Steric Control of *S*-Oxidation of 1,4-Oxathian Derivatives

By A. B. FOSTER

(*Chester Beatty Research Institute, Institute of Cancer Research: Royal Cancer Hospital, Fulham Road, London, S.W.3*)

and Q. H. HASAN, D. R. HAWKINS, and J. M. WEBBER*

(*Chemistry Department, The University, P.O. Box 363, Birmingham 15*)

IN continuing our study of an approach[1] to the stereospecific synthesis of naturally occurring asymmetric sulphoxides,[2] which utilises 1,4-oxathian derivatives formed from simple glycosides, the response of these compounds to *S*-oxidation reagents[3] has been further examined .

In contrast to the behaviour of 4-substituted thians, which undergo preponderant *ax*-*S*-oxygenation with periodate[4] to give *cis*-*S*-oxides, (2*R*, 6*S*)-2-hydroxymethyl-6-methoxy-1,4-oxathian [(I), derived[5] from methyl α-D-glucopyranoside] reacts[3] under similar conditions to give > 90% of the *eq*-sulphoxide (II). This behaviour has been rationalised[3] in terms of steric hindrance to *ax*-*S*-oxygenation by the *ax*-methoxyl-group at the anomeric centre, assuming that the sulphide (I) reacts in the chair conformation depicted; the chair conformation (I) is favoured[3,6] in chloroform at room temperature. The above steric effect should be absent from 1,4-oxathian derivatives carrying *eq*-substituents, and we now report on the synthesis and reaction with periodate of (2*R*, 6*R*)-2-hydroxymethyl-6-methoxy-1,4-oxathian (III) and the related compounds (XIII) and (XVIII).

Treatment of methyl 6-*O*-trityl-β-D-glucopyranoside in sequence[5] with lead tetra-acetate, borohydride, and azobenzene-*p*-sulphonyl chloride–pyridine gave the diazobenzene-*p*-sulphonate {(IV), m.p. 64—65°, $[\alpha]_{5461}^{24}$ +33°}.† The sulphonate (IV), with sodium sulphide–boiling methanol,[5] afforded (2*R*,6*R*)-2-methoxy-6-trityloxymethyl-1,4-oxathian {(V), m.p. 116—117°, $[\alpha]_{D}^{30}$ −56°} which was hydrogenolysed over palladised charcoal to give (2*R*,6*R*)-2-hydroxymethyl-6-methoxy-1,4-oxathian {(III), b.p. 115—120° (bath)/0·05 mm., $[\alpha]_{D}^{27}$ −108° (MeOH)}. Treatment of the sulphide (III) with aqueous, ethanolic sodium periodate gave a mixture of the sulphoxides (VI) and (VII), in the ratio *ca.* 10 : 1, from which the *ax*-sulphoxide {(VI), m.p. 121—123°, $[\alpha]_{D}^{30}$ −132°; monohydrate, m.p. 76—78°, $[\alpha]_{D}^{30}$ −132°} was isolated by chromatography on silica gel. With ozone, the

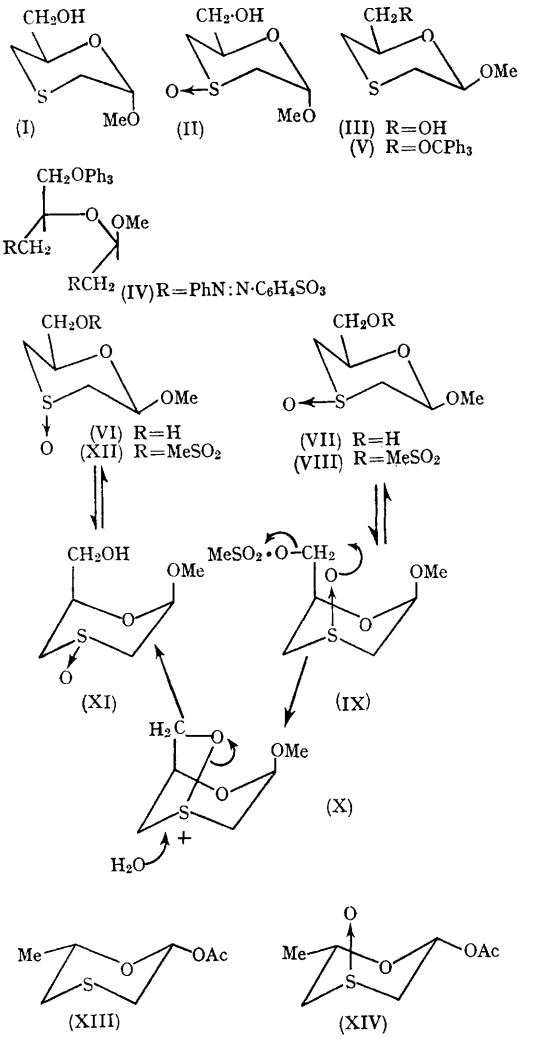
† [α]-Values for $CHCl_3$, unless stated otherwise.

sulphide (III) gave an approximately equimolar mixture of the sulphoxides (VI) and (VII) from which the *eq*-sulphoxide {(VII), m.p. 115—116°, $[\alpha]_D^{30}$ −125°} was isolated by chromatography.

The configuration of the *eq*-sulphoxide (VII) was established from the observation that its methanesulphonate {(VIII), m.p. 105—107°, $[\alpha]_D^{27}$ + 52°} underwent complete solvolysis in less than 1 hr. in water at 95° when the pH was maintained at 7. The sole detectable product was the *ax*-sulphoxide (VI) which was presumably formed[3,7] by the reaction sequence (VIII) → (IX) → (X) → (XI) → (VI). The sequence is depicted for convenience in terms of chair conformations but, clearly, other conformations may be involved. The methanesulphonate {(XII), m.p. 63—64°, $[\alpha]_D^{27}$ +76°} of the *ax*-*S*-oxide (VI) reacted slowly (*ca.* 5% in 3·5 hr.) under the above solvolytic conditions to give the parent sulphoxide (VI) (chromatographic identification). No conformation is possible for the methanesulphonate (XII) which will permit intramolecular attack by the sulphoxide oxygen atom on the methylsulphonyloxymethyl group.

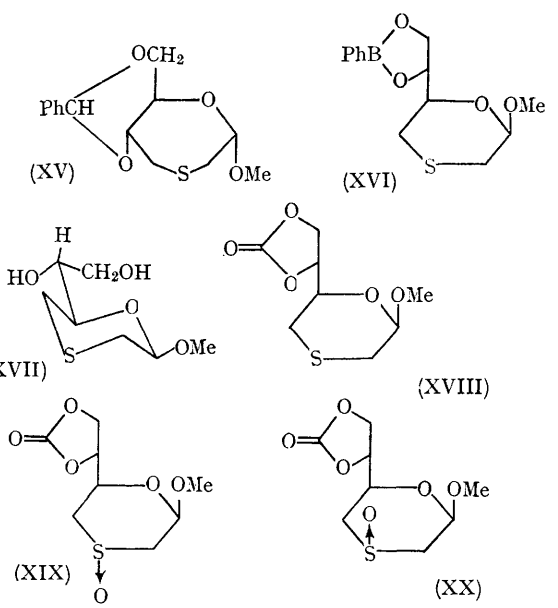
Treatment of methyl 4,6-*O*-benzylidene-α-D-glucopyranoside in sequence[5] with periodate, borohydride, methanesulphonyl chloride–pyridine, and sodium sulphide–boiling methanol afforded (1*R*, 3*S*, 7*R*, 9*R*)-3-methoxy-9-phenyl-2,8,10-trioxa-5-thiabicyclo[5,4,0]undecane {(XV), m.p. 154—155°, $[\alpha]_D^{25}$ +126°}. With hot 1% methanolic hydrogen chloride, compound (XV) yielded a mixture of the 6*R* and 6*S* forms of (1′*R*,2*R*)-2-(1′,2′-dihydroxyethyl)-6-methoxy-1,4-oxathian, in the ratio *ca.* 2 : 1, from which the 6*R* isomer (XVII, m.p. 77—78°, $[\alpha]_D^{25}$ −61°) was isolated *via* conversion into the benzeneboronate {(XVI), m.p. 94—95°, $[\alpha]_D^{25}$ +18°} and saponification[8] with Amberlite resin IRA-400 (HO^- form). The *R* configuration[9] at position 6 in compound (XVII) was established by treatment in sequence with periodate, borohydride, and triphenylmethyl chloride–pyridine, which gave a trityl ether (m.p. 115—116°, $[\alpha]_D^{30}$ −71°) identical with compound (V). The diol (XVII) underwent glycol cleavage with 1 mol. of periodate without detectable *S*-oxidation.

With phosgene–pyridine, the diol (XVII) gave the cyclic carbonate {(XVIII), m.p. 110—111°, $[\alpha]_D^{25}$ −43·5°} which, with periodate–50% aqueous ethanol, afforded the *ax*-sulphoxide {(XIX), m.p. 154—155°, $[\alpha]_D^{25}$ −80°} with only traces of the *eq*-isomer (XX). However, with ozone–dichloromethane, the cyclic carbonate (XVIII) gave a mixture of sulphoxides (*ax* : *eq* ratio, *ca.* 2 : 1) from which the *eq*-sulphoxide {(XX), m.p. 173—174°, $[\alpha]_D^{25}$ −39°} was isolated by chromatography on silica gel. The configuration of sulphoxide (XIX) was established when treatment with barium hydroxide gave a diol which, with periodate and borohydride in sequence, gave the *ax*-*S*-oxide (VI). Likewise, the sulphoxide (XX) was converted into the *eq*-*S*-oxide (VII).



The behaviour of the 1,4-oxathian derivatives (III) and (XVIII) with periodate thus corresponds closely with that of 4-substituted thians. In each case, there is preponderant *ax*-*S*-oxygenation, provided it is assumed that the compounds react in the chair conformation having equatorial substituents. It has been established by the n.m.r. method[6] that, in chloroform solution, the 1,4-oxathian (III) and the sulphoxides (VI) and (VII) exist in the equatorially-substituted chair

conformations depicted. Under these conditions, a similar conformation (XIII) is adopted[6] by (2*R*,6*S*)-2-acetoxy-6-methyl-1,4-oxathian which also gives mainly the *ax*-*S*-oxide (XIV) with periodate.[10]



With ozone, there is a significant difference in the behaviour of the oxathians and the 4-substituted thians. Whereas the latter compounds undergo markedly preponderant *eq*-*S*-oxygenation with this reagent, the oxathians (III) and (XVIII) give substantial proportions (~50 and ~65%, respectively) of the *ax*-sulphoxides. This behaviour, coupled with the difficulties associated with the large-scale separation of mixtures of stereoisomeric sulphoxides such as (VI) and (VII) and (XIX) and (XX), largely deprives oxidant variation of utility as an approach to the large-scale preparation of pairs of stereoisomeric sulphoxides in the 1,4-oxathian series. The control of *S*-oxidation of derivatives of 2-hydroxy-1,4-oxathian is best achieved by variation of configuration at the anomeric centre; an *ax*-substituent (*e.g.*, OMe or OAc) engenders *eq*-*S*-oxygenation,[3,6] whereas, as shown here, an *eq*-anomeric substituent leads to an *ax*-*S*-oxide.

Clearly, there is a delicate balance of steric effects in these reactions, and this confers valuable flexibility in the selection of synthetic routes. Moreover, the reactions described herein illustrate the variety of synthetic methods usable in the 1,4-oxathian *S*-oxide series, since, in no case, was evidence obtained for sulphoxide racemisation.

(*Received, May 27th*, 1968; *Com.* 682.)

[1] K. W. Buck, F. A. Fahim, A. B. Foster, A. R. Perry, and J. M. Webber, Abs. Amer. Chem. Soc. Meeting, Atlantic City, September, 1965, p. 18D.
[2] A. I. Virtanen, *Angew. Chem. Internat. Edn.*, 1962, **1**, 299; A. Kjaer, *Pure Appl. Chem.*, 1963, **7**, 229.
[3] K. W. Buck, A. B. Foster, A. R. Perry, and J. M. Webber, *Chem. Comm.*, 1965, 433.
[4] C. R. Johnson, *J. Amer. Chem. Soc.*, 1963, **85**, 1020; C. R. Johnson and D. McCants, *ibid.*, 1964, **86**, 2935; 1965, **87**, 1109.
[5] K. W. Buck, F. A. Fahim, A. B. Foster, A. R. Perry, M. H. Qadir, and J. M. Webber, *Carbohydrate Res.*, 1966, **2**, 14.
[6] A. B. Foster, T. D. Inch, M. H. Qadir, and J. M. Webber, following Communication.
[7] J. C. Martin and J. J. Uebel, *J. Amer. Chem. Soc.*, 1964, **86**, 2936.
[8] A. B. Foster, A. H. Haines, T. D. Inch, M. H. Randall, and J. M. Webber, *Carbohydrate Res.*, 1965, **1**, 145.
[9] R. S. Cahn, C. K. Ingold, and V. Prelog, *Experientia*, 1956, **12**, 81.
[10] K. W. Buck, A. B. Foster, W. D. Pardoe, M. H. Qadir, and J. M. Webber, *Chem. Comm.*, 1966, 759.