The Stereochemical Course of Substitution at Sulphur in a Sulphite Diester

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A single diastereoisomer of phenyl epiandrosterone sulphite and the single diastereoisomer of benzyl epiandrosterone sulphite derived from it by nucleophilic substitution with benzyl alcohol have both been shown by X-ray crystallographic analysis to have the R_s configuration and hence the reaction proceeds with inversion at sulphur.

The configurational assignment of phenyl [(*R*)-^{16}O,^{17}O,^{18}O]-sulphate, whose synthesis has been reported,[1] is dependent on knowing the absolute configuration at sulphur of the intermediate phenyl epiandrosterone sulphite. We now report that this has been determined by X-ray crystallographic analysis.† The structure is shown in Fig. 1 and is seen to have the *R*-configuration at sulphur.

As far as we are aware the stereochemical course of nucleophilic displacement at sulphur in a sulphite diester has

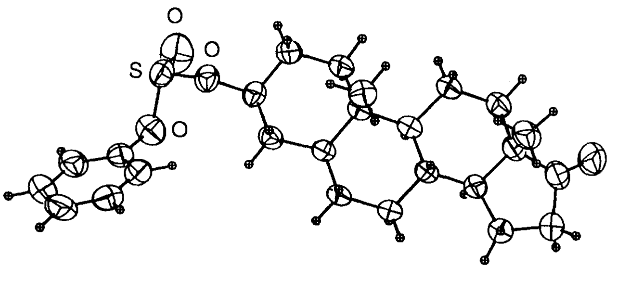

Fig. 1 The structure of phenyl epiandrosterone sulphite determined by X-ray crystallographic analysis

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† *Crystal data*: A crystal of phenyl epiandrosterone sulphite measuring 0.1 × 0.2 × 0.7 mm was mounted on an Enraf-Nonius CAD-4F diffractometer equipped with a Cu-Kα radiation source (λ = 1.54180 Å), $C_{25}H_{34}O_4S_1$. M_r 430.603, space group $P2_1$, monoclinic, $a = 6.628(2)$, $b = 10.179(1)$, $c = 17.133(4)$ Å, $\beta = 84.74(3)$, $Z = 2$, $D_c = 1.242$ g cm^{-3}, $U = 1150.95$ Å. Data were collected in an $\omega - 2\theta$ scan mode from 1 to 75° to yield 2508 unique reflections of which 1901 were considered observed having $I > 3\sigma(I)$. The structure was solved using SHELXS-86 (G. Sheldrick, SHELXS-86 User Guide, Göttingen, F.R.G., 1986) and refined using CRYSTALS (D. J. Watkin, J. R. Carruthers and P. W. Betteridge. CRYSTALS User Guide, Chemical Crystallography Laboratory, Oxford University, Oxford, UK, 1985) to give a final $R = 4.49\%$ ($R_w = 5.43\%$).

not been determined hitherto. The availability of phenyl epiandrosterone sulphite of known absolute configuration at sulphur gave us the opportunity to explore this stereochemical problem. After investigating a number of achiral primary alcohols, benzyl alcohol was selected as it gave a crystalline product suitable for X-ray analysis. Phenyl epiandrosterone (*R*)-sulphite was treated with two mole equivalents of benzyl alcohol in dichloromethane at room temperature. The reaction was monitored by TLC (1 : 1 diethyl ether–hexane) and by ^{1}H NMR spectroscopy [benzyl epiandrosterone sulphite has a characteristic multiplet at δ 4.35 (owing to C_3-H) as well as a pair of doublets at δ 4.95 and 5.10 (owing to the diastereotopic benzylic protons, $PhCH_2$–)]. The reaction was complete in a few hours. The reaction product was investigated by a variety of techniques but only one diastereoisomeric sulphite diester could be detected. Benzyl epiandrosterone sulphite was isolated and recrystallised from diethyl ether–hexane to give colourless crystals (75%, m.p. 99–100 °C).‡ The X-ray crystal structure is shown in Fig. 2. The nucleophilic displacement reaction was shown in a separate experiment to be catalysed by *p*-toluenesulphonic acid.

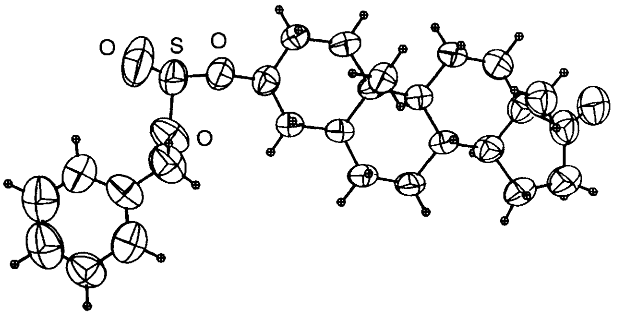

Fig. 2 The structure of benzyl epiandrosterone sulphite determined by X-ray crystallographic analysis

The benzyl epiandrosterone sulphite has the *R*-configuration at sulphur,§ and hence the displacement of phenol from phenyl epiandrosterone sulphite by benzyl alcohol occurs with inversion at sulphur. This is the first demonstration that displacement at sulphur in a sulphite diester occurs with inversion and hence by an 'in line' mechanism.

Received, 29th July 1991; Com. 1/03928H

Reference

1 C. L. L. Chai, T. W. Hepburn and G. Lowe, *J. Chem. Soc., Chem. Commun.*, 1991, 1403.

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‡ *Crystal data*: A crystal of benzyl epiandrosterone sulphite measuring 0.3 × 0.4 × 0.7 mm was mounted on an Enraf-Nonius CAD-4F diffractometer equipped with a Cu-Kα radiation source (λ = 1.54180 Å), $C_{26}H_{36}O_4S_1$. M_r 444.630, space group $P2_12_12_1$, orthorhombic, a = 7.951(3), b = 9.296(2), c = 32.775(11) Å, Z = 4, D_c = 1.219 g cm^{-3}, U = 2422.53 Å. Data were collected in an $\omega - 2\theta$ scan mode from 1 to 75° to yield 2765 unique reflections of which 1831 were considered observed having $I > 3\sigma(I)$. The structure was solved using SHELXS-86 and refined using CRYSTALS to give a final R = 6.64% (R_w = 7.92%).

For both structures atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Notice to Authors, Issue No. 1.

§ Although both the phenyl- and benzyl-epiandrosterone sulphite have the *R*-configuration at sulphur, the reaction has proceeded with inversion. This is a consequence of the change in order of priority between phenyl and C-3 of the steroid and benzyl and C-3 of the steroid when applying the Cahn, Ingold and Prelog rules.