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Stereochemistry of Alkylation of Cyclic β-Ketosulfoxides. III.[1] Alkylation and Deuteration of the Dianion of Isothiochroman-4-one 2-Oxide

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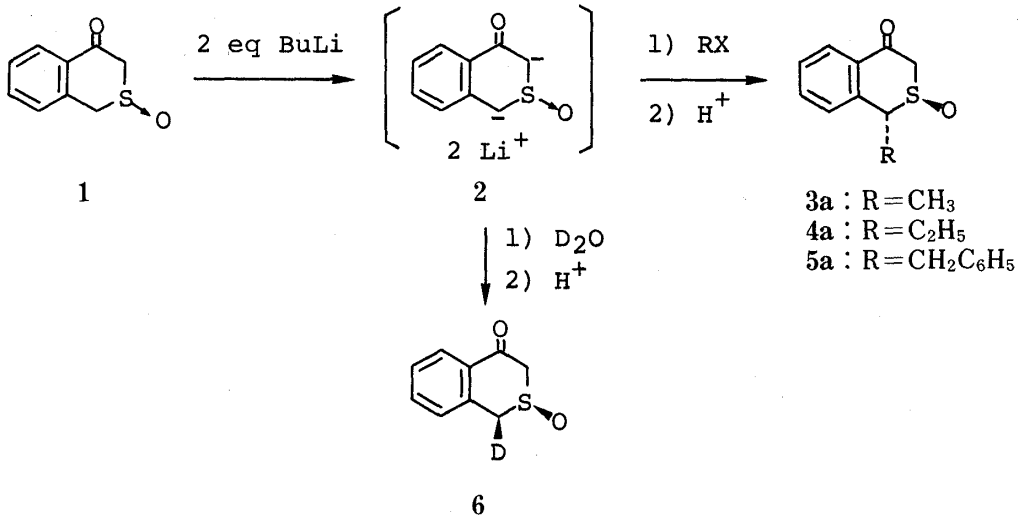
Alkylation of the 1,3-dianion (**2**) of isothiochroman-4-one 2-oxide (**1**) with alkyl halide was shown to occur stereospecifically *trans* to the S–O bond at the C-1 position, whereas deuteration of the dianion with deuterium oxide at the same position occurred *cis* to the S–O bond.

Keywords——alkylation; deuteration; dianion; isothiochroman-4-one; isothiochroman-4-one 2-oxide; β-ketosulfoxide; cyclic sulfoxide stereochemistry

In a preceding paper,[2] we reported that the C-3 alkylation of 3-methylisothiochroman-4-one 2-oxide with alkyl halide occurred *trans* to the S–O bond with high stereoselectivity. We have now examined the C-1 alkylation and deuteration of the 1,3-dianion (**2**) of isothiochroman-4-one 2-oxide (**1**) and found that alkylation with alkyl halide occurred *trans* to the S–O bond, while deuteration with deuterium oxide occurred *cis* to the S–O bond.



1 2 **3a** : R=CH_3, **4a** : R=C_2H_5, **5a** : R=$CH_2C_6H_5$ **6**

Chart 1

The dianion (**2**) was generated by metallation of **1** with 2 eq of *n*-butyllithium in anhydrous tetrahydrofuran (THF) at −78 °C.[3] Alkylations of **2** with methyl iodide, ethyl iodide, and benzyl bromide afforded *trans*[4]-1-methyl- (**3a**), *trans*-1-ethyl- (**4a**), and *trans*-1-benzyl-isothiochroman-4-one 2-oxide (**5a**) as sole products in 84, 63, and 66% yields, respectively. Quenching of the dianion (**2**) with deuterium oxide gave *cis*-1-deuterioisothiochroman-4-one 2-oxide (**6**) in 85% yield.

The structures of the products (**3a**, **4a**, and **5a**) and their *cis* isomers (**3b**, **4b**, and **5b**),

which were prepared by the route shown in Chart 2, were determined on the basis of the proton nuclear magnetic resonance (^{1}H-NMR) spectra. The spectral data are listed in Table I. In an earlier paper,[2] it was demonstrated that the ring of isothiochroman-4-one 2-oxide derivative preferentially takes a pseudo chair conformation. In the ^{1}H-NMR spectra of **5a** and **5b** using a shift reagent, Eu(fod)$_3$, a long-range (zigzag) coupling[5] (J=2 Hz) was

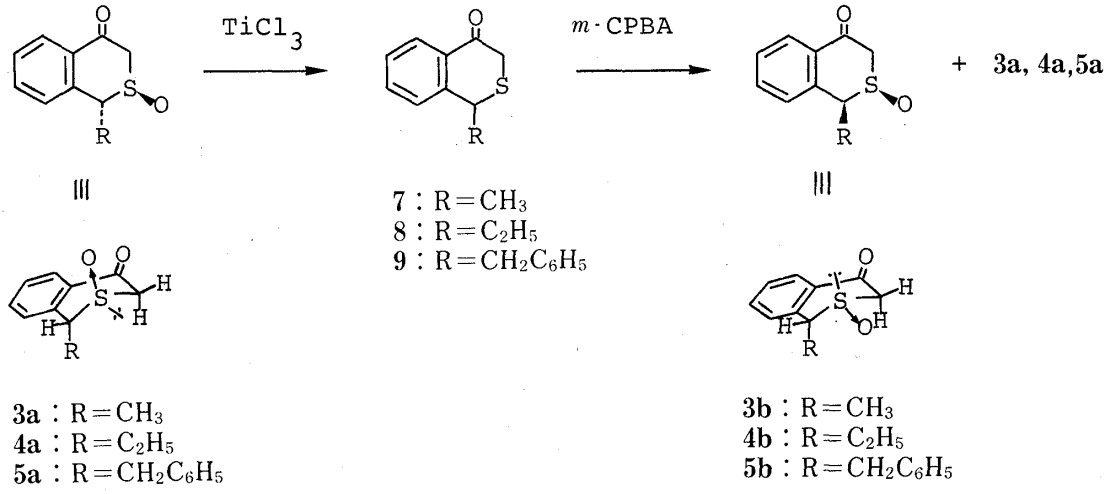


Chart 2

observed between two equatorial protons on C-1 and C-3 (see Table I), which indicates that the benzyl groups on C-1 of **5a** and **5b** have axial configuration. The lanthanide-induced shift (LIS)[6] value (Δ 0.39) of the C-3 axial proton of **5a** is smaller than that (Δ 1.47) of the C-3 axial proton of **5b**, indicating that the S–O bond of **5a** is axial and that of **5b** is equatorial. Consequently, compound (**5a**) was assigned as a *trans* isomer having a diaxial S–O bond and benzyl group, and compound (**5b**) was assigned as a *cis* isomer having an equatorial S–O bond and an axial benzyl group. Similarly, the *trans* diaxial structures of **3a** and **4a** were proved by the presence of a long-range coupling (J=2 Hz) between their C-1 and C-3 equatorial protons and by the resemblance of their LIS values to those of **5a** (see Table I). Similarity of the LIS values of **3b** and **4b** to those of **5b** at the C-1 and C-3 protons indicates that **3b** and **4b** are *cis* isomers having the same configuration as **5b**, though no long-range coupling was observed in **3b** and **4b**. An axial preference of the alkyl substituents on C-1 of **3a**, **b**, **4a**, **b**, and **5a**, **b** is probably attributed to the allylic strain [A$^{(1,2)}$].[7] The structure of **6** was determined by comparison of its ^{1}H-NMR spectrum with that of **1**. Thus, the signal at δ 4.30 (s) due to C-1 protons of **1** was converted to two doublets on addition of increasing amounts of Eu(fod)$_3$, and the low-field doublet at δ 5.04 due to the proton *cis* to the S–O bond was missing in the spectrum of **6**.

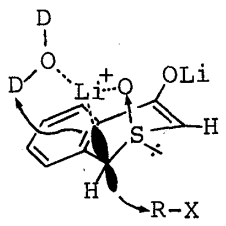


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Chart 3

TABLE I. ^{1}H-NMR Spectral Data for **3a, b**, **4a, b**, **5a, b**, **1**, and **6**

Compound		Chemical shift[a]			
		C-1 ax.	C-1 eq.	C-3 ax.	C-3 eq.
3a	δ	CH_3 1.76 (d)[b]	H 4.23 (br q)[b]	H 4.10 (d)[c]	H 3.89 (dd)[d]
	δ_{Eu}	CH_3 2.18 (d)[b]	H 5.21 (br q)[b]	H 4.44 (d)[c]	H 4.84 (br d)[e]
	δ_Δ	CH_3 (0.42)	H (0.98)	H (0.34)	H (0.95)
3b	δ	CH_3 1.73 (d)[b]	H 4.18 (q)[b]	2H 3.92 (s)	
	δ_{Eu}	CH_3 2.67 (d)[b]	H 5.17 (q)[b]	H 5.42 (d)[c]	H 4.93 (d)[c]
	δ_Δ	CH_3 (0.94)	H (0.99)	H (1.50)	H (1.01)
4a	δ	CH_2 1.4—2.3 (m)	H 4.10 (br dd)[e]	2H 3.88 (s)	
	δ_{Eu}	CH_2 1.85—2.65 (m)	H 5.02 (m)	H 4.23 (d)[f]	H 4.82 (dd)[g]
	δ_Δ	CH_2 (0.40)	H (0.92)	H (0.35)	H (0.94)
4b	δ	CH_2 1.4—1.9 (m) 2.4—2.9 (m)	H 4.02 (m)	2H 4.00 (s)	
	δ_{Eu}	CH_2 2.6—3.1 (m) 4.0—4.5 (m)	H 5.10 (m)	H 5.50 (d)[h]	H 5.12 (d)[h]
	δ_Δ	CH_2 (1.2) (1.6)	H (1.08)	H (1.50)	H (1.12)
5a	δ	CH_2 2.92 (dd)[i] 3.35 (dd)[j]	H 4.44 (dd)[e]	2H 3.87 (s)	
	δ_{Eu}	CH_2 3.35 (dd)[i] 3.79 (dd)[j]	H 5.59 (m)	H 4.26 (d)[k]	H 5.10 (dd)[l]
	δ_Δ	CH_2 (0.43) (0.44)	H (1.15)	H (0.39)	H (1.23)
5b	δ	CH_2 2.86 (dd)[m] 3.90 (dd)[n]	H 4.30 (dd)[o]	2H 4.05 (s)	
	δ_{Eu}	CH_2 3.98 (dd)[m] 5.96 (dd)[n]	H 5.60 (m)	H 5.52 (d)[c]	H 5.10 (dd)[d]
	δ_Δ	CH_2 (1.12) (2.06)	H (1.30)	H (1.47)	H (1.05)

Compound		C-1 *trans*	C-1 *cis*	C-3 *trans*	C-3 *cis*
1	δ	2H 4.30 (s)		2H 3.95 (s) 3.97 (s)	
	δ_{Eu}	H 4.80 (br d)[p]	H 5.04 (br d)[p]	H 4.53 (dd)[d]	H 4.77 (dd)[d]
	δ_Δ	H (0.50)	H (0.74)	H (0.57)	H (0.81)
6	δ	H 4.30 (br s)		2H 3.96 (s)	
	δ_{Eu}	H 4.80 (br s)	—	H 4.53 (dd)[d]	H 4.77 (d)[c]
	δ_Δ	H (0.50)	—	H (0.57)	H (0.81)

a) δ = ppm relative to tetramethylsilane in $CDCl_3$; δ_{Eu} = chemical shifts obtained by adding 0.15 molar eq of Eu(fod)$_3$, δ_Δ = LIS values ($\delta_{Eu} - \delta$); signals due to $CH_2C\underline{H}_3$ of **4a** and **4b** appear at δ 1.15 (t, J = 7 Hz) and at δ 1.12 (t, J = 7 Hz), respectively; signals due to aromatic protons appear at δ *ca.* 7.2—7.8 (3H, m) and 8.0—8.15 (1H, m) for **3a, b**, **4a, b**, **1**, and **6**, and at δ 6.7—7.6 (9H, m) and 8.0—8.15 (1H, m) for **5a, b**.
b) J = 7 Hz. *c*) J = 16 Hz. *d*) J = 16 and 2 Hz. *e*) J = 9 and 6 Hz. *f*) J = 17.5 Hz.
g) J = 17.5 and 2 Hz. *h*) J = 17 Hz. *i*) J = 14 and 9 Hz. *j*) J = 14 and 6 Hz.
k) J = 18 Hz. *l*) J = 18 and 2 Hz. *m*) J = 14 and 11 Hz. *n*) J = 14 and 4 Hz.
o) J = 11 and 4 Hz. *p*) J = 15 Hz.

It is well known that alkylation with alkyl halide and deuteration with deuterium oxide towards α-lithiosulfoxides generally occur *trans* and *cis*, respectively, to the S–O bond with high stereoselectivity.[8] Biellmann[9] and Marquet[10] have proposed a planar (sp^2) structure for the α-sulfinyl carbanion on the basis of the carbon-13 nuclear magnetic resonance spectra, and they explained the stereoselectivity in terms of "lithiation" at the sulfinyl oxygen. The present results can likewise be rationalized in terms of this concept, as shown in Chart 3. The sp^2 carbanion on C-1 (part of an ion pair) reacts with inversion with alkyl halide to give the *trans* alkylated product (**3a**, **4a**, and **5a**), whereas the carbanion reacts with retention with a chelating agent such as deuterium oxide to give the *cis* deuterated product (**6**).

Experimental[11]

***trans*-1-Methylisothiochroman-4-one 2-Oxide (3a)**——*n*-Butyllithium in hexane (2.9 ml of 1.59 M, 4.6 mmol) was added dropwise (*via* a syringe) to a stirred solution of **1**[12] (400 mg, 2.2 mmol) in anhydrous THF (45 ml) at −78 °C under an argon atmosphere. The reaction mixture was stirred at the same temperature for 10 min, then methyl iodide (0.143 ml, 2.3 mmol) was added (*via* a syringe) and the mixture was allowed to warm to room temperature with stirring. The reaction was quenched by the addition of wet silica gel (5 g), which was removed by filtration. The solvent was evaporated off, and the residue was chromatographed on silica gel with AcOEt as an eluent, to give **3a** (358 mg, 84%), mp 178—179 °C (from benzene). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1670 (CO), 1045 (SO). MS *m/e*: 194 (M^+). *Anal.* Calcd for $C_{10}H_{10}O_2S$: C, 61.83; H, 5.19. Found: C, 61.82; H, 5.11.

***trans*-1-Ethylisothiochroman-4-one 2-Oxide (4a)**——By the same procedure as described above for the preparation of **3a**, compound **4a** was obtained from **1** (400 mg, 2.2 mmol) and ethyl iodide (0.184 ml, 2.3 mmol) in 63% (288 mg) yield, mp 115—116 °C (from benzene). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1670 (CO), 1045 (SO). MS *m/e*: 208 (M^+). *Anal.* Calcd for $C_{11}H_{12}O_2S$: C, 63.44; H, 5.81. Found: C, 63.28; H, 5.75.

***trans*-1-Benzylisothiochroman-4-one 2-Oxide (5a)**——By the same procedure as described above for the preparation of **3a**, compound **5a** was obtained from **1** (400 mg, 2.2 mmol) and benzyl bromide (0.273 ml, 2.3 mmol) in 66% (392 mg) yield, mp 104—105 °C (from benzene). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1670 (CO), 1045 (SO). MS *m/e*: 270 (M^+). *Anal.* Calcd for $C_{16}H_{14}O_2S$: C, 71.09; H, 5.22. Found: C, 71.08; H, 5.18.

***cis*-1-Deuterioisothiochroman-4-one 2-Oxide (6)**——By the same procedure as described above for the preparation of **3a**, compound **6** was obtained from **1** (400 mg, 2.2 mmol) and deuterium oxide (0.042 ml, 2.3 mmol) in 85% (338 mg) yield, mp 169—170 °C (from benzene and *n*-hexane, 1 : 1). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1675 (CO), 1045 (SO). MS *m/e*: 181 (M^+).

***cis*-1-Methylisothiochroman-4-one 2-Oxide (3b)**——Titanium trichloride solution (20%, 2.3 ml) was added to a solution of **3a** (500 mg, 2.58 mmol) in methanol (5 ml) with stirring at 0 °C, and the mixture was stirred at the same temperature for 30 min. The reaction mixture was diluted with water (15 ml) and extracted with CH_2Cl_2 (10 ml × 3). The combined organic layer was washed with water and dried ($MgSO_4$). Removal of the solvent gave 1-methylisothiochroman-4-one (**7**) (450 mg, 98%), mp 90.5—91.5 °C (from *n*-hexane), lit.[13] 90—91 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.75 (3H, d, J=7 Hz), 3.47 (1H, d, J=16 Hz), 3.77 (1H, d, J=16 Hz), 4.07 (1H, q, J=7 Hz), 7.1—7.6 (3H, m), 8.00 (1H, m). *m*-Chloroperbenzoic acid (*m*-CPBA) (80%) (4.25 mg, 2.08 mmol) was added in small portions to a stirred solution of **7** (370 mg, 2.08 mmol) in $CHCl_3$ (60 ml) at 0 °C during 5 min. The mixture was stirred at room temperature for 1 h, then the reaction mixture was washed successively with 5% $NaHCO_3$ and water, and dried ($MgSO_4$). The solvent was evaporated off and the residue was chromatographed on silica gel with AcOEt as an eluent, to give **3b** (141 mg, 35%), mp 133—134 °C (from benzene). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1670 (CO), 1040 (SO). MS *m/e*: 194 (M^+). *Anal.* Calcd for $C_{10}H_{10}O_2S$: C, 61.83; H, 5.19. Found: C, 61.63; H, 5.25. Further elution with the same solvent gave **3a** (178 mg, 44%), whose physical data are in accord with those of the compound obtained by reaction of the dianion (**2**) with methyl iodide. Compounds **3a** and **3b** were converted to the same sulfone by oxidation with *m*-CPBA. mp 148—149 °C (from hexane). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1685 (CO), 1330 (SO_2), 1110 (SO_2). *Anal.* Calcd for $C_{10}H_{10}O_3S$: C, 57.13; H, 4.79. Found: C, 57.25; H, 4.69.

***cis*-1-Ethylisothiochroman-4-one 2-Oxide (4b)**——By the same procedure as described above for the preparation of **3b**, compound **4b** was prepared from **4a** *via* 1-ethylisothiochroman-4-one (**8**) in 26% yield as an oil, together with **4a** (40%). **4b**: IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1670 (CO), 1040 (SO). MS *m/e*: 208 (M^+). Oxidation of **4a** and **4b** with *m*-CPBA gave the same sulfone, mp 166—167 °C (from hexane). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1680 (CO), 1320 (SO_2), 1015 (SO_2). *Anal.* Calcd for $C_{11}H_{12}O_3S$: C, 58.91; H, 5.39. Found: C, 58.77; H, 5.38.

***cis*-1-Benzylisothiochroman-4-one 2-Oxide (5b)**——By the same procedure as described above for the preparation of **3b**, compound **5b** was prepared from **5a** *via* 1-benzylisothiochroman-4-one (**9**) in 16% yield as an oil together with **5a** (35%). **5b**: IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1680 (CO), 1040 (SO). MS *m/e*: 270 (M^+). Oxidation of **5a** and **5b** with *m*-CPBA gave the same sulfone, mp 105—106 °C (from hexane). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1680 (CO), 1325 (SO_2), 1110 (SO_2). *Anal.* Calcd for $C_{16}H_{14}O_3S$: C, 67.11; H, 4.93. Found: C, 67.02; H, 4.81.

References and Notes

1) Part II: Y. Tamura, J. Uenishi, and H. Ishibashi, *Chem. Pharm. Bull.*, **32**, 898 (1984).
2) Y. Tamura, J. Uenishi, and H. Ishibashi, *Chem. Pharm. Bull.*, **32**, 891 (1984).
3) α,α′-Dianions of acyclic β-ketosulfoxides have already been reported: Y. Tamura, H. Shindo, J. Uenishi, and H. Ishibashi, *Chem. Pharm. Bull.*, **27**, 3186 (1979).
4) The terms *trans* and *cis* used here refer to the relationship between the substituent and S–O bond.
5) J. B. Lambert, H. F. Shurvell, L. Verbit, R. G. Cooks, and G. H. Stout, "Organic Structural Analysis," Macmillan Publishing Co., Inc. New York, 1976, pp. 71—77.
6) R. R. Fraser, T. Durst, M. R. McClory, R. Viau, and Y. Y. Wigfield, *Int. J. Sulfur Chem.* (*A*), **1**, **1971**, 133.
7) F. Johnson, *Chem. Rev.*, **68**, 375 (1968).

8) G. Chassaing and A. Marquet, *Tetrahedron*, **34**, 1399 (1978); R. Lett and G. Chassaing, *ibid.*, **34**, 2705 (1978) and references therein.
9) J. F. Biellmann and J. J. Vicens, *Tetrahedron Lett.*, **1978**, 467.
10) G. Chassaing, R. Lett, and A. Marquet, *Tetrahedron Lett.*, **1978**, 471.
11) All melting points were determined with a Yanagimoto micro melting point apparatus and are uncorrected. The infrared (IR) spectra were recorded with a JASCO IRA-1 spectrophotometer. The ^{1}H-NMR spectra were measured on a Hitachi R-22 (90 MHz) spectrometer, with tetramethylsilane as an internal standard. Mass spectra (MS) were obtained with a TMS D-300 instrument with a direct inlet system operating at 70 eV.
12) M. S. Chauhan and I. W. J. Still, *Can. J. Chem.*, **53**, 2880 (1975).
13) D. A. Pulman and D. A. Whiting, *J. Chem. Soc., Perkin Trans. 1*, **1973**, 410.