

Synthesis of Phenyl [(*R*)¹⁶O,¹⁷O,¹⁸O]Sulphate and the Stereochemical Course of a Sulphuryl Transfer Reaction

Christina L. L. Chai, Timothy W. Hepburn and Gordon Lowe*

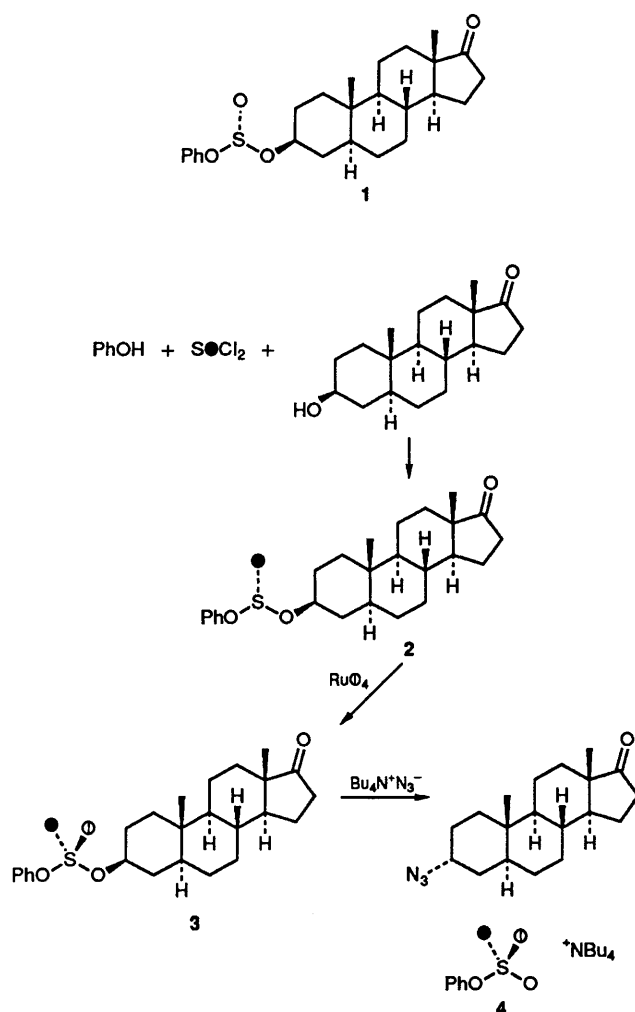
The Dyson Perrins Laboratory, Oxford University, South Parks Road, Oxford OX1 3QY, UK

Phenyl [(*R*)¹⁶O,¹⁷O,¹⁸O]sulphate is synthesised and the stereochemical course of sulphuryl transfer to a secondary alcohol shown to proceed with inversion of configuration at sulphur.

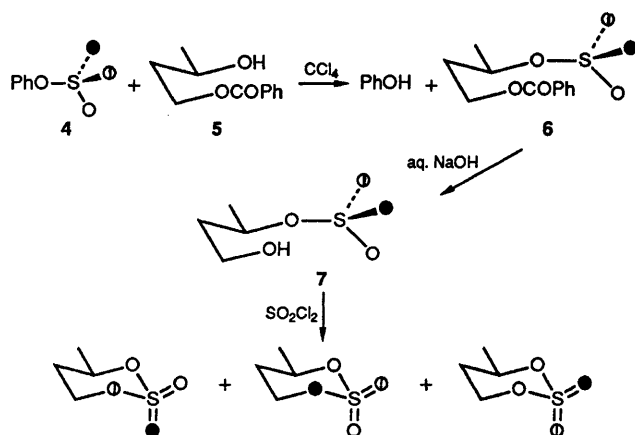
In order to study the stereochemical course of chemical and enzyme catalysed sulphuryl transfer reactions, a general strategy for the synthesis of chiral [¹⁶O,¹⁷O,¹⁸O]sulphate monoesters has been developed.^{1,2} A chirally labelled aryl sulphate was now required to further these investigations. A preliminary search for a chiral alcohol that would form a crystalline sulphite diester with phenol and thionyl chloride, and would not be susceptible to oxidation by ruthenium tetroxide led us to select 3β-cholestanol and epiandrosterone. Both of these steroidal alcohols form phenyl sterol sulphite diesters when one molar equivalent of phenol and 3β-cholestanol or epiandrosterone is reacted successively with thionyl chloride in the presence of pyridine. A single diastereoisomer of phenyl epiandrosterone sulphite diester crystallised readily and is shown to have the (*R*_S)-configuration **1**, by X-ray crystal structure analysis.³ With this knowledge phenyl [(*R*)¹⁶O,¹⁷O,¹⁸O]sulphate was synthesised by the route outlined in Scheme 1.

[¹⁸O]Thionyl chloride was prepared from sulphur [¹⁸O]₂dioxide (99 atom% ¹⁸O) and 1,4-bis(trichloromethyl)-benzene in the presence of a catalytic amount of iron(III) chloride in a sealed tube at 20 °C for 3 days: the [¹⁸O]thionyl chloride (83%) was purified by fractional distillation.⁴ One equivalent of phenol in benzene solution was added slowly to a stirred solution of the [¹⁸O]thionyl chloride in benzene in the presence of pyridine and this was allowed to react for 1 h. Epiandrosterone (1 equiv.) in benzene solution was then added and the reaction mixture stirred for 15 min. The [¹⁸O]sulphite diester **2** was obtained (43%) after flash chromatography on silica gel,⁵ and was recrystallised from ether-hexane prior to oxidation. The [¹⁸O]sulphite diester **2** was oxidised to the corresponding [¹⁷O,¹⁸O]sulphate diester **3** using a modification of our previously described method for the oxidation of sulphites to labelled sulphates.⁶ The [¹⁸O]sulphite **2** is an aryl sulphite diester, unlike the previously studied sulphites diesters,^{1,2,6} and is not stable under the aqueous conditions of the catalytic oxidation method.⁶ Ruthenium tetroxide was prepared, therefore, from ruthenium dioxide dihydrate (200 mg, 1.18 mmol) and sodium metaperiodate (600 mg, 2.8 mmol) in a vigorously stirred, biphasic system consisting of CCl₄ (25 ml) and water (5 ml); the organic layer containing the ruthenium tetroxide was dried (over Na₂SO₄) and [¹⁷O]water (45.0% ¹⁷O, 20.2% ¹⁶O, 34.8% ¹⁸O, 0.5 ml) containing anhydrous Na₂HPO₄ (10 mg) added and isotope exchange allowed to occur by vigorously stirring the mixture for 24 h.[†] The ruthenium [¹⁷O]₄tetroxide solution was dried and used (in a slightly greater than stoichiometric amount) to oxidise the [¹⁸O]sulphite diester **2** at 0 °C (reaction time 10 min) to phenyl epiandrosterone [¹⁷O,¹⁸O]sulphate **3** in 76% yield.

Having previously established the configuration at sulphur of the unlabelled sulphite diester **1** and knowing that the oxidation of sulphites to sulphates with ruthenium tetroxide



Scheme 1 Synthesis of phenyl [(*R*)¹⁶O,¹⁷O,¹⁸O]sulphate. ○ = ¹⁷O; ● = ¹⁸O.



Scheme 2 The stereochemical course of a sulphuryl transfer reaction. The product **6**, after debenzoylation and cyclization was analysed by FTIR spectroscopy (see Fig. 1). ○ = ¹⁷O; ● = ¹⁸O.

† Basic conditions have been found to catalyse the exchange of oxygen isotopes into RuO₄. Preliminary studies were performed under similar conditions using 99% [¹⁸O]H₂O. The resulting ruthenium [¹⁸O]₄tetroxide reacted with racemic *cis*-4-methyl-2-oxo-1,3,2-dioxathiane to give the corresponding 4-methyl-2,2-[¹⁸O]dioxo-1,3,2-dioxathiane in very high enrichment (by FTIR), indicating that isotope exchange had reached equilibrium.

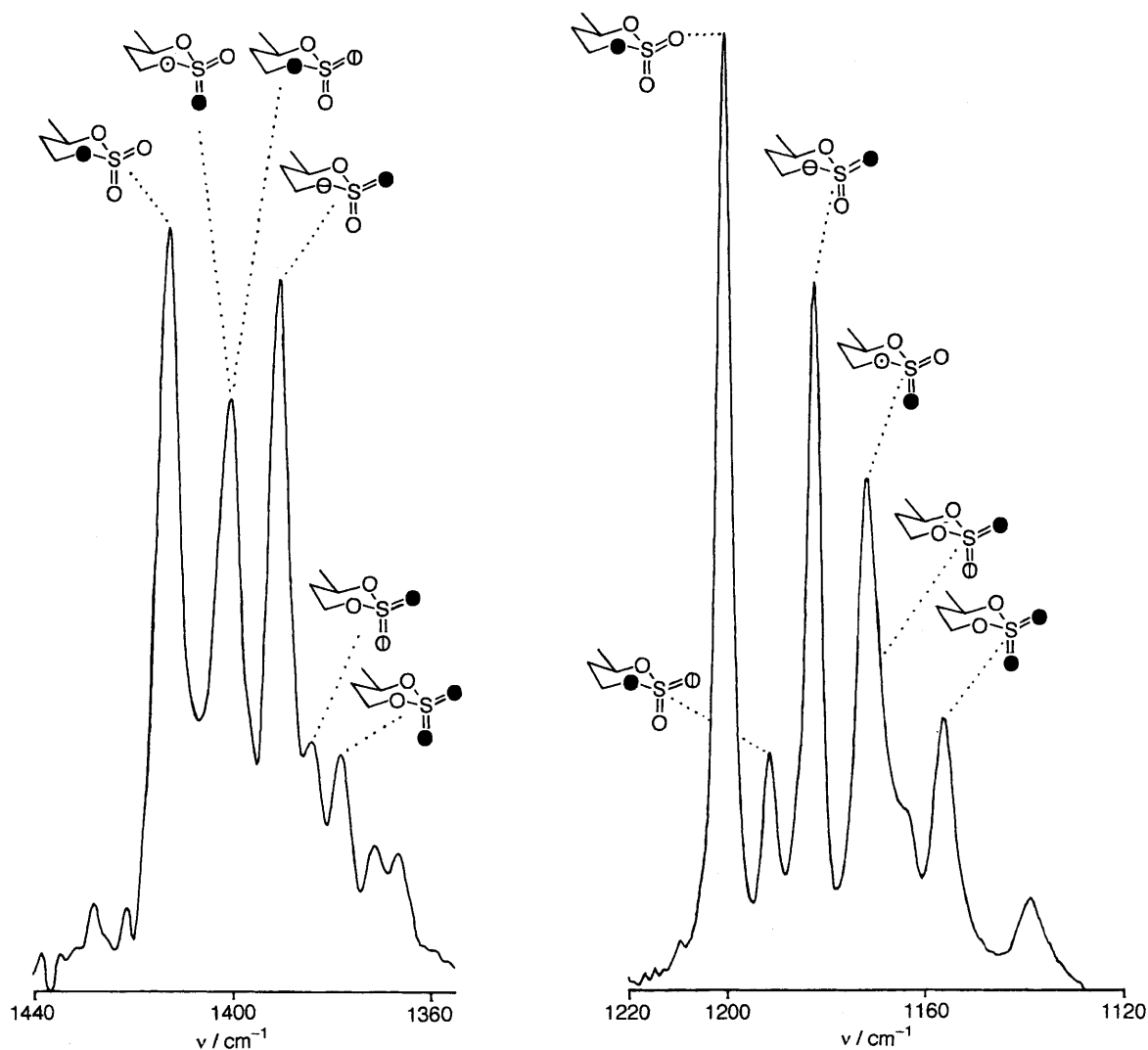


Fig. 1 The FTIR spectrum showing the antisymmetric (1414–1378 cm^{-1}) and symmetric (1201–1157 cm^{-1}) $>\text{SO}_2$ stretching frequencies of the mixture of isotopomers derived by cyclizing (1*R*)-3-hydroxy-1-methylpropyl [^{16}O , ^{17}O , ^{18}O]sulphate **7** with sulphuryl chloride. The resolution was enhanced by Fourier deconvolution; for the antisymmetric stretching region a linewidth of 20 cm^{-1} and an enhancement factor of 2.0 was used, whereas for the symmetric stretching region a linewidth of 10 cm^{-1} and an enhancement factor of 1.5 was used. Isotopes in a bridging position do not influence the $>\text{SO}_2$ stretching frequencies.² ⊕ = ^{17}O ; ● = ^{18}O ; ⊖ = ^{17}O and ^{18}O ; ⊙ = ^{16}O , ^{17}O and ^{18}O .

occurs with retention of configuration,⁶ the [^{17}O , ^{18}O]sulphate diester **3** must have the (*R_S*)-configuration as shown. Phenyl epiandrosterone [(*R*)- ^{17}O , ^{18}O]sulphate diester **3** on treatment with tetrabutylammonium azide⁷ in CH_2Cl_2 at room temperature for 18 h was converted to phenyl [(*R*)- ^{16}O , ^{17}O , ^{18}O]sulphate tetrabutylammonium salt **4** in 45% yield after purification on Sephadex G-10.

Phenyl [(*R*)- ^{16}O , ^{17}O , ^{18}O]sulphate tetrabutylammonium salt **4** was incubated with (1*R*)-3-benzoyloxy-1-methylpropan-1-ol **5**,⁸ in carbon tetrachloride at 100 °C for 16 h (in a reaction vial) by which time sulphuryl transfer was essentially complete. The (1*R*)-3-benzoyloxy-1-methylpropyl [^{16}O , ^{17}O , ^{18}O]sulphate **6** was debenzoylated with aqueous sodium hydroxide solution and the (1*R*)-3-hydroxy-1-methylpropyl [^{16}O , ^{17}O , ^{18}O]sulphate **7** as its pyridinium salt cyclized with sulphuryl chloride.² The mixture of isotopomers so generated was investigated by FTIR; the spectrum of the symmetric and antisymmetric stretching frequencies are shown in Fig. 1. The distribution of isotopomers is that expected from the *S_S* enantiomer

of (1*R*)-3-hydroxy-1-methylpropyl [^{16}O , ^{17}O , ^{18}O]sulphate,^{2‡} indicating that the sulphuryl transfer reaction has proceeded with inversion of configuration at sulphur.

Phenyl [^{16}O , ^{17}O , ^{18}O]sulphate was also prepared by way of the crystalline diastereoisomer of phenyl 3β-cholestanol [^{18}O]sulphite. Although an X-ray crystallographic structural analysis of the unlabelled phenyl 3β-cholestanol sulphite was not performed, the phenyl [^{16}O , ^{17}O , ^{18}O]sulphate was shown to have the same configuration as the phenyl [(*R*)- ^{16}O , ^{17}O , ^{18}O]sulphate obtained from phenyl epiandrosterone [^{17}O , ^{18}O]sulphate **3**, by transfer of the labelled sulphuryl group to (1*R*)-3-benzoyloxy-1-methylpropan-1-ol (*vide supra*), followed by alkaline hydrolysis, cyclization with

‡ The ' ^{17}O -water' used for the preparation of the ruthenium [$^{17}\text{O}_4$]tetroxide contained 45% ^{17}O , 20.2% ^{16}O and 34.8% ^{18}O so where sites are shown as ^{17}O it should be realised that a fraction of those sites will contain ^{16}O and ^{18}O .

sulphuryl chloride and FTIR analysis.² Hence the phenyl 3 β -cholestanol sulphite must also have the (*R*_S)-configuration.

The authors gratefully acknowledge support for this work from the SERC and for a Violette and Samuel Glasstone Research Fellowship (to C. L. L. C.).

Received, 15th July 1991; Com. 1/03589D.

References

- 1 G. Lowe and S. J. Salamone, *J. Chem. Soc., Chem. Commun.*, 1984, 466.
- 2 G. Lowe and M. J. Parratt, *J. Chem. Soc., Chem. Commun.*, 1985, 1075; G. Lowe and M. J. Parratt, *Bioorg. Chem.*, 1988, **16**, 283.
- 3 C. L. L. Chai, V. Humphreys, K. Prout and G. Lowe, *J. Chem. Soc., Chem. Commun.*, in the press.
- 4 T. W. Hepburn and G. Lowe, *J. Labelled Compd. Radiopharm.*, 1990, **28**, 617.
- 5 W. C. Still, M. Kahn and A. Mitra, *J. Org. Chem.*, 1978, **43**, 2923.
- 6 G. Lowe and S. J. Salamone, *J. Chem. Soc., Chem. Commun.*, 1983, 1392.
- 7 A. Brandstrom, B. Lamm and I. Palmertz, *Acta Chem. Scand., Sect. B.*, 1974, **28**, 699.
- 8 Prepared from (*R*)-butane-1,3-diol, [α]_D²¹ – 31° (c 1, EtOH) by the method of S. Kim, H. Chang and W. J. Kim, *J. Org. Chem.*, 1985, **50**, 1751.