Sulphoxides of Methyl 2,6-Anhydro-2-thio-α-D-altropyranoside. Comments on the Assignment of Sulphoxide Configuration by the Nuclear Magnetic Resonance Method

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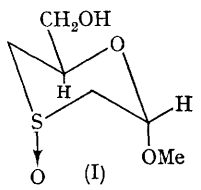
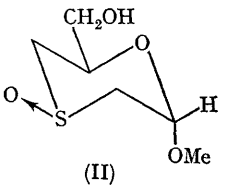
THE n.m.r. spectra of 1,4-oxathian *S*-oxide derivatives, possessing an axial sulphoxide group (*e.g.*, I and III) reveal significant deshielding (0·75–0·80 p.p.m. in $CDCl_3$) of the protons in *syn*-axial positions [H-6 in (I), H-2 and H-6 in (III)] in comparison with the isomeric sulphoxides (II and IV). The deshielding was attributed[1] to a proximity effect[2] and/or acetylenic type anisotropy of the S → O bond (collectively, the *syn*-axial effect), and attention was drawn[1] to the possibility of utilising this effect as an additional method of assigning absolute configuration to suitable pairs of stereoisomeric sulphoxides. Such a method would be of particular value in a proposed approach[3] to the stereospecific synthesis of naturally occurring, asymmetric sulphoxides. Comparable *syn*-axial effects have been reported recently by Dodson and co-workers[4] and the wealth of data now available indicates that the n.m.r. method of assigning sulphoxide configuration may be reliably applied in the appropriate cases.

In the crystal state,[5] sulphoxide (II) has essentially the structure shown, but, because of the potential flexibility of the molecule [and of the analogues, (I), (III), and (IV)] it is uncertain which conformation is adopted in solution. The existence of compounds (I)—(IV) in the chair forms depicted has been provisionally inferred[1] from the


(I)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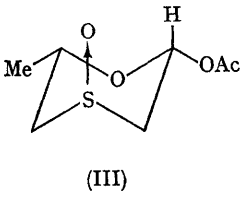
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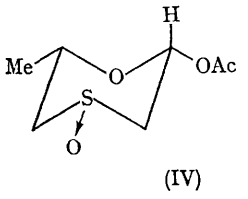
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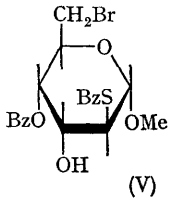
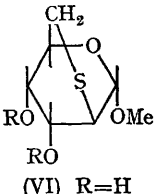
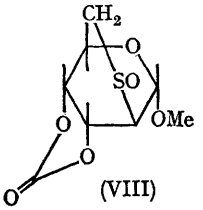
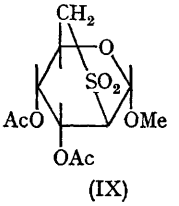

(V)


(VI) R=H
(VII) R=Ac


(VIII)


(IX)

nature of the signal for the respective anomeric protons (H-2), but confirmation must await a full analysis of the n.m.r. spectra. In order to validate the magnitude of the *syn*-axial effect and to obtain information on the effect of the S → O group on other neighbouring protons, measurements on suitable rigid molecules are desirable and we now report on the synthesis and relevant n.m.r. data for the sulphoxides of methyl 2,6-anhydro-2-thio-α-D-altropyranoside (VI).

Reaction of methyl 2-*S*-benzoyl-4,6-*O*-benzylidene-2-thio-α-D-altropyranoside[6] with *N*-bromosuccinimide[7] followed by treatment of the resulting non-crystalline bromo-compound (V) with methanolic sodium methoxide at 0° gave the anhydride (VI) {m.p. 71—72°, $[\alpha]_D$ +45° ($CHCl_3$); diacetate (VII), m.p. 102—103°, $[\alpha]_D$ +100° ($CHCl_3$)}. The structure of (VI) was established by reductive desulphuration,[8] followed by treatment with phenyl isocyanate which gave the known[9] dicarbanilate of methyl 2,6-dideoxy-D-*ribo*-hexopyranoside. The 3,4-cyclic carbonate {m.p. 127—128° (decomp.), $[\alpha]_D$ +79° ($CHCl_3$)} of (VI) reacted with boiling aqueous ethanolic sodium metaperiodate to give the sulphoxides (VIII) {*R*, m.p. 189—190°, $[\alpha]_D$ +78·5° (pyridine); and *S*, m.p. 204—205°, $[\alpha]_D$ +53° (pyridine)}. Saponification of the sulphoxides (VIII) gave the diol sulphoxides (XI) {*R*, m.p. 170—171°, $[\alpha]_D$ +36° ($CHCl_3$); diacetate (XIII), m.p. 192—193°, $[\alpha]_D$ −143° ($CHCl_3$)} and (X) {*S*, m.p. 164—165°, $[\alpha]_D$ +20° ($CHCl_3$); diacetate (XII), m.p. 101—102°, $[\alpha]_D$ +230° ($CHCl_3$)}. The diol sulphoxides, (X) and (XI), [also obtainable by the action of hydrogen peroxide on (VI)] were converted into the same sulphone {m.p. 212—213°, $[\alpha]_D$ +21° (pyridine); syrupy diacetate (IX)} by peracetic acid.

The n.m.r. data for the diacetates, (VII, IX, XII, and XIII) are recorded in the Table. The spectra could be analysed by first-order methods, and confirmatory decoupling experiments were carried out. Only the salient features of the spectra are noted herein; a full analysis will be presented elsewhere.

Each ring of the oxathiabicyclo[2,2,2]octane system in the diol (VI) and its derivatives is constrained to a near-boat conformation, but, unlike the carbocyclic analogue, there is limited flexibility. The favoured conformation will permit the greatest alleviation of the non-bonded interactions between the oxygen atoms attached to C-1, C-3, and C-4 and this will involve distortion of the ring system towards the conformation with a dihedral angle of *ca.* +13° for H-3–H-4 (with consequent dihedral angles of *ca.* 51° and *ca.* 69° for H-5–H-6 and H-5–H-6′). The values of the coupling constants, $J_{3,4}$, $J_{5,6}$, and $J_{5,6'}$, shown in the Table for the sulphoxide diacetates, (XII) and (XIII), are consistent with such a distortion towards this conformation, although precise dihedral angles cannot be associated with the *J* values.[10]

The operation of a *syn*-axial effect should result in deshielding by the S → O group of H-1 in the (*S*)-sulphoxide (XII) and H-3 in the (*R*)-isomer (XIII) since, in the respective isomers, H-1 or H-3 and the S → O group are in positions closely similar to the *syn*-axial arrangement in a chair conformation. The chemical shift data in the Table show that the H-1 signal in the sulphoxide diacetate (XII), m.p. 101—102°, is at relatively low field, as is the H-3 signal in the isomer (XIII), m.p. 192—193°, and a confident assignment of (*S*)- and (*R*)-chirality, respectively, at the sulphoxide centres may be made. These assignments are

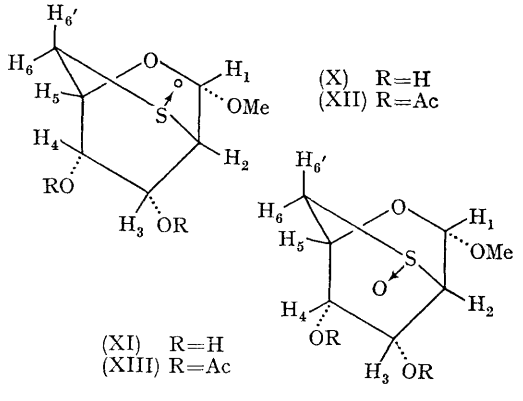
TABLE

N.m.r. data[a] *for methyl* 3,4-*di*-O-*acetyl*-2,6-*anhydro*-2-*thio*-α-D-*altropyranoside*[b] (VII) *and the derived sulphoxides* (XII and XIII) *and sulphone* (IX).

Compound	H-1	H-2	H-3	H-4	H-5	H-6	H-6′	OMe	OAc	$J_{1,2}$	$J_{1,3}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6}$	$J_{5,6'}$	$J_{6,6'}$
(VII)	4·87	6·94	4·71	5·02	5·60	6·92	7·32	6·57	7·98 7·91	1·2	1·2	2·9	8·8	1·2	3·8	2·2	12·0
(XIII) (*R*) (m.p. 192—193°)	5·33	6·38	4·24	4·68	5·63	6·30	7·57	6·54	7·92 7·89	1·5	0·9	1·5	9·0	2·2	5·0	1·3	14·1
(XII) (*S*) (m.p. 101—102°)	4·62	6·43	5·27	5·08	5·48	7·22	6·70	6·50	7·92 7·89	1·8	1·2	1·5	8·5	2·2	5·2	1·5	15·0
(IX)	4·53	6·43	4·32	4·72	5·35	6·44	6·72	6·51	7·92 7·88	1·5	1·5	1·5	8·9	2·3	5·5	1·6	13 8

[a] N.m.r. spectra were obtained at 100 Mc./sec. with a JEOL, JNM-4H-100 spectrometer for 5% solutions in $CDCl_3$ with tetramethylsilane as internal reference. Chemical shifts are given on the τ scale and J values in c./sec. The overall pattern was not changed when acetone or [$^2H_6$]dimethyl sulphoxide was used as solvent.

[b] A comparable complete first-order analysis was also obtained for the (*R*)-{m.p. 139—140° (decomp.), $[\alpha]_D$ −44° ($CHCl_3$)} and (*S*)-ditoluene-*p*-sulphonates {m.p. 158—159°, $[\alpha]_D$ +116° ($CHCl_3$)} derived from the (*R*)- and (*S*)-diol sulphoxides, (XI)and (X).



supported by other chemical shift data. The signals for H-6′ in the (*S*)-sulphoxide (XII) and for H-4 and H-6 in the (*R*)-isomer (XIII) also indicate deshielding. In the case of H-6 and H-6′, this is a vicinal effect and is well illustrated by a comparison of the relevant chemical shifts for compounds (VII, IX, XII, and XIII). The similar chemical shifts for H-2 (and also for H-5) in the sulphoxide diacetates (XII and XIII), are to be expected because of the near-symmetrical location of these protons and the S→O bond. These results suggest that the chemical shift data for all protons in the immediate environment of a sulphoxide group may be of value in assigning configuration.

The magnitude of the *syn*-axial effect for H-1 and H-3 in the sulphoxide diacetates, (XII and XIII), is 0·71 and 1·03 p.p.m. respectively, which is of similar magnitude to that (0·75—0·80) observed for the pairs of sulphoxides (I) and (II), and (III) and (IV). Confirmation is thus provided for the chair conformations (I)—(IV) previously assigned to these oxathian derivatives.

(*Received, July 11th*, 1967; *Com.* 720.)

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