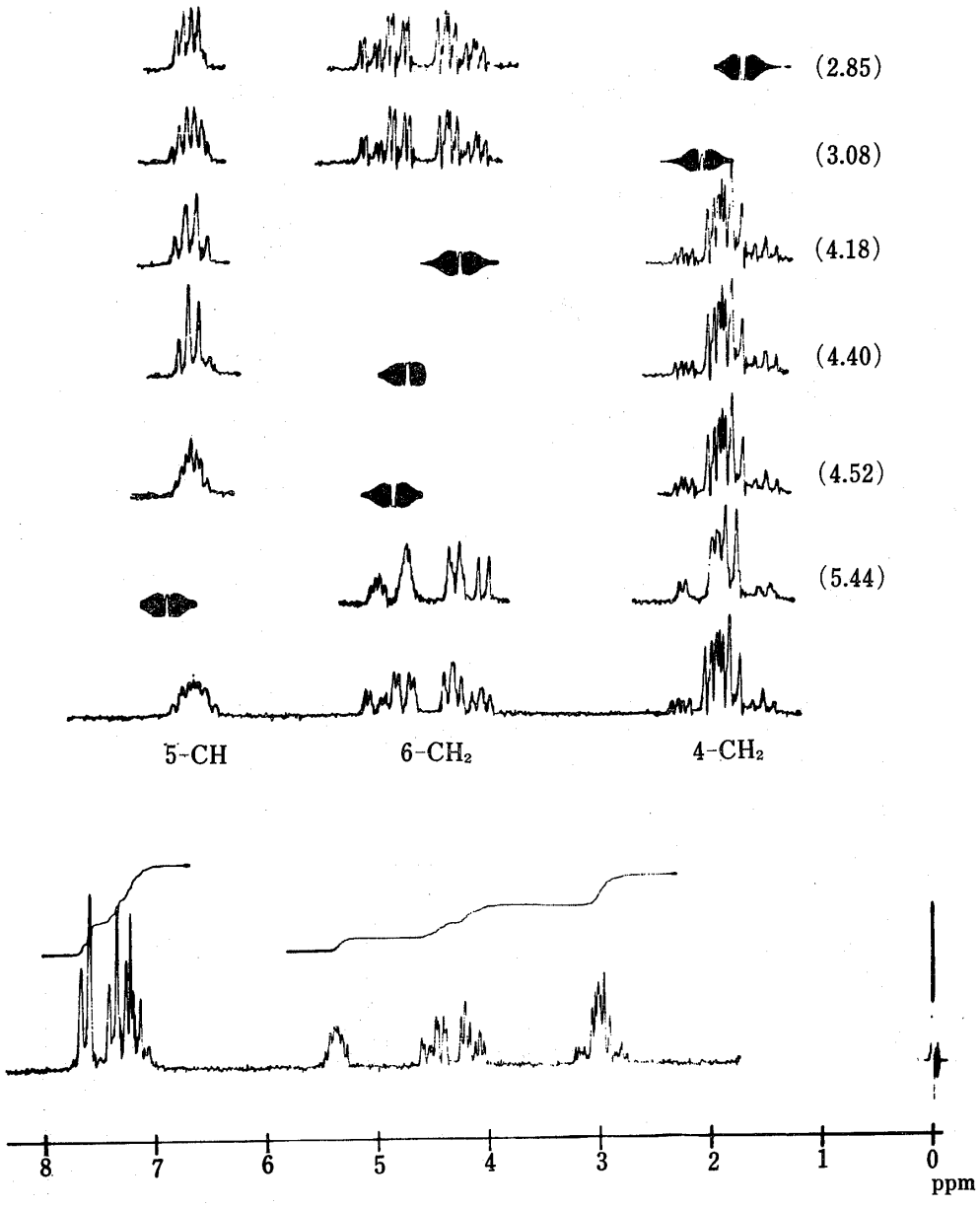


Fig. 3. NMR Spectra of Compound **3a**-III

The top seven spectra are expanded (×2) and irradiated at parenthesized δ (ppm).

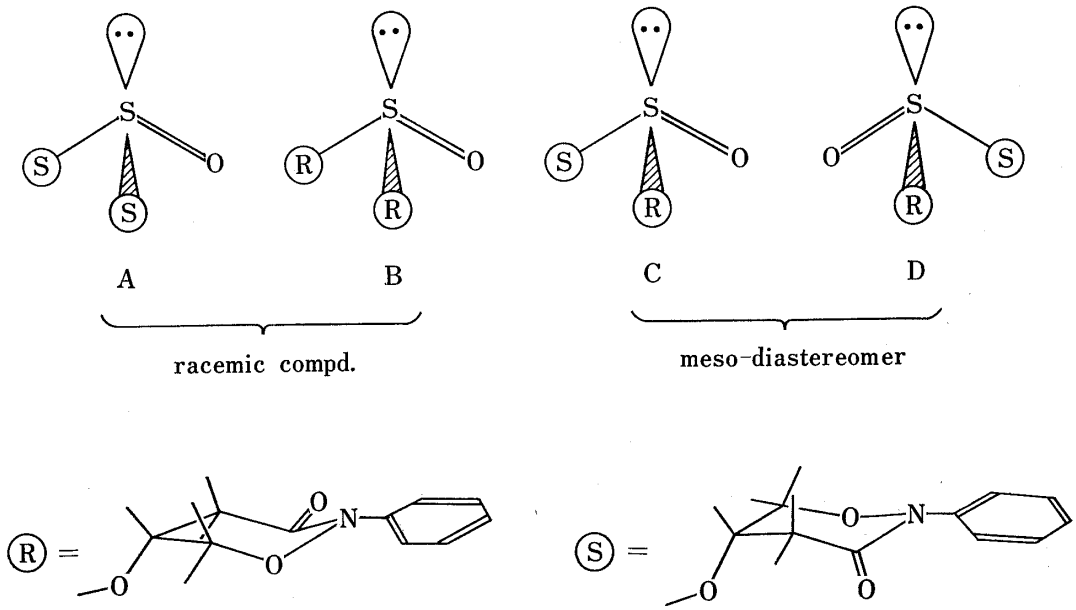


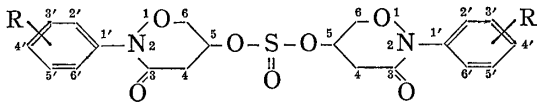
Fig. 4

4.10—4.68 ppm regions changed to overlapping AB quartet signals on irradiation, as shown in Fig. 3.

Similar spectral changes were observed in NMR decoupling experiments on **3b**-I—III (see Table I).

Based on the above spectral considerations, it was deduced that the two 1,2-oxazine moieties of the product (III) were not enantiomeric and showed slightly different chemical shifts. On the other hand, those of the products (I) and (II) were enantiomeric and showed single quartet signals of the AB part of an ABX system on irradiation. Similar results have been presented by Pritchard *et al.*, who isolated diastereoisomers of an optically active organic sulfite, methyl (diphenacyl)maleate sulfite, by fractional crystallization.[4] Thus the product

TABLE II. ^{13}C Chemical Shifts of **3**[a]



	3a			**3b**		
	I	II	III	I	II	III
C-3	166.06	165.94	166.11 165.88	165.65	165.82	166.07 165.82
4	38.23	38.05	38.05 37.77	37.94	38.05	38.01 37.72
5	69.30	69.42	69.59 69.30	69.42	69.30	69.68 69.39
6	75.13	75.24	75.36 75.13	75.13	75.01	75.38 75.14
1′	138.09	138.09	138.03	135.55	135.50	135.67 135.56
2′, 6′	118.66	118.54	118.54 118.43	118.95	119.06	119.19 119.00
3′, 5′	128.81	128.81	128.75	129.29	129.27	129.33
4′	125.52	125.52	125.40	135.44	135.44	135.47
tolyl	—	—	—	20.87	20.87	20.91

a) δ^{TMS} (ppm) measured in $CDCl_3$.

(III) could be assigned as a racemic compound depicted as A+B in Fig. 4. The products (I) and (II) were assigned as the two meso-diastereoisomers, C and D, or *vice versa.*

These conclusions were supported by the results of ^{13}C–NMR experiments. Namely, ^{13}C–NMR spectra of the product (III) showed split signals assignable to the ester moieties (C-3, 4, 5, 6, 1′, 2′, and 6′), as shown in Table II. On the other hand, the corresponding carbon resonances of the products (I) and (II) appeared as single signals.

Experimental

All melting points are uncorrected. IR spectra were run on a Hitachi 215 spectrometer. NMR spectra were measured with a JEOL PS–100 spectrometer at 100 MHz using TMS as an internal standard. All signals are expressed as the ppm downfield from TMS (δ value) and the following abbreviations are used: quartet (q), octet (o), and multiplet (m). ^{13}C–NMR spectra were measured with a JEOL FX–100 spectrometer at 25.0 MHz in $CDCl_3$ using 10 mm spinning tubes at 20° with TMS as an internal standard. Data were accumulated with a maximum of 1.0 Hz per point. Mass spectra were taken on a Hitachi RMU-7 mass spectrometer. CD data were obtained on a JASCO J-40 AS spectropolarimeter.

Bis(3-oxo-2-phenyltetrahydro-2*H*-1,2-oxazine-5-yl) Sulfite (**3a**)——A mixture of 5-hydroxy-2-phenyltetrahydro-2*H*-1,2-oxazin-3-one (**2a**) (96.5 mg, 0.5 mmol), thionyl chloride (30 mg, 0.25 mmol), and pyridine (40 mg, 0.5 mmol) in dry CCl_4 (25 ml) was refluxed for 1 hr, then $CHCl_3$ (50 ml) was added and the solution was washed with 5% HCl, 5% $NaHCO_3$, and water, and dried over $MgSO_4$. After removal of the solvent, the residue was subjected to HPLC using a Kusanokagaku KP–6H apparatus and CIG-15 column (SiO_2 50 μ; detector, UVILOG 254). Elution with $CHCl_3$ afforded three stereoisomers, **3a**-I, **3a**-II, and **3a**-III, which were recrystallized from benzene or $CHCl_3$–hexane mixture (1 : 1) to give colorless needles (total yield, 97.6 mg, 83%). Mp, analytical and spectral data are listed in Table I. The retention times and the proportions were determined using a Spectro Physics SP-8000 apparatus with a Wako SiO_2 (10 μ) column.

Bis[3-oxo-2-(*p*-tolyl)-tetrahydro-2*H*-1,2-oxazine-5-yl] Sulfite (**3b**)——Following the above procedure, 5-hydroxy-2-(*p*-tolyl)-tetrahydro-2*H*-1,2-oxazin-3-one (**2b**) (103.5 mg, 0.5 mmol) was allowed to react with $SOCl_2$ (30 mg, 0.25 mmol) in the presence of pyridine (40 mg, 0.5 mmol) and CCl_4 (25 ml) to give **3b** (total yield: 86 mg, 75%). On HPLC, **3b**-I, **3b**-II, and **3b**-III were obtained as colorless scales (recrystallized from $CHCl_3$). Mp, analytical and spectral data are listed in Table I.

Acknowledgement The authors are grateful to Dr. K. Oka for valuable discussions, and to Prof. S. Hara, Mr. A. Dobashi, and Astech Co., Ltd. for making available the SP-8000 apparatus. They are also indebted to Miss C. Takagai for measurement of NMR and ^{13}C–NMR spectra, and to Mr. Y. Shida and Mr. S. Suzuki for measurement of mass spectra and for micro analyses.

4) M.K. Hargreaves, P.G. Modi, and J.G. Pritchard *Chem. Commun.*, **1968**, 1306.