

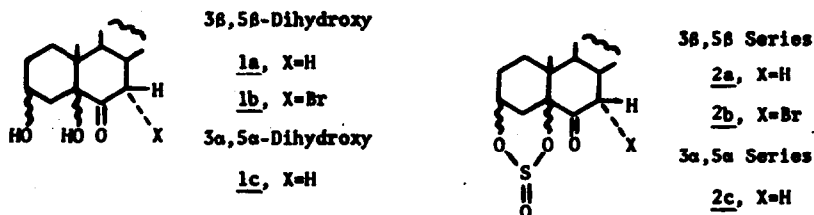
ISOMERIC SULFITE ESTERS OF SOME 1,3-DIHYDROXYCHOLESTANONES

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Isomeric cyclic sulfites that differ in configuration at the sulfur atom have been the subject of much investigation.¹ A recent report² sought to resolve some of the conflicting conclusions previously reached on the conformational aspects of substituted trimethylene sulfites by examination of their dipole moments. Of the three isomeric sulfites obtained from 2,4-pentanediol, the two meso forms were regarded as existing in chair conformations, one with S=O axial and the other with S=O equatorial, while the dl isomer was considered to be in a flexible form.² The chair isomer with S=O equatorial was reported to be the first cyclic sulfite known to exist with this orientation of the oxygen.



In the course of a study of the effectiveness of the cyclic sulfite group in neighboring group participation reactions leading to steroid 3-oxetanones, we have found that isomeric sulfites derived from 3β,5-dihydroxy-5β-cholestan-6-one (1a) exist in boat conformations with the S=O axial or equatorial.

Treatment of 1a with thionyl chloride-pyridine at -15° or at 1° yielded sulfite³ with the same mp as the product obtained at 40° and as the sulfite isolated previously⁴ from 1a by reaction with thionyl chloride in chloroform. Differences were noted, however, in several physical constants of these materials. Furthermore, reduction of the cyclic sulfite 2a (prepared from 1a by the thionyl chloride-pyridine procedure) with lithium aluminum tri-*t*-butoxy hydride gave two isomeric sulfites, one of which was a 3,5-cyclic sulfite (3) of 5β-cholestan-3β,5,6β-triol.⁵ Oxidation of 3 with chromic oxide-acetone-acetic acid gave a

6-oxo cyclic sulfite which differed from those obtained directly from 1a. The results are summarized in Table I. All of the cyclic sulfites gave 1a upon saponification and each had α_D^{20} of 293 ± 1 m_D ($c \sim 40$) in ethanol.

TABLE I*

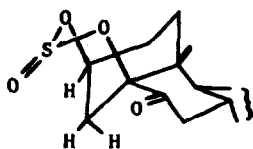
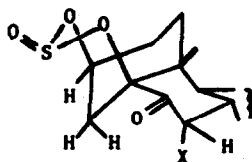
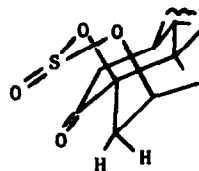
PHYSICAL CONSTANTS OF 3 β ,5 β -DIOL-6-ONE CYCLIC SULFITES

Source	Physical Data [α_D^{20} ; $\bar{\nu}_{max}(S=O)$; nmr (Hz)]
<u>1a</u> + SOCl ₂ -C ₅ H ₅ N, -15°	191-194° dec; -30°; 1230 cm ⁻¹ ; 19-H (55), 4 β -H (147, one of the doublets, J=3), 3 α -H (294, $\bar{W}_{1/2} = 7$) - H ratios: 3/1/1.
<u>1a</u> + SOCl ₂ -C ₅ H ₅ N, 1°	192-194° dec; -33°; 1230 cm ⁻¹ ; 19-H (55), 4 β -H (148, one of the doublets, J=3), 3 α -H (295, $\bar{W}_{1/2} = 7$) - H ratios: 3/1/1.
<u>1a</u> + SOCl ₂ -C ₅ H ₅ N, 40°	192-194° dec; -52°; 1227, 1190 cm ⁻¹ ; 19-H (55), 4 β -H (210, d of d, J = 15 and 4), 3 α -H (283, $\bar{W}_{1/2} = 8$), 3 α -H (294, $\bar{W}_{1/2} = 7$) - H ratios: 6/1/1/1.
Ox. of <u>3</u>	204-205° dec; -78°; 1200 cm ⁻¹ ; 19-H (54.5), 4 β -H (d of d at 211, J = 15 and 4), 3 α -H (284, $\bar{W}_{1/2} = 8$) - H ratios: 3/1/1.

*Optical rotations in CHCl₃; ir spectra in CCl₄; nmr spectra in CDCl₃ at 60 MHz with TMS standard.

It is clear from examination of the data that the sulfite obtained from 3 contains the heterocyclic ring in a boat conformation with the S=O axial (4a). The ir absorption at 1200 cm⁻¹ is characteristic of a cyclic sulfite that has the S=O axial,⁶ while the deshielding of the 4 β -H observed in the nmr spectrum occurs under the influence of the axially oriented oxygen. Decoupling experiments readily verified that the signal at 211 Hz was indeed due to the 4-H and not one at C-1. On the other hand, the sulfite produced from 1a by thionyl chloride-pyridine treatment at -15° or 1° exhibits no significant downfield shift of the C-4 hydrogen (one of the doublets appears near the end of the methylene envelope -- see Table I). Since the ir absorption of the S=O falls at 1230 cm⁻¹ for this compound it must have an equatorially oriented oxygen⁶ with the heterocyclic ring in a boat conformation (4b), as deshielding of the axial C-1 hydrogen and the C-19 hydrogens would be expected if the ring were in a chair conformation.

The sulfite obtained from 1a by treatment with thionyl chloride-pyridine at 40° represents approximately a 1:1 mixture of 4a and 4b, judging by the specific rotation and nmr data.

4a4b, X=H4c, X=Br4d

The conclusion reached in an earlier investigation that the 6-desoxo analog of 2a has an equatorial S=O ($\bar{\nu}_{\max}$ reported 1190 cm^{-1})^{7a} must now be altered. We intend to verify the belief that this material will have a boat, S=O axial arrangement.

Treatment of 3 α ,5-dihydroxy-5 α -cholestan-6-one (1c)^{7b} with thionyl chloride-pyridine at 1° gave a single cyclic sulfite (2c), mp 163-164°; $[\alpha]_D + 26^\circ$; ir 1203 cm^{-1} (S=O); uv max $301\text{ m}\mu$ (ϵ 39); nmr 50 (19-H), 211 (4 α -H, d of d, $J = 15$ with unresolved legs), 287 (3 β -H, $M_{1/2} = 8$) Hz. The ir absorption points to an axial S=O while the deshielding of the 4 α -H clearly indicates that the heterocyclic ring also exists in a boat conformation (4d). The identity of the signals found for the 4 β -H in 4a and the 4 α -H in 4d results from the similarity of their environments in the heterocyclic rings.

Preparation of the sulfite ester (2b) of the 7 α -bromo steroid 1b⁸ in like fashion gave one compound with mp 194-195°; $[\alpha]_D -13^\circ$; ir 1236 cm^{-1} (S=O); uv max $319.5\text{ m}\mu$ (ϵ 100); nmr 57 (19-H), 156 (4 α -H, d of d with poorly resolved legs, $J = 16$), 187 (4 β -H, d of d, $J = 16$ and 2), 264 (7 β -H, d, $J = 3$), 293 (3 β -H, $M_{1/2} = 7$) Hz. In this instance the heterocyclic ring must again exist in a boat conformation with the S=O equatorial (4c). The 4 α -H (deshielded by the 7 α -bromine⁸) and 4 β -H both appear downfield and substantiate the boat assignment.

The formation of cyclic sulfites from 1,3-glycols in polycyclic systems has previously been conducted solely as a device for ascertaining the spacial relationship of the hydroxy groups.⁹ From the results of the work reported here, however, it seems that the more interesting configurational-conformational aspects of the sulfites are amenable to analysis by nmr and other methods. We are continuing investigations along this line.

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REFERENCES

- (*) To whom inquiries should be addressed.
- (1) The subject has been reviewed: F. G. Riddell, Quart. Revs., 21, 364 (1967). See also C. Romers, C. Altona, H. R. Buys, and E. Havinga in "Topics in Stereochemistry," Vol. IV, N. L. Allinger and E. L. Eliel, Ed., Interscience Publishers, New York, 1969, p 48.
 - (2) G. Wood and M. H. Miskow, Tetrahedron Letters, 1109 (1969).
 - (3) Satisfactory elemental analyses were obtained for all new compounds reported here.
 - (4) A. T. Rowland, Steroids, 7, 527 (1966).
 - (5) Details of the reduction are described in the accompanying communication.
 - (6) D. G. Hellier, J. G. Tillett, H. F. Van Woerden, and R. F. M. White, Chem. and Ind., 1956 (1963). See also H. F. Van Woerden and E. Havinga, Rec. Trav. Chim., 86, 341 (1967).
 - (7) (a) P. B. D. de la Mare, W. Klyne, D. J. Millen, J. G. Pritchard, and D. Watson, J. Chem. Soc., 1813 (1956). (b) G. Snatzke, Ann. Chem., 686, 167 (1965).
 - (8) A. T. Rowland, P. J. Bennett, and T. S. Shoupe, J. Org. Chem., 33, 2426 (1968).
 - (9) E.g., see J. R. Bull, J. Chem. Soc. (C), 1128 (1969).