The Absolute Configuration of Sulphoxides: 2-Thia-5α-androstan-17β-ol Oxides

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IN order to correlate the absolute configurations of cyclic sulphoxides with their o.r.d. spectra,[1] the isomeric 2-thia-5α-androstan-17β-ol oxides [(II) and (III)] were studied. Because of the ease of location of the shifts of the angular methyl groups, the n.m.r. spectra were most useful in assigning absolute configurations. Assignments, so made, were correlated with assignments of configuration based on stereoselective oxidation,[1,2] chromatographic behaviour,[1,2] and infrared spectra.[3]

2-Thia-5α-androstan-17β-ol (I), n.m.r.† ($CDCl_3$), 45 (18-CH_3), 64 (19-CH_3) c./sec. was prepared from 17β-acetoxy-5α-androst-1-en-3-one (IV) by the series of reactions depicted below.[4] Oxidation of (I) with perbenzoic acid gave 2-thia-5α-androstan-17β-ol 2α-oxide (II), m.p. 262—263° (87·5% yield);

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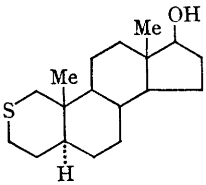
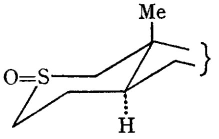
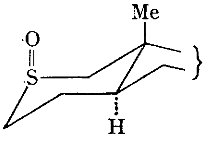
† The n.m.r. spectra were recorded at 60 Mc./sec. and are measured downfield from tetramethylsilane.



(I)

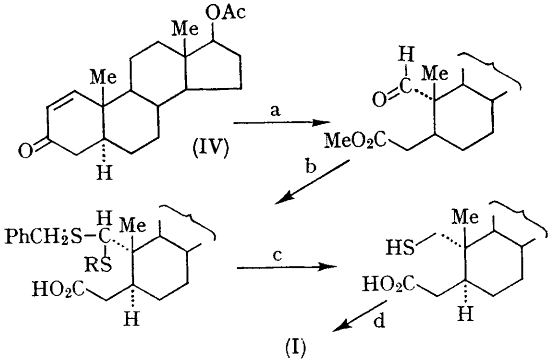


(II) (*S*)



(III) (*R*)

λ_{max} ($CHCl_3$) 1028 cm.$^{-1}$; n.m.r. ($CDCl_3$) 45 (18-CH_3), 59 (19-CH_3) c./sec. 2-Thia-5α-androstan-17β-ol 2β-oxide (III), m.p. 236—237°; λ_{max} ($CHCl_3$) 1023 cm.$^{-1}$; n.m.r. ($CDCl_3$) 45 (18-CH_3), 80 (19-CH_3) c./sec. was obtained by isomerization of (II) with hydrogen chloride–dioxan[5] and separation of (II) and (III) chromatography.



R=$PhCH_2$

Reagents: a, O_3, NaOH, MeOH; b, $PhCH_2SH$; c, Li–NH_3; d, $LiAlH_4$, H^+–toluene.

Configurations were assigned to sulphoxides (II) and (III) from the fact that perbenzoic acid stereoselectively oxidized (I) to predominately the equatorial sulphoxide,[1,2] (II), from their chromatographic behaviour [(III) was eluted prior to (II)],[1,2] and from their infrared spectra.[3]

Excellent corroboration for these configurations was obtained from studies of the n.m.r. spectra of (II) and (III). Very recently Buck and his co-workers,[6] by a study of the n.m.r. spectra of diastereomeric sulphoxides, whose structures were established by *X*-ray analysis of one of them, have shown that the anisotropy of the S=O bond is of the acetylenic type (relative to the free electron pair on the same sulphur atom). A complete analysis of the n.m.r. spectra of *cis*- and *trans*-2,4-diphenylthietanes,[7] their mono- and di-oxides, has led to the same conclusion. A similar conclusion was reached by Samitov[8] from the analysis of the n.m.r. spectra of cyclic sulphites. Analysis of the spectra of the cyclic sulphites of pentane-2,4-diol, prepared by Lauterbur *et al.*,[9] with the structures assigned by Overberger *et al.*,[10] also led to this same conclusion.

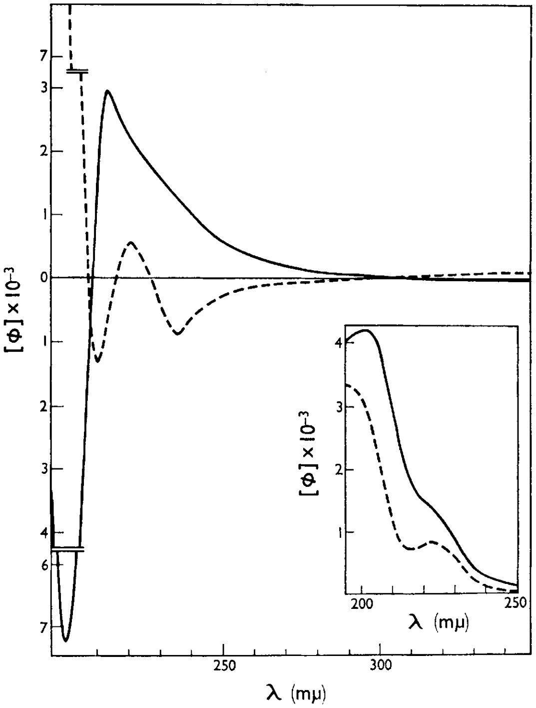


FIGURE. *Optical rotatory dispersion curves and ultraviolet spectra of 2-thia-5α-androstan-17β-ol 2α-oxide* (II) (- - -) *and 2-thia-5α-androstan-17β-ol 2β-oxide* (III) (——). *All spectra were determined in acetonitrile solution.*

The shift of the 19-CH_3 group in the n.m.r. spectra [64 c./sec for (I), 59 for (II), and 80 for (III) ($CDCl_3$)] clearly establishes the configurations assigned to (II) and (III). This conclusion was further verified by determination of the n.m.r. spectra of (II) and (III) in benzene [19-CH_3 group of (II), 40 c./sec.; 19-CH_3 group of (III), 76]. The change of the 19-CH_3 shift with change of solvent [($CDCl_3$–C_6H_6) = 19 c./sec. for 19-CH_3 of (II); =4 for 19-CH_3 of (III)] is in agreement with expectations for dipoles oriented as in (II) and (III) above.[11]

The u.v. and o.r.d. spectra of (II) and (III) are shown in the accompanying figure. Comparison of these spectra with those in the preceding Communication provide evidence for the following tentative conclusions: (1) The absolute configuration of dissymmetric, β-substituted thian oxides can be determined from their o.r.d. spectra if the perturbing groups are hydrocarbon residues. β-Substituted thian oxides (chair conformation) with an *R*-configuration have a positive Cotton effect associated with the electronic transition found at short wavelength (*ca.* 200 mμ). (2) Both electronic transitions, that at *ca.* 220 mμ as well as that at *ca.* 200 mμ, are optically active. (3) While the configurations at sulphur of these *R* and *S* sulphoxides are opposite to each other, the dissymmetrically substituted sulphoxide chromophores are diastereomeric, and not enantiomeric. Consequently, the o.r.d. spectra are not enantiomeric. The difference (other than that of sign) between the o.r.d. spectra for the *R* and the *S* epimers, reflect the differences in the relative positions of the hydrocarbon residues surrounding the symmetric sulphoxide chromophore. As can be seen, the differences in spatial orientation of these hydrocarbon residues have a pronounced effect on the o.r.d. spectra. Any detailed analysis of the o.r.d. spectra of optically active sulphoxides must take into consideration configurational and conformational effects. (4) It may be possible to distinguish between axial and equatorial thian oxides by comparison of their u.v. spectra. The two transitions (at *ca.* 200 and 220 mμ) are closer together in axial sulphoxides.‡ Equatorial sulphoxides show a distinctly separated maximum rather than merely a shoulder for the electronic transition at *ca.* 220 mμ.

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‡ The anomolous ultraviolet spectrum of *endo*-1,8,8-trimethyl-3-thiabicyclo[3,2,1]octane oxide may be explained on this basis.

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[11] See P. Laszlo and D. H. Williams, *J. Amer. Chem. Soc.*, 1966, **88**, 2799, and references contained therein for similar studies on ketones. J. Ronayne and D. H. Williams, *Chem. Comm.*, 1966, 712.