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The Isomeric Sulfites of Dihydrofukinolidol

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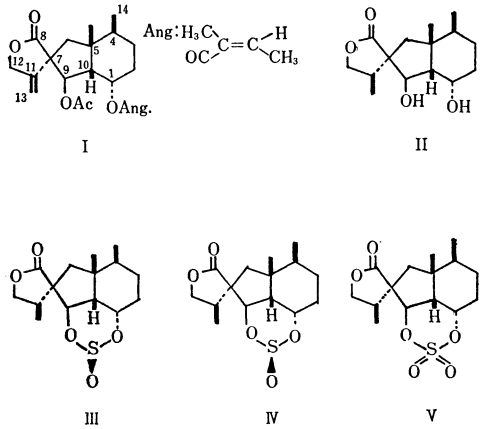
We have already elucidated the structure of fukinolide (I) isolated from *Petasites japonicus* Maxim. In this structural study, dihydrofukinolidol (II) was obtained by the hydrogenation of fukinolide I with platinum oxide-acetic acid, followed by alkaline hydrolysis;[1] it was tentatively assigned to the stereoformula II with a 13-β methyl group, considering the approach of the catalyst from the back of the attached site of the ester groups in the hydrogenation process.

This paper will deal with the configurational assignment of the two isomeric sulfites prepared from dihydrofukinolidol II. The isomeric cyclic sulfites derived from the 1,3-diol system have recently been much investigated in order to provide decisive information for the conformational assignment, especially with regard to the correct orientation of the S–O group.[2]

For the purpose of clarifying the 1,3-relationship, including the configurations between the two hydroxyl groups in dihydrofukinolidol II, the compound II, $C_{15}H_{24}O_4$, mp 190—191°C, was treated with thionyl chloride-pyridine to afford a mixture of two isomeric sulfites. The crude product was separated by column chromatography with silica gel-benzene. The faster-running product (III) formed colorless prisms, mp 190.5—191.5°C (dec.), $[\alpha]_D^{22}$ −80° and the slower one (IV), colorless needles, mp 187.5—188.5°C (dec.), $[\alpha]_D^{22}$ −145°. Though the mixed melting point of III and IV showed a slight depression (mp 186.5—187.0°C dec.), both the products were found to possess the same molecular formula, $C_{15}H_{22}O_5S$; both regenerated dihydrofukinolidol II by alkaline hydrolysis, and were converted to the same sulfate by oxidation with perbenzoic acid.



I II III IV V

Fig. 1. Stereoformulas of Fukinolide I, Dihydrofukinolide II, Sulfites III and IV, Sulfate V.

It was suggested that these isomers were derived from the different configurations of the sulfite S=O groups. In addition, the higher melting product III was less soluble in methanol and chloroform. In view of the *cis-trans* isomerism,[3] the compounds III and IV were supposed to have *trans*- and *cis*-characters respectively, according to the above properties (mp, solubility, and adsorption).

Table 1. Comparison of chemical shifts (ppm as δ-values) in the NMR spectra[a] of fukinolidol (I), dihydrofukinolidol (II), sulfites (III) and (IV)

Proton assignment	Compounds I	II	III	IV
1-H	5.10m	4.10m	4.75q (J=6)	5.00m
6-H	1.90d (J=15)	1.50d (J=14)	1.56d (J=14)	1.55d (J=14)
	2.55d (J=15)	2.00d (J=14)	2.04d (J=14)	2.04d (J=14)
9-H	5.77d (J=12)	4.61d (J=11)	5.26d (J=12)	4.45d (J=12)
10-H	2.82dd (J=6, 12)	2.55dd (J=6, 12)	2.95dd (J=7, 13)	3.65dd (J=7, 13)
12-H		4.23t (J=8)	4.35t (J=7.7)	4.35t (J=7.7)
		4.10q (J=8.5, 10)	3.90q (J=8.5, 10)	3.90q (J=8.5, 10)
13-Me		1.15d (J=7)	1.20d (J=7)	1.20d (J=7)
14-Me	0.90d (J=7.5)	0.78d (J=4)	0.88d (J=7)	0.90d (J=7)
15-Me	1.12s	1.00s	1.12s	1.18s

a) NMR spectra were taken in $CDCl_3$ at 60 MHz with TMS standard.

The configurational difference between the two sulfites was well defined by a comparison of the NMR spectra (Table 1 and Fig. 2). The most remarkable difference between the NMR spectra of the two isomers, III and IV, is the strong deshielding of 9-H in III, and of 10-H and 1-H in IV. This contrast may be expected to occur under the influence of the axially-oriented S=O groups in the chair and boat conformations. Furthermore, the compounds III and IV exhibited the IR absorptions of the axial S=O groups[4] at 1190 and 1200 cm^{-1} respectively.

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1) K. Naya, I. Takagi, M. Hayashi, S. Nakamura, M. Kobayashi, and S. Katsumura, *Chem. Ind.* (London), **1968**, 318.

2) A. T. Rowland, T. B. Adams, H. W. Atland, W. S. Creasy, S. A. Dressner, and T. M. Dyott, *Tetrahedron Lett.*, **1970**, 4405; H. F. Van Woerden and E. Havinga, *Rec. Trav. Chim. Pays-Bas*, **86**, 341 (1967); E. L. Eliel and N. L. Allinger, "Topics in Stereochemistry," Vol. 4, Willey-Interscience, New York (1967), p. 48.

3) E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill (1962), p. 326.

4) D. G. Hellier, J. G. Tilett, H. F. Van Woerden, and R. F. M. White, *Chem. Ind.* (London), **1963**, 1956; O. R. S. Edmundson, *Tetrahedron Lett.*, **1965**, 1649.

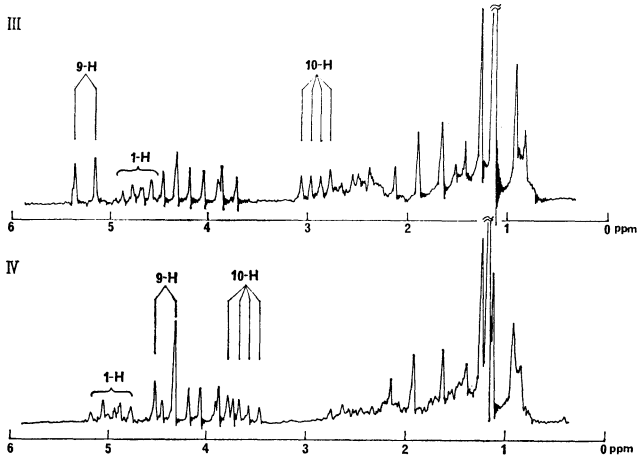

Fig. 2. NMR spectra of sulfites III and IV.

As the absolute configuration of dihydrofukinolidol had been completely established except for the 13β-methyl of the formula II,[5] the above evidence makes possible the assignment of the stereoformula A for III and that of B for IV among the possilbe configurations (A—D, Fig. 3).[6]

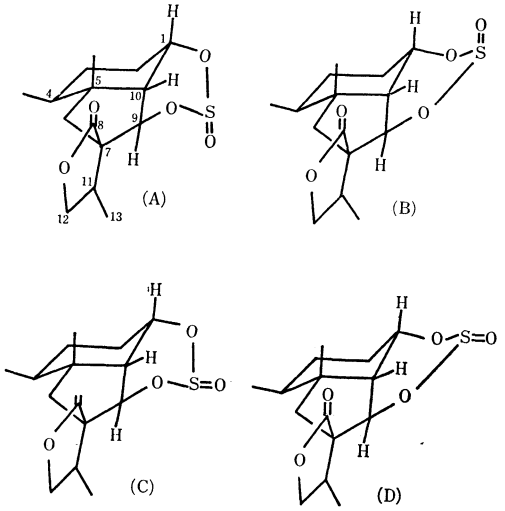

Fig. 3. Possible stereoformulas of sulfites III and IV.

Experimental

All the melting points are uncorrected. The IR spectra were recorded with a JASCO DS-402G spectrophotometer, while the UV spectra were obtained with a Cary Model 14 spectrophotometer. The optical rotations were measured with a Hitachi EPU-2A spectrophotometer. The NMR spectra were determined with a Hitachi R-20A spectrometer, using TMS as the internal standard (δ=0) and $CDCl_3$ as the solvent.

Preparation of Isomeric Sulfites of Dihydrofukinolidol (II). A solution of dihydrofukinolidol[1] (870 mg, mp 190—191°C) in dry pyridine (16 m*l*) was stirred, drop by drop, into a mixture of thionyl chloride (3.4 m*l*) and dry pyridine (16 m*l*) at −35——45°C over a 2 hr period; after the mixture had then been stirred at room temperature for additional 2 hr, the solvent was removed *in vacuo*. The residue was poured into water and extracted with ether. The extract was washed with water and dried over anhydrous sodium sulfate. After the removal of the solvent, the residual solid (1.04 g) was chromatographed over silica gel (20 g); subsequent elution with benzene afforded III (320 mg) as colorless prisms, mp 190.5—191.5°C (dec.) (from ethyl acetate-light petroleum), $[\alpha]_D^{22}$ −80° (*c*, 1.0, chloroform); IR (KBr): 1764, 1190 cm^{-1}; tlc (Merck Kieselgel G): R_f, 0.67 (benzene-ethyl acetate, 5: 1).

Found: C, 57.48; H, 6.99; S, 10.41%. Calcd for $C_{15}H_{22}O_5S$: C, 57.30; H, 7.05; S, 10.20%.

Further elution with the same solvent gave IV (240 mg) as colorless needles, mp 187.5—188.5°C (dec.) (from ethyl acetate-light petroleum), $[\alpha]_D^{22}$ −145° (*c*, 1.0, chloroform); IR (KBr): 1765, 1200 cm^{-1}; tlc: R_f, 0.48 (benzene-ethyl acetate, 5: 1).

Found: C, 57.57; H, 6.97; S, 10.50%. Calcd for $C_{15}H_{22}O_5S$: C, 57.30; H, 7.05; S, 10.20%. A mixed-melting-point determination with III and IV showed a slight depression (mixed mp 186.5—187.0°C dec.).

Hydrolysis of the Sulfites (III) and (IV). a) The cyclic sulfite III (28 mg) in ethanol (5 m*l*) was added to a 10% potassium hydroxide-methanol solution (3 m*l*), left at room temperature for 2 days, and then warmed at 40—50°C for 10 hr. After acidification with dilute sulfuric acid, the mixture was diluted with water and extracted with ether, washed with a saturated sodium hydrogen carbonate solution and water, and dried over anhydrous sodium sulfate. The subsequent evaporation of the solvent gave II (21 mg) as colorless needles, mp 189—191°C (from ethyl acetate-light petroleum), IR (KBr): 3550, 3460, 1760 cm^{-1}; tlc: R_f, 0.48 (benzene-ethyl acetate, 1: 1).

b) The cyclic sulfite IV (35 mg) was treated as above to give II (22 mg), mp 188—189.5°C (from ethyl acetate-light petroleum). The products from a) and b) showed no melting point depression on admixture with dihydrofukinolidol II, mp 190—191°C.

Oxidation of Cyclic Sulfites with Perbenzoic Acid. a) To a solution of III (20 mg) in chloroform (0.5 m*l*), a solution of 0.117N perbenzoic acid-chloroform (1.6 m*l*) was added; the mixture was then left at room temperature for 16 days. The mixture was extracted with ether, and the extract was washed with a saturated sodium hydrogen carbonate solution and with water. The dried extract was concentrated to afford a solid (19 mg). Chromatography over silica gel (3 g) by means of elution with benzene gave the starting material (8 mg) and an oxidation product V (5 mg); mp 135—138°C (from ethyl acetate-light pertoleum); tlc: R_f, 0.55 (benzene-ethyl acetate, 5: 1).

b) A solution of 0.117N perbenzoic acid-chloroform (3.2 m*l*) was added to a solution of IV (42 mg) in chloroform (1 m*l*), after which the mixture was left at room temperature for 6 days. Working-up as above gave a crude product (71 mg) which was chromatographed on silica gel (5 g) by elution with benzene to furnish crystalline V as colorless leaflets; mp 141.5—142°C (dec.) (from ethyl acetate-light petroleum); tlc: R_f, 0.55 (benzene-ethyl acetate, 5: 1).

Found: C, 54.67; H, 6.63; S, 9.57%. Calcd for $C_{15}H_{22}O_6S$: C, 54.53; H, 6.71; S, 9.67%. The mixed melting point of the two products from a) and b) showed no depression (mixed mp 136—138°C).

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5) C. Katayama, A. Furusaki, I. Nitta, M. Hayashi, and K. Naya, This Bulletin, **43**, 1976 (1970).

6) The result of the X-ray analysis connected with this work will soon be presented in this Bulletin.