The Absolute Configuration of Sulphoxides: Mass Spectra of 3β-Hydroxy-20-thia-17(α and β)-pregn-5-ene Oxides

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WE have used mass spectra to correlate the absolute configurations of the isomeric, optically active sulphoxides [(I), (II), (III), and (IV)]. These compounds were synthesized by methods previously described[1] and were interrelated by the reactions depicted in Chart 1. The absolute configurations[2] of the sulphoxides were assigned initially by comparison of the o.r.d. and c.d. spectra of (V) and (VI) with those of dissymmetric alkyl aryl sulphoxides[3–5]; c.d. (MeCN), (V), λ_1 243 mμ, $[\theta]$ $-$ 25,800°; λ_2 217 mμ, $[\theta]$ $+$ 52,300°; (VI), λ_1 252·5 mμ, $[\theta]$ $+$ 17,600°; λ_2 215 mμ, $[\theta]$ $-$ 52,000°. These assignments were confirmed by a study of the relative rates of pyrolysis of (I) and (II).[4] Thus, (II) was converted into androsta-5,16-dien-3β-ol (82% yield) when heated in xylene (139°) for 6 hr. Similar treatment of (I) resulted in recovery of 85% of the unchanged starting material.

The relative importance of the reactions shown in Chart 2 were determined for each isomer [(I)—(IV)] by calculating the relative abundance of the ions $C_{20}H_{32}OS^+$ (reaction A), $C_{19}H_{29}O^+$ (reaction B), and $C_{19}H_{28}O^+$ (reaction C) from mass spectra[6]† of each isomer. With the 17α-compounds, the rate of reaction C for the (*R*)-sulphoxide (II) should be greater than that for the (*S*)-sulphoxide (I). With a planar transition state for the *cis*-elimination reaction, the 21-methyl group of compound (I) is *ca.* 1·2 Å from the 12α-H atom (methyl-C, 12α-H distance). For the (*R*)-sulphoxide (II), only the unshared pair of electrons on sulphur could be in a sterically crowded position in the planar-transition state. On the other hand, the rates of reactions A and B for the 17α-sulphoxides (I, II) should be influenced far less by the configuration of the sulphoxides. Consequently, differences in the ratios of rates for the reactions

Ratios of ion abundances

Compound		$\frac{C_{19}H_{28}O^+}{C_{20}H_{32}OS^+}$	$\left[\frac{k_C}{k_A}\right]$	$\frac{C_{19}H_{28}O^+}{C_{19}H_{29}O^+}$	$\left[\frac{k_C}{k_B}\right]$
		3rd	*4th*	*3rd*	*4th*
(I)	(17α, *S*)	0·75	0·89	1·71	1·67
(II)	(17α, *R*)	3·53	3·77	2·84	2·74
(III)	(17β, *S*)	0·19	0·20	0·58	0·50
(IV)	(17β, *R*)	0·12	0·15	0·43	0·42

† Throughout, the identities of the M $-$ [O] (reaction A) and the M $-$ [H_2O] ions were easily established from the relative intensities of the 316 to 322 *m/e* peaks. In a similar way the identities of the $C_{19}H_{29}O^+$ and $C_{19}H_{28}O^+$ ions were established from the relative intensities of the 268 to 275 *m/e* peaks. With the exception of the latter ions from (II) (275 *m/e* was too large) the experimental and calculated values for 274, 275, 321 and 322 *m/e* were within experimental error.

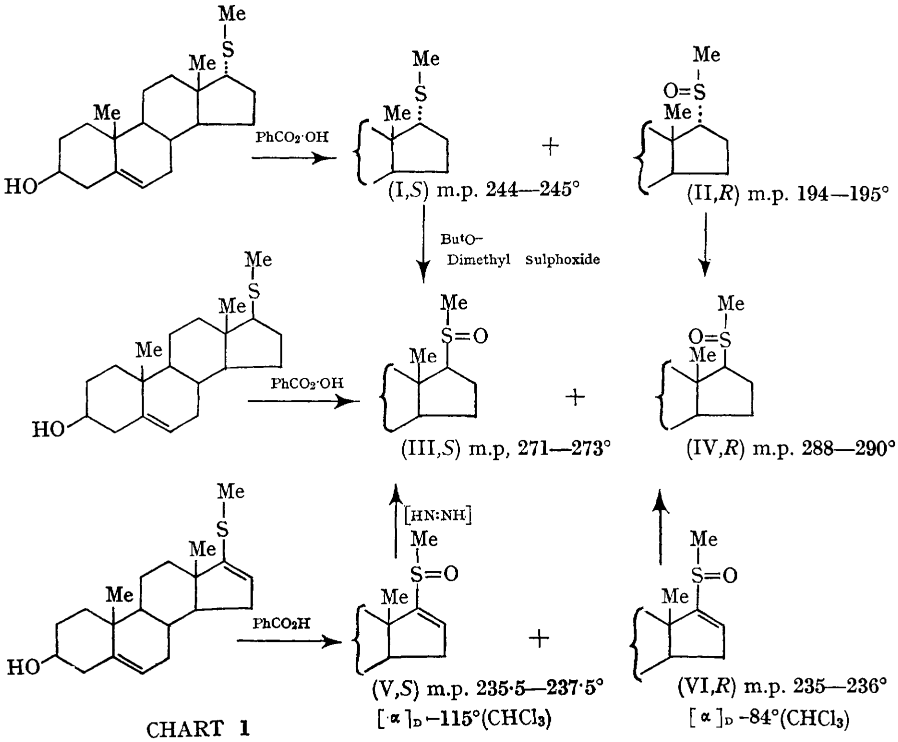

CHART 1

(k_C/k_A or k_C/k_B) should reflect differences in the configurations of the sulphoxides (I and II). The relative rates of the reactions, in turn, should be directly related to the relative abundance of the ions found in the mass spectra. The ratios of ion abundances are given in the Table. The values of the ratios for these sulphoxides fit the above predictions. It should be noted that the configurations of the sulphoxides (I and II) are destroyed by reactions A, B, and C. The relative abundance of *identical* ions from sulphoxides (I and II) are compared. Further fragmentation of these ions should be largely independent of source.

Similarly, with the 17β-isomers, the rate of reaction C should be greater with the (S)-oxide than with the (R)-oxide, while reactions A and B should be influenced to a lesser extent by the configuration of the sulphoxides. Again, these predictions are reflected in the ratios of ion abundances listed in the Table.‡

Compounds (II) and (IV) sublimed virtually unchanged when heated for 1 min. at 190° at

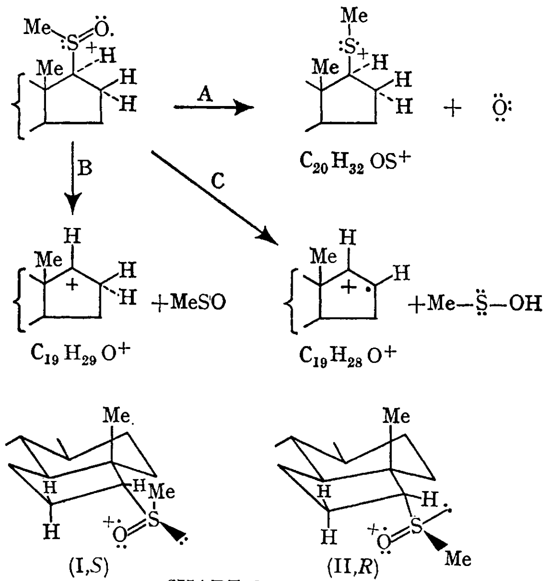

CHART 2

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‡ The mass spectra of (III) and (IV) were originally run at 210° with full scans from 12 to 400 *m/e*. The time of each scan, though not carefully measured, was considerably longer than that of the spectra reported above. The M — [O] peak was considerably weaker than in the spectra obtained rapidly at 190°. The ratios of ions $[C_{19}H_{28}O^+]/[C_{20}H_{32}OS^+]$ and $[C_{19}H_{28}O^+/[C_{19}H_{29}O^+]$ from (III) and (IV) from mass spectra obtained at 210° followed the same pattern as shown in the Table.

10^{-4} mm. This provides evidence for the vaporization of the unchanged sulphoxides [(I)—(IV)] in the mass spectrometer. Nevertheless, concomitant with the unimolecular ionic reactions depicted in Chart 2 are possible pyrolytic decompositions of the isomeric sulphoxides. For this reason spectra were determined under conditions as nearly comparable as possible. Approximately equal quantities of the compound [(I)—(IV)] in capillary tubes were introduced *via* the direct inlet probe at a temperature of 190°. Scanning from 200 to 370 *m/e* was initiated immediately and continued until the total ion current was stable for a period of two or more scans. Each scan took approximately seventy seconds; the third and fourth scans for each compound were satisfactory. Since the pyrolytic reaction proceeds largely through a mechanism comparable to C and is subject to similar steric effects, addition of the results of the pyrolytic reaction to those of the ionic reactions would not change the stereochemical conclusions reached above.

Stereochemical differences have been destroyed in the ions $C_{19}H_{28}O^+$ (reaction C) and $C_{19}H_{29}O^+$ (reaction B) from any of the four isomers [(I)—(IV)]. Comparisons of the ratios of these ions enable one to compare relative rates of reactions C and B for pseudo-axial and pseudo-equatorial side-chains. As can be seen from the Table, this ratio is greater for those compounds with a pseudo-axial than for those with pseudo-equatorial side-chain. This could imply that the differences in energy of the transition states of reactions of type C for axial and equatorial side-chains are greater than the differences in energy of the transition states of reaction of type B for axial and equatorial side-chains. On the other hand, the greater ratios for the 17α-isomers may merely indicate a greater contribution of the pyrolytic reaction.

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[1] R. M. Dodson and P. B. Sollman, U.S. Pat., 2,753,361/1956; 2,806,042/1957; 2,847,427/1958.

[2] Structural formulas conform to the convention adopted by L. F. Fieser for depicting isomeric 20-hydroxypregnanes (L. F. Fieser and M. Fieser, "Steroids," Reinhold, New York, 1959, 337).

[3] K. Mislow, M. M. Green, P. Laur, J. T. Mellio, T. Simmons, and A. L. Ternay, *J. Amer. Chem. Soc.*, 1965, **87**, 1958. An optically-impure sample of *trans-R*(+)-methyl propenyl sulphoxide also had an o.r.d. spectrum similar to that of compound (VI). For the absolute configuration of *trans*-(+)-methyl propenyl sulphoxide see P. Bickart, M. Axelrod, J. Jacobus, and K. Mislow, *J. Amer. Chem. Soc.*, 1967, **89**, 697.

[4] D. N. Jones and M. J. Green, *J. Chem. Soc.* (*C*), 1967, 532; D. N. Jones, M. J. Green, M. A. Sneed, and R. D. Whitehouse, *Chem. Comm.*, 1967, 1003; S. I. Goldberg and M. S. Sahli, *J. Org. Chem.*, 1967, **32**, 2059.

[5] Superimposed on the o.r.d. spectra of the αβ-unsaturated sulphoxides is the spectrum of the $\Delta^{5,6}$ double bond (A. Yogev, D. Amar, and Y. Mazur, *Chem. Comm.*, 1967, 339.) However, since the Cotton effect for the latter chromophore occurs at lower wavelength and since it probably will be the same for both isomers (V) and (VI), it should not interfere with the interpretation of the spectra. These spectra provide additional evidence that αβ-unsaturated sulphoxides are inherently dissymmetric (ref. 3 and 4).

[6] The mass spectra were determined with a Hitachi Perkin-Elmer model RMU-6D mass spectrometer; ionizing voltage, 50 e.v. at 100 microamperes. Molecular ion peaks were not apparent in any of the spectra, although a weak $M + 1$ peak appeared for compound (I) (190°) and compound (III) (210°). For a general discussion of the mass spectra of sulphoxides see J. H. Bowie, D. H. Williams, S. O. Lawesson, J. O. Madsen, C. Nolde, and G. Schroll, *Tetrahedron*, 1966, 3515.