Steroidal Sulphur Compounds. Part IX.[1] 6α- and 6β-Methylsulphinylcholest-4-ene and Related Compounds; Stereochemical Aspects of the Allyl Sulphoxide–Sulphenate Rearrangement

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The rates of several [2,3] sigmatropic allyl sulphoxide–sulphenate rearrangements in the steroidal system have been shown to be influenced by chirality at sulphur. The configuration of the alcohols formed by trapping the sulphenates with piperidine showed that the rearrangements were cleanly suprafacial with respect to the allyl system. The results of kinetic investigations and equilibration studies suggested that the rate differences were attributable mainly to differences in free energy of the transition states, and consideration of the relative steric compressions in model transition states led to allocations of configuration at sulphur in the sulphoxides. N.m.r. data were in accord with the configurational assignments, and enabled tentative conformational assignments to four of the sulphoxides to be made.

THE steroidal sulphoxides (I)—(VIII) were required for an investigation of the chiroptical properties of allyl sulphoxides.[2] It was necessary to establish their absolute configurations, but from the start we expected that the method used hitherto for determining configuration at sulphur in steroidal sulphoxides, based on their relative rates of thermolysis to olefins,[3] might be invalid for (I)—(VIII) because of thermally induced stereomutation

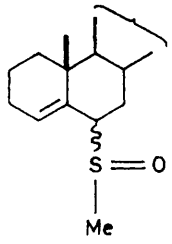
[1] Part VIII, D. N. Jones, E. Helmy, and R. D. Whitehouse, *J.C.S. Perkin I*, 1972, 1329.

[2] D. N. Jones, E. Helmy, R. J. K. Taylor, and A. C. F. Edmonds, *Chem. Comm.*, 1971, 1401.

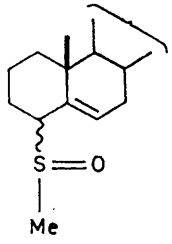
[3] D. N. Jones and M. J. Green, *J. Chem. Soc.* (*C*), 1967, 532, and subsequent papers in that series.

at sulphur,[4] proceeding by reversible [2,3] sigmatropic rearrangement to transient allyl sulphenates, as illustrated in Scheme 1 for the unsaturated 6β-sulphoxides (I) and (II). Such rearrangements occurred readily for other allyl sulphoxides.[4] However we considered that this phenomenon could itself provide a method (which is explained later) for the elucidation of configuration at sulphur.

Preparation of the Sulphoxides.—As intermediates in the preparation of the sulphoxides (I)—(VIII) we required the unsaturated sulphides (IX), (X), (XVII), and

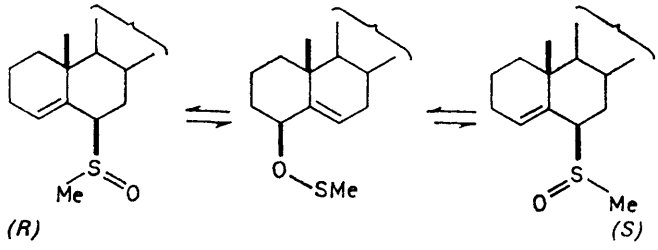


(I) (*R*)-6β
(II) (*S*)-6β
(III) (*R*)-6α
(IV) (*S*)-6α



(V) (*R*)-4β
(VI) (*S*)-4β
(VII) (*R*)-4α
(VIII) (*S*)-4α

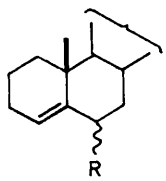
(XVIII). Initially we prepared 6β-methylthiocholest-4-ene (IX) and 4β-methylthiocholest-5-ene (XVII) by solvolysis of 6β-chlorocholest-4-ene in methanethiol, a



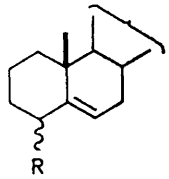
(I) (XXIII) (II)

SCHEME 1

method suggested by the known hydrolytic behaviour of this allyl chloride.[5] The potential advantage of obtaining two useful intermediates concurrently and stereoselectively from one precursor was negated by the impossibility of separating the unsaturated sulphides (IX) and (XVII), a situation which was not ameliorated by oxidation of the mixture, because the resulting mixture of sulphoxides (I), (II), (V), and (VI) was separated only with difficulty by chromatography. We therefore adopted an alternative method of preparing the sulphides (IX), (X), (XVII), and (XVIII) which was both regioselective and stereoselective, based on the reported



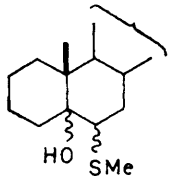
(IX) 6β-SMe
(X) 6α-SMe
(XI) 6β-SO_2Me
(XII) 6α-SO_2Me
(XIII) 6β-OH
(XIV) 6α-OH
(XV) 6β-OSMe
(XVI) 6α-OSMe



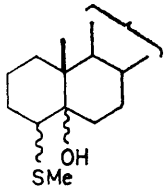
(XVII) 4β-SMe
(XVIII) 4α-SMe
(XIX) 4β-SO_2Me
(XX) 4α-SO_2Me
(XXI) 4β-OH
(XXII) 4α-OH
(XXIII) 4β-OSMe
(XXIV) 4α-OSMe

reactions of epoxides with nucleophiles under non-acidic conditions.[6,7]

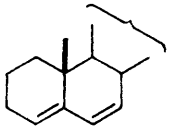
Treatment of 5α-cholestane 5,6α-epoxide and 5α-cholestane 4α,5-epoxide with sodium methanethiolate in ethanol gave respectively 6β-methylthiocholestan-5α-ol (XXV) (84%) and 4β-methylthiocholestan-5α-ol (XXVII) (95%); similar treatment of 5β-cholestane 5,6β-epoxide and 5β-cholestane 4β,5-epoxide gave 6α-methylthiocholestane-5β-ol (XXVI) (86%) and 4α-methylthiocholestane-5β-ol (XXVIII) (91%), respectively. The regioselectivity and stereoselectivity observed in the opening of the epoxide rings by methanethiolate anions find analogy in the reactions of steroidal 5,6-epoxides with cyanide ions, azide ions, and amines,[6,7] and was expected on mechanistic grounds since under non-acidic conditions the nucleophilic attack on the epoxide ring should occur at the least substituted carbon atom with inversion of configuration.[8] Diequatorial ring opening by thiolate anions has been observed for other cyclohexane epoxide derivatives.[9]



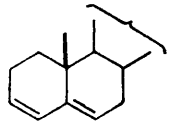
(XXV) 5α,6β
(XXVI) 5β,6α



(XXVII) 4β,5α
(XXVIII) 4α,5β



(XXIX)



(XXX)

Dehydration of the hydroxy-sulphides (XXV), (XXVII), (XXVI), and (XXVIII) by thionyl chloride

[4] (*a*) P. Bickart, F. W. Carson, J. Jacobus, E. G. Miller, and K. Mislow, *J. Amer. Chem. Soc.*, 1968, **90**, 4869; (*b*) R. Tang and K. Mislow, *ibid.*, 1970, **92**, 2100.

[5] R. E. Ireland, T. I. Wrigley, and W. G. Young, *J. Amer. Chem. Soc.*, 1958, **80**, 4604.

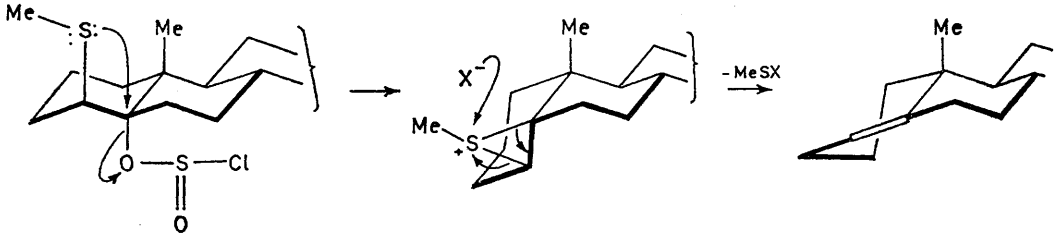
[6] A. Bowers, E. Denot, M. B. Sanchez, L. M. Sanchez-Hidalgo, and H. J. Ringold, *J. Amer. Chem. Soc.*, 1959, **81**, 5233; E. Batres, G. Monroy, and H. J. Ringold, *J. Org. Chem.*, 1961, **26**, 878; W. J. Wechter, *ibid.*, 1966, **31**, 2136; C. L. Hewett and D. S. Savage, *J. Chem. Soc.* (*C*), 1968, 1134.

[7] C. L. Hewett and D. S. Savage, *J. Chem. Soc.* (*C*), 1967, 582.

[8] A. Rosowsky in ' Heterocyclic Compounds with Three- and Four-Membered Rings,' ed. A. Weissberger, Interscience, London, 1964, Part 1, pp. 270, 327.

[9] W. L. Scott and D. A. Evans, *J. Amer. Chem. Soc.*, 1972, **94**, 4779.

in pyridine gave, respectively, 6β-methylthiocholest-4-ene (IX), 4β-methylthiocholest-5-ene (XVII), 6α-methylthiocholest-4-ene (X), and 4α-methylthiocholest-5-ene (XVIII). The yields were not reproducible, and although they were satisfactory (80—98%) for 6β- and 6α-methylthiocholest-4-ene, they were poor (25—49%) for 4β- and 4α-methylthiocholest-5-ene, from which the major product was cholest-4-ene. This olefin probably arose by participation of the methylthio-group in the heterolysis of the initially formed 5-chlorosulphite, to form a methylthiiranium ion which suffered nucleophilic attack at sulphur to generate cholest-4-ene and a derivative of methanesulphenic acid (*e.g.* Scheme 2). The



SCHEME 2

generation of thiiranium ions by analogous reactions,[10] and attack at sulphur in thiiranium ions to give olefins [10,11] have been exemplified previously, but we are not aware of previous examples of the formation of olefins by the formal elimination of methanesulphenic acid from vicinal hydroxy-sulphides. The best stereoelectronic conditions for ready formation of the thiiranium ion, an antiperiplanar arrangement of methylthio- and hydroxy-groups, are present in 4β-methylthiocholestan-5α-ol (XXVII) and are readily attainable in 4α-methylthiocholestan-5β-ol (XXVIII) by conformational change of ring A into a flexible form, so that the formation of appreciable amounts of cholest-4-ene from these compounds on treatment with thionyl chloride is understandable. The transformation of 6α-methylthiocholestan-5β-ol (XXVI), where the relevant groups are both equatorially orientated with respect to ring B, into a conformation in which both reacting groups are antiperiplanar requires both ring A and ring B to adopt a boat-like conformation of relatively high energy according to models; this may inhibit the formation of an intermediate thiiranium ion and thus account for the virtual absence of cholest-5-ene as product. The reluctance of 6β-methylthiocholestan-5α-ol (XXV) to form cholest-5-ene despite the apparently favourable antiperiplanar disposition of reacting groups is more difficult to explain however, and casts some doubt on the validity of the above rationalisations. Yields of the unsaturated sulphides (XVII) and (XVIII) were raised to *ca.* 63% when the hydroxy-sulphides (XXVII) and (XXVIII) were dehydrated by use of (methoxycarbonylsulphamoyl)triethylammonium hydroxide inner salt, which brings about overall *cis*-elimination of water by a mechanism involving ion-pair intermediates, the carbonium-ion component of which shows a marked reluctance to undergo intramolecular nucleophilic attack or rearrangement.[12]

Oxidation of 6β-methylthiocholest-4-ene (IX) with peroxydodecanoic acid in light petroleum gave a mixture of the (*R*)- and (*S*)-6β-sulphoxides (I) and (II), which were readily separated by chromatography, and in a similar manner the (*R*)- and (*S*)-4β-sulphoxides (V) and (VI) were generated from 4β-methylthiocholest-5-ene (XVII). The sulphoxides (I) and (II) were separately oxidised to the same sulphone (XI), and the sulphoxides (V) and (VI) to the sulphone (XIX), confirming the stereochemical relationships at sulphur. With peroxydodecanoic acid in light petroleum 6α-methylthiocholest-4-ene (X) gave only (*S*)-6α-methylsulphinylcholest-4-ene (IV), and 4α-methylthiocholest-5-ene (XVIII) was converted stereospecifically into (*R*)-4α-methylsulphinylcholest-5-ene (VII), but with hydrogen peroxide in acetic acid, a reagent which displays lower stereoselectivity than peroxydodecanoic acid in the oxidation of acyclic sulphides to sulphoxides,[13] the 6α-sulphide (X) furnished a mixture of the (*R*)- and (*S*)-6α-sulphoxides (III) and (IV) in the ratio 37 : 63 whilst the 4α-sulphide (XVIII) gave a mixture of (*R*)-4α-methylsulphinylcholest-5-ene (VII) and (*S*)-4α-methylsulphinylcholest-5-ene (VIII) in the ratio 3 : 2. In contrast, hydrogen peroxide and *m*-chloroperbenzoic acid displayed little difference in stereoselectivity in the oxidation of cyclic sulphides to their sulphoxides.[14] The mixtures of sulphoxides (III) and (IV), and (VII) and (VIII) could not be separated into their components by chromatography or by fractional crystallisation, but the presence and composition of the mixtures was revealed by n.m.r. spectroscopy and kinetic analysis (see later).

In an attempt to prepare the 6α-sulphoxides (III) and (IV) from the 6β-sulphoxides (I) and (II), we treated the latter separately with potassium t-butoxide in dimethyl sulphoxide at 80°, conditions which caused the isomerisation of (*R*)- and (*S*)-6β-methylsulphinyl-5α-cholestanes to their respective 6α-isomers with retention of con-

[10] *Inter alia* G. H. Schmid and P. H. Fitzgerald, *J. Amer. Chem. Soc.*, 1971, **93**, 2547; G. H. Schmid and V. M. Csizmadia, *Chem. and Ind.*, 1968, 1811.

[11] D. C. Owsley, G. K. Helmkamp, and S. N. Spurlock, *J. Amer. Chem. Soc.*, 1969, **91**, 3606.

[12] E. M. Burgess, H. R. Penton, and E. A. Taylor, *J. Org. Chem.*, 1973, **38**, 26; P. Crabbe and C. Leon, *ibid.*, 1970, **35**, 2594.

[13] A. C. F. Edmonds, unpublished observations.

[14] C. R. Johnson and D. McCants, *J. Amer. Chem. Soc.*, 1965, **87**, 1109; C. R. Johnson, H. Diefenbach, J. E. Keiser, and J. C. Sharp, *Tetrahedron*, 1969, **25**, 5649; W. O. Siegl and C. R. Johnson, *J. Org. Chem.*, 1970, **35**, 3657.

figuration at sulphur.[15a] However the unsaturated 6β-sulphoxides (I) and (II) gave only mixtures of dienes at 80 and at 56°, whereas at room temperature they were inert. There was no detectable epimerisation at C-6, nor did equilibration with αβ-unsaturated sulphoxides, which happens in other cases,[16] occur to any detectable extent. Treatment of the 4β-sulphoxides (V) and (VI) with base also gave only dienes. Similar results were obtained with a variety of bases. It appears that base-catalysed elimination of methanesulphenic acid, which has been observed with other sulphoxides,[17] occurred particularly readily in these unsaturated sulphoxides because of the allylic location of the methylsulphinyl groups.

N.m.r. Properties.—The n.m.r. characteristics (Table 1)

TABLE 1

N.m.r. data for steroidal sulphur compounds *

	Geminal H			Vinyl			
				SMe	H	10-Me	13-Me
Compound		τ	$W_{\frac{1}{2}}$ or J	τ	τ	τ	τ
(I)	6α(*eq*)	6·83(d)	5	7·56	4·29	9·07	9·30
(II)	6α(*eq*)	6·87	7	7·45	4·35	8·80	9·32
(III)	6β(*ax*)	6·49(d)	12	7·44	4·70	9·00	9·33
(IV)	6β(*ax*)	6·90(d)	12	7·38	4·56	9·00	9·33
(V)	4α(*eq*)	6·86	8	7·43	4·40	8·84	9·32
(VI)	4α(*eq*)	6·84	7	7·57	4·35	9·10	9·34
(VII)	4β(*ax*)	6·86(d)	11	7·40	4·52	8·99	9·32
(VIII)	4β(*ax*)	6·46(d)	12	7·50	4·73	8·99	9·32
(IX)	6α(*eq*)	6·64(d)	5	8·05	4·65	8·76	9·30
(X)	6β(*ax*)	6·72(d)	13	7·96	4·19	8·97	9·31
(XI)	6α(*eq*)	6·31(d)	7	7·16	4·28	8·78	9·29
(XII)	6β(*ax*)	6·40(d)	12	7·10	3·86	8·99	9·33
(XVII)	4α(*eq*)	6·60	7	8·04	4·65	8·73	9·33
(XVIII)	4β(*ax*)	6·64(d)	12	7·96	4·20	8·99	9·33
(XIX)	4α(*eq*)	6·32(d)	6	7·16	4·31	8·78	9·30
(XX)	4β(*ax*)	6·34(d)	10	7·09	3·87	8·97	9·31
(XXV)	6α(*eq*)	7·54	7	7·94		8·91	9·34
(XXVII)	4α(*eq*)	7·47	7	7·92		8·91	9·35
(XXVI)	6β(*ax*)	7·80(d)	15	7·89		9·07	9·34
(XXVIII)	4β(*eq*)	7·26	15	7·91		9·08	9·35

* Determined on a Varian HA-100 spectrometer for $CDCl_3$ solutions; *eq* = equatorial, *ax* = axial; $W_{\frac{1}{2}}$ = band width at half-height in Hz; bands which appeared as doublets are indicated by d, and the following figure refers to the coupling constant in Hz.

of the steroidal derivatives were in accord with structures allocated. The presence, according to the n.m.r. spectra, of one vinyl proton and one proton geminal to the methylthio-group in the allyl sulphides was consistent only with regiospecific attack by methanethiolate anions at C-6 in the cholestane 5,6-epoxides, and at C-4 in the cholestane 4,5-epoxides; attack at C-5 would have given allyl sulphides having two vinyl and no geminal protons. Comparison of the spectra of pairs of compounds differing only in the configuration of a methylthio- or methylsulphonyl group revealed the orientation of these groups, on the basis of the criteria that axial protons geminal to a functional group in a cyclohexane ring resonate at higher fields than epimeric equatorial protons,[18a] and give rise to bands of greater width because of stronger coupling with vicinal protons.[18b] In addition, the fact that 10-methyl groups resonate at lower fields in compounds bearing axial 6β- or 4β-groups than in their 6α- or 4α-epimers[15,19] was utilised to confirm configurational assignments. The vinyl protons resonated at lower field in the 6α- and 4α-sulphides (X) and (XVIII) than in their respective β-isomers (IX) and (XVII), and at lower field in the 6α- and 4α-sulphones (XII) and (XX) than in the 6β- and 4β-sulphones (XI) and (XIX), presumably because of the greater proximity of the methylthio- and methylsulphonyl groups to the vinyl protons in the equatorially orientated α-isomers than in the axial β-isomers; according to Dreiding models the distance between the sulphur atom and vinyl hydrogen atom is 2·24 Å in (X) and (XVIII), and 3·76 Å in (IX) and (XVII). This behaviour finds analogy in the deshielding of the 4α-proton by the 6-alkylthio-group in 6-alkylthiocholest-5-enes,[1] and in the deshielding of the 6α-proton by the ethylthio-group in 4-ethylthiocholest-4-en-3-one.[20] The pattern of n.m.r. behaviour of the geminal protons and vinyl protons in the allyl sulphides and allyl sulphones did not extend to the sulphoxides (I)—(VIII), undoubtedly as a consequence of the complex anisotropy of the sulphinyl bond. This approximates qualitatively in some respects to that of the acetylenic triple bond, but deviates from it in other respects because of the lack of true cylindrical symmetry of the sulphinyl bond, and because of the little-understood screening effect of the lone electron pair on sulphur.[21] In view of these uncertainties, it was not easy to interpret the observation that oxidation of the 6β-sulphide (IX) to the sulphoxides (I) and (II) was attended by a downfield shift of 36 and 30 Hz, respectively in the 4-vinyl signal, whereas this signal was moved upfield by 51 and 37 Hz on oxidation of the 6α-sulphide (X) to the sulphoxides (III) and (IV), respectively. The 6β-protons in the (*R*)- and (*S*)-6α-sulphoxides (III) and (IV), and the 4β-protons in the (*R*)- and (*S*)-4α-sulphoxides (VII) and (VIII) were also markedly anisochronous, but since Dreiding models provided no reliable clue as to the preferred conformations of these sulphoxides we refrain from speculative interpretation of this n.m.r. behaviour in order to allocate preferred conformations and configurations. The significant shifts in the signals due to the 10-methyl groups which accompanied the oxidation of 6β-methylthiocholest-4-ene (IX) to the 6β-sulphoxides (I) and (II), and the absence of comparable shifts when the 6α-sulphide (X) was oxidised to the sulphoxides (III) and (IV) was also consonant with the *syn*-axial relationship of the methylsulphinyl and 10-methyl groups in (I) and (II);[15,19] the 10-methyl

[15] (*a*) D. N. Jones, M. J. Green, and R. D. Whitehouse, *J. Chem. Soc.* (*C*), 1969, 1166; (*b*) D. N. Jones, D. Mundy, and R. D. Whitehouse, *ibid.*, p. 1668.

[16] D. E. O'Connor and W. I. Lyness, *J. Amer. Chem. Soc.*, 1964, **86**, 2840.

[17] T. J. Wallace, J. E. Hofmann, and A. Schriesheim, *J. Amer. Chem. Soc.*, 1963, **85**, 2739.

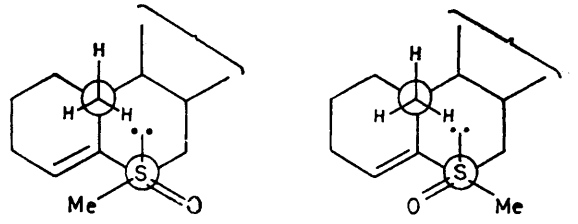
[18] L. M. Jackman and S. Sternhell, 'Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry,' 2nd edn., Pergamon, London, 1969, (*a*) p. 238; (*b*) p. 283.

[19] R. J. Abraham and J. S. E. Holker, *J. Chem. Soc.*, 1963, 806; K. Tori and T. Komeno, *Tetrahedron*, 1965, **21**, 309.

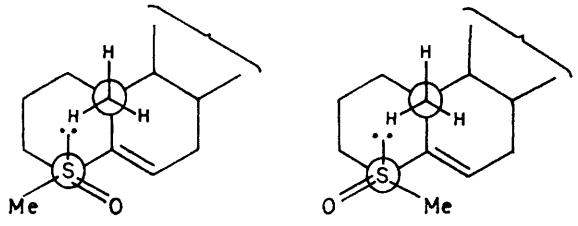
[20] M. Tomoeda, M. Inuzuka, T. Furuta, and M. Shinozuka, *Tetrahedron*, 1968, **24**, 959.

[21] For references, and a discussion, see R. D. G. Cooper, P. V. DeMarco, J. C. Cheng, and N. D. Jones, *J. Amer. Chem. Soc.*, 1969, **91**, 1408.

groups in (I) and (II) resonated 27 Hz apart, which is rational in terms of the known features of the anisotropy of the sulphoxide bond,[21] and the adoption of the preferred conformations (A) and (B) by the (*R*)- and (*S*)-6β-sulphoxides (I) and (II), respectively. In (B) the 10-methyl group lies in the deshielding cone of the sulphoxide bond, whereas in (A) it does not. Similar n.m.r. behaviour of the 10-methyl groups encountered in (*R*)- and



(A) (B)



(C) (D)

(*S*)-6β-methylsulphinyl-5α-cholestanes and other 6β-alkylsulphinylcholestanes was also interpreted in terms of the adoption of preferred conformations analogous to (A) and (B),[15] and these similarities led to tentative allocations of configuration at sulphur in (I) and (II). In the same way the configurations and preferred conformations of the 4β-sulphoxides (V) and (VI) were tentatively deduced to be (C) and (D), respectively. Examination of Dreiding models suggested that the preferred conformations of the sulphoxides are those depicted, rotation about the C(6)–S bond and C(4)–S bond, and the adoption of alternative staggered conformations being inhibited by severe steric repulsive interactions between the *S*-methyl groups and the 10-methyl groups. That the 10-methyl groups in the 6α-sulphoxides (III) and (IV) were isochronous was consistent with the allocated structures, since in them the 10-methyl groups were too far from the equatorial 6α-methylsulphinyl groups for their anisotropy to have any effect. The (*R*)- and (*S*)-6α-sulphoxides were inseparable, but the presence of both diastereoisomers in the mixture was revealed by the non-coincidence of the signals associated with the 6β-protons, the vinyl protons, and the protons of the *S*-methyl groups in the respective sulphoxides. The relative intensities of the signals due to the vinyl protons showed that the mixture obtained by oxidation of the 6α-sulphide (X) with hydrogen peroxide in acetic acid contained the (*R*)- and (*S*)-isomers in the ratio 37 : 63, and that with peroxydodecanoic acid the only sulphoxide produced was the (*S*)-isomer (IV). The configurations at sulphur in the 6α-sulphoxides (III) and (IV) could not be deduced from their n.m.r. spectra, but were later revealed by their relative rates of rearrangement. The n.m.r. spectra of the (*R*)- and (*S*)-4α-sulphoxides (VII) and (VIII) were similar to those of the (*S*)- and (*R*)-6α-sulphoxides (IV) and (III), respectively, which is reasonable because (VII) and (IV) on one hand and (VIII) and (III) on the other are pseudoenantiomeric; our interpretations of the n.m.r. spectral characteristics of (VII) and (VIII) therefore reflected those described above for (IV) and (III).

The unsaturated 6β-sulphoxides (I) and (II) were not reduced by hydrogen over 5% palladium–charcoal although such catalysts are not normally poisoned by sulphoxides,[22] and when platinum was used the sole product was 5α-cholestane. Attempted reduction by di-imide was unsuccessful, which accords with the known reluctance of di-imide to attack hindered trisubstituted olefins.[23] In the light of these results, and because other experiments (see later) were more fruitful, the reduction of the olefinic bonds in the other unsaturated sulphoxides was not investigated.

Thermal Rearrangements and Eliminations of the Sulphoxides; Allocations of Configuration.—In boiling benzene the (*R*)- and (*S*)-6β-sulphoxides (I) and (II) equilibrated at sulphur, and (*S*)-4β-methylsulphinylcholest-4-ene (VI) underwent stereomutation at sulphur to give some of the (*R*)-4β-isomer (V). Analogy with the mechanism established for the stereomutation of allyl aryl sulphoxides [4] indicated that the (*R*)- and (*S*)-6β-sulphoxides (I) and (II) equilibrated by reversible [2,3] sigmatropic rearrangement to the transient 4β-sulphenate (XXIII) (Scheme 1), and that the 6β-sulphenate (XV) was involved in the stereomutation of the (*S*)-4β-sulphoxide (VI). Equilibration was accompanied by elimination, the (*R*)- and (*S*)-6β-sulphoxides (I) and (II) giving cholesta-4,6-diene (XXIX), and the (*S*)-4β-sulphoxide (VI) giving cholesta-3,5-diene (XXX). A mixture of (*R*)- and (*S*)-6α-methylsulphinylcholest-4-ene (III) and (IV) eliminated methanesulphenic acid readily in boiling benzene to give a mixture of cholesta-4,6-diene (XXIX) and cholesta-3,5-diene (XXX) in the ratio 4 : 1; (*R*)-4α-methylsulphinylcholest-5-ene (VII) gave only cholesta-3,5-diene (XXX). The regioselectivity of these eliminations from the βγ-unsaturated sulphoxides suggests that they proceed by the *syn*-intramolecular mechanism which occurs with saturated sulphoxides,[15,24] and that heterolytic mechanisms involving allyl carbonium ions (which should give mixtures of dienes) are not important.

Equilibration of the sulphoxides in benzene at 56° occurred appreciably faster than elimination, according to t.l.c. and n.m.r. evidence. Therefore the configurations at sulphur in these sulphoxides could not be

[22] P. N. Rylander, 'Catalytic Hydrogenation over Platinum Metals,' Academic Press, London, 1967, p. 21.

[23] S. Hunig, H. R. Muller, and W. Thier, *Angew. Chem. Internat. Edn.*, 1965, **4**, 271.

[24] C. A. Kingsbury and D. J. Cram, *J. Amer. Chem. Soc.*, 1960, **82**, 1810.

determined by the method used previously for saturated steroidal sulphoxides,[3,15] which involved an interpretation of the relationship between configuration at sulphur and the rate of olefin-forming elimination. The equilibrium constants, determined by measurement of the relative intensities of appropriate signals in the n.m.r. spectra of the equilibrium mixtures, and free-energy differences are recorded in Table 2. Difficulties due to the overlapping of signals diminished the precision of the measurements, and precluded measurement of the kinetics of stereomutation of the 6β- and 4β-sulphoxides by the n.m.r. technique, but it was possible to do so for a mixture of (*R*)- and (*S*)-6α-methylsulphinylcholest-4-enes enriched in the latter isomer, and for pure (*R*)-4α-methylsulphinylcholest-5-ene. The data (Table 2) must be regarded only as approximate.

TABLE 2

Equilibration of steroidal allyl sulphoxides in benzene at 56°

	K	$-\Delta G^0$/kcal mol^{-1}
(II) ⇌ (I)	4·5	0·98 ± 0·2
(III) ⇌ (IV)	4·5	0·98 ± 0·2
(V) ⇌ (VI)	8·6	1·4 ± 0·2
(VIII) ⇌ (VII)	1·6	0·32 ± 0·2

Encouraged by the easy stereomutation of the steroidal unsaturated sulphoxides, and armed with the information that asymmetric induction had been observed in the rearrangement of allyl sulphenates to sulphoxides [4,25] we devised a means of establishing configuration at sulphur in the sulphoxides (I)—(VIII) which utilised the fact that allyl sulphenates react rapidly with thiophiles to give allyl alcohols.[26,27] The method is illustrated by taking the (*R*)- and (*S*)-6β-sulphoxides (I) and (II) as examples. The transition state (E) connecting the (*R*)-6β-sulphoxide (I) to the 4β-sulphenate (XXIII) should be of higher energy than the diastereoisomeric transition state (F) arising from the (*S*)-6β-sulphoxide (II) because steric compressions involving the *S*-methyl group, the 10-methyl group, and the 8β-hydrogen atom are greater in (E) than in (F). If the difference in free energy between the transition states (E) and (F) were greater than that between the sulphoxides (I) and (II), the activation energy for the conversion of the (*R*)-6β-sulphoxide (I) into the 4β-sulphenate (XXIII) would be greater than that for conversion of the (*S*)-6β-sulphoxide (II) into (XXIII), and the (*S*)-6β-sulphoxide (II) would therefore rearrange the faster. The relative rates of rearrangement could be measured directly by trapping the sulphenate (XXIII) with piperidine. In order to ensure the validity of the method it was necessary to confirm by kinetic measurements that the rearrangements were concerted, and that they occurred suprafacially with respect to the allyl system. The alternative antarafacial mode of rearrangement, although geometrically less favourable, also conserves orbital symmetry and is therefore ' allowed,' [28] but despite the growing synthetic significance of the allyl sulphoxide-sulphenate rearrangement [27,29] this stereochemical facet had not been investigated previously. Indeed the asymmetric induction (the direction of which was not clear) observed in the rearrangement of but-2-enyl toluene-*p*-sulphenates to α-methylallyl *p*-tolyl sulphoxides was rationalised in terms of suprafacial transition states without proof or justification of this stereochemical course,[25] and only in a Wittig rearrangement had unambiguous proof been presented for the suprafacial mode of a [2,3] sigmatropic rearrangement.[28a]

In chlorobenzene containing an excess of piperidine at 56° (*S*)-6β-methylsulphinylcholest-4-ene (II) gave 4β-hydroxycholest-5-ene (XXI) (97%) after 2·5 h, whereas after this time the (*R*)-6β-isomer (I) was recovered unchanged (98%). After 92 h however the (*R*)-6β-sulphoxide (I) gave 4β-hydroxycholest-5-ene (XXI) (95% based on sulphoxide consumed) together with starting material (4%). (*S*)-4β-Methylsulphinylcholest-5-ene (VI) was unchanged after 2 h at 56° in benzene and was converted into 6β-hydroxycholest-4-ene (XIII) (91% based on sulphoxide consumed) together with starting material (30%) only after heating at 95° for 3 h. When a mixture of the (*R*)- and (*S*)-6α-sulphoxides (III) and (IV) containing 65% of the (*S*)-isomer (IV) was treated with chlorobenzene–piperidine at 56° for 4 h, 4α-hydroxycholest-5-ene (XXII) (93% based on sulphoxide consumed) was formed, and the recovered sulphoxide (42%) consisted of pure (*S*)-6α-methylsulphinylcholest-4-ene (IV). The (*R*)-6α-sulphoxide (III) therefore reacted faster than the (*S*)-6α-sulphoxide (IV). Similarly, a mixture of (*R*)- and (*S*)-4α-methylsulphinylcholest-5-ene gave, after 42 min in chlorobenzene–piperidine at 56°, 6α-hydroxycholest-4-ene (XIV) (92% based on sulphoxide consumed) together with pure (*R*)-4α-methylsulphinylcholest-5-ene (VII) (52%), indicating that the (*S*)-4α-isomer rearranged the faster. There was no detectable isomerisation at sulphur during the formation of these allyl alcohols, indicating that the intermediate sulphenates were efficiently trapped by piperidine, and since sulphenates are converted into alcohols with retention of configuration under these conditions,[26,27] the configuration of the alcohols formed showed that the rearrangements were cleanly suprafacial.

A kinetic investigation, in which the reactions were followed polarimetrically, revealed that the (*S*)-6β-sulphoxide (II) rearranged 322 times faster than the (*R*)-6β-sulphoxide (I) at 56° in a clean first-order reaction (Table 3). Lack of sufficient material precluded a precise kinetic investigation of the rearrangement of the

[25] V. Rautenstrauch, *Chem. Comm.*, 1970, 526.
[26] D. J. Abbott and C. J. M. Stirling, *J. Chem. Soc.* (*C*), 1969, 818.
[27] D. A. Evans and G. C. Andrews, *J. Amer. Chem. Soc.*, 1972, **94**, 3672.
[28] (*a*) J. E. Baldwin and J. E. Patrick, *J. Amer. Chem. Soc.*, 1971, **93**, 3556; (*b*) R. B. Woodward and R. Hoffmann, *Angew. Chem. Internat. Edn.*, 1969, **1**, 781; K. Fukui, *Accounts Chem. Res.*, 1971, **4**, 57.
[29] D. A. Evans, G. C. Andrews, and C. L. Sims, *J. Amer. Chem. Soc.*, 1971, **93**, 4956; D. A. Evans, G. C. Andrews, T. T. Fujimoto, and D. Wells, *Tetrahedron Letters*, 1973, 1385, 1389.

4β-sulphoxides (V) and (VI). Kinetic data for the rearrangement of a mixture of (*R*)- and (*S*)-6α-methylsulphinylcholest-5-ene (III) and (IV) in chlorobenzene–piperidine (*e.g.* Figure 1) were typical of those for two parallel first-order reactions producing a common product,[30a] and on analysis furnished good first-order plots for the rearrangement of the individual isomers. One isomer rearranged 34 times faster than the other at 56°. The ratio of 6α-sulphoxides [(III) to (IV)] obtained by oxidation of the 6α-sulphide (X) with hydrogen peroxide was 2 : 3 according to the kinetic data, which agreed well with that (37 : 63) determined by analysis of the n.m.r. spectrum of the mixture. A similar analysis of the rate data (*e.g.* Figure 2) for the rearrangement of a mixture of (*R*)- and (*S*)-4α-methylsulphinylcholest-5-ene (VII) and (VIII) to 6α-hydroxycholest-4-ene (XIV) revealed that one isomer rearranged 26 times faster than the other at 56°, and that the isomers (VII) and (VIII) were present in the mixture obtained by oxidation of the 4α-sulphide (XVIII) by hydrogen peroxide in the ratio 3 : 2, which corresponded with the ratio determined by n.m.r. spectroscopy.

TABLE 3

First-order rate constants and activation parameters for the reactions of steroidal allyl sulphoxides in chlorobenzene–piperidine *

Compound	Temp. (°C)	$k \times 10^3$/s^{-1}	log$_{10}$A	E_a /kcal mol^{-1}	$\Delta G^{\ddagger}$ /kcal mol^{-1}	$\Delta H^{\ddagger}$ /kcal mol^{-1}	$\Delta S^{\ddagger}$/ cal deg^{-1} mol^{-1}
(I)	56·0	2·08 × 10^{-3}	12·1	26·8	27·9	26·1	−5·5
(I)	60·0	3·38 × 10^{-3}					
(I)	70·0	1·25 × 10^{-2}					
(I)	80·0	3·2 × 10^{-2}					
(II)	50·0	0·351	9·93	19·8	24·6	19·1	−15·4
(II)	56·0	0·671					
(II)	60·0	0·889					
(II)	65·0	1·40					
(III)	55·0	1·01	13·2	24·3	23·8	23·7	−0·3
(III)	60·0	1·67					
(III)	65·0	3·04					
(IV)	55·0	2·96 × 10^{-2}	12·9	26·2	26·1	25·6	−1·6
(IV)	60·0	5·60 × 10^{-2}					
(IV)	65·0	9·70 × 10^{-2}					
(VII)	51·0	3·12	10·7	22·2	25·5	21·6	−11·8
(VII)	56·0	5·23					
(VII)	60·0	7·91					
(VIII)	51·0	0·873 × 10^{2}	9·84	18·8	23·3	18·2	−15·7
(VIII)	56·0	1·36 × 10^{2}					
(VIII)	60·0	1·92 × 10^{2}					

* Determined for *ca.* 0·02M solutions of the sulphoxides in chlorobenzene–piperidine (70 : 16 v/v).

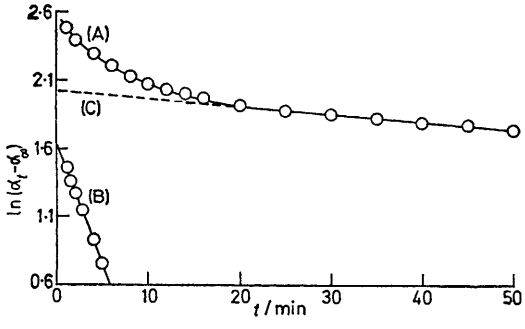


FIGURE 1 (A) is a typical plot of $\ln(\alpha_t - \alpha_\infty)$ *vs.* *t* for the reaction (at 55°) of *ca.* 0·02M-solutions of a mixture of (*R*)- and (*S*)-6α-methylsulphinylcholest-4-ene in chlorobenzene–piperidine (70 : 16 v/v); the straight lines (B) and (C), derived by analysis of (A), are the first-order rate plots for the reactions of the (*R*)-6α-sulphoxide (III) and (*S*)-6α-sulphoxide (IV), respectively

The magnitude and sign of the activation parameters (Table 3) were similar to those for the racemisation of allyl *p*-tolyl sulphoxide, which was shown to involve reversible [2,3] sigmatropic rearrangement to allyl toluene-*p*-sulphenate.[4a] The negative entropies of activation for the rearrangements of (I), (II), (VII), and

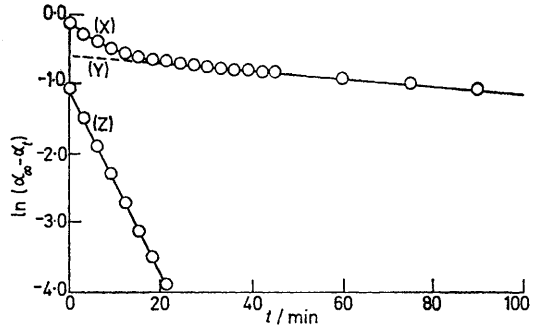


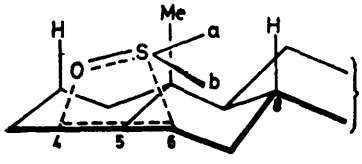
FIGURE 2 (X) is a typical plot of $\ln(\alpha_\infty - \alpha_t)$ *vs.* *t* for the reaction (at 56°) of *ca.* 0·02M-solutions of a mixture of (*R*)- and (*S*)-4α-methylsulphinylcholest-5-ene in chlorobenzene–piperidine (70 : 16 v/v); the straight lines (Y) and (Z), derived by analysis of (X), are the first-order rate plots for the reactions of the (*R*)-4α-sulphoxide (VII) and (*S*)-4α-sulphoxide (VIII), respectively

[30] A. A. Frost and R. G. Pearson, 'Kinetics and Mechanism,' 2nd edn., Wiley, New York, 1961, (*a*) p. 162, (*b*) p. 110, (*c*) p. 13, (*d*) p. 186.

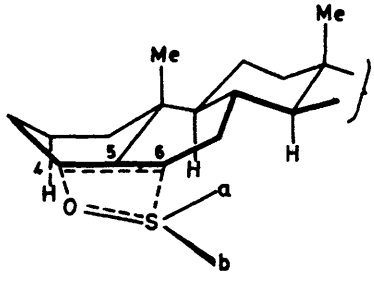
(VIII) indicated that the development of the relevant transition states involved a diminution in the degrees of freedom of the system, and their magnitude was typical of many unimolecular reactions proceeding by the formation of cyclic transition states.[30b] That the entropies of activation for (III) and (IV) and (I) were significantly more positive than for the others may be due to greater solvation of the former sulphoxides relative to their transition states. Analogous phenomena have been observed elsewhere,[4] but the reasons for the apparent differences in solvation in these steroidal sulphoxides is not clear. The differences in free energy between sulphoxides differing only in configuration at sulphur (Table 2) were in each case smaller than the differences in free energy of activation for rearrangement (Table 3), suggesting that the differences in rates of rearrangement of sulphoxides diastereoisomeric at sulphur were due primarily to differences in the relative energies of the cyclic transition states. This conclusion is probably valid despite the difference in solvent during rearrangement and equilibration; from the differences in free energies of activation of the rearrangements it may be calculated that differences in solvation would invalidate our arguments only if K in chlorobenzene–piperidine were at least 29 for the 4α- and 6α-sulphoxides, and at least 155 for the 6β-sulphoxides. We consider it unlikely that these equilibria are so solvent-dependent.

These results suggested that all the requirements for the application of the method outlined earlier for determining configuration at sulphur in the unsaturated steroidal sulphoxides were satisfied, and accordingly consideration of the transition states (E) and (F) arising, respectively, from the (*R*)- and (*S*)-6β-sulphoxides (I) and (II) led to the identification of the faster-rearranging sulphoxide as (*S*)-6β-methylsulphinylcholest-4-ene (II). Assignments of configuration at sulphur to the (*R*)- and (*S*)-4β-sulphoxides (V) and (VI) followed from a comparison of their n.m.r. spectra, their equilibrium composition, and chromatographic behaviour with those of the (*R*)- and (*S*)-6β-sulphoxides (I) and (II); the pseudo-enatiomeric relationship of the (*R*)-6β-sulphoxide (I) with the (*S*)-4β-sulphoxide (VI), and of the (*S*)-6β-sulphoxide (II) with the (*R*)-4β-sulphoxide (V) was clearly apparent in all these properties.

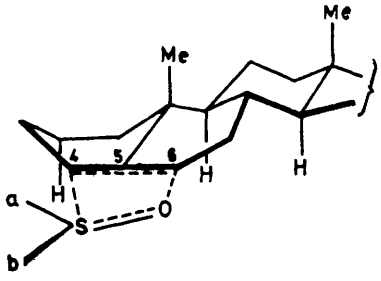
Examination of Dreiding models showed that good continuous orbital overlap during the development of the transition states (E) and (F) could be achieved with relatively little conformational distortion of rings A and B, since the axial C(6)–S bond in the sulphoxides was roughly parallel to the π-electron system of the olefinic double bonds in each case. In the 6α-sulphoxides (III) and (IV) and 4α-sulphoxides (VII) and (VIII) however the equatorial C(6)–S and C(4)–S bonds are roughly orthogonal to the π-electron systems of the olefinic double bonds, and good continuous orbital overlap in the rearrangements to the 4α-sulphenate (XXIV) and 6α-sulphenate (XVI), respectively, is possible only if rings A and B undergo considerable conformational change. Consideration of the transition states (G) and (H) derived in this way from the (*R*)- and (*S*)-6α-sulphoxides (III) and (IV) revealed that there are steric repulsions between the *S*-methyl group and the bottom face of ring B in (H), which are absent in (G), so that the isomer which rearranged the faster had the (*R*)-configuration at sulphur, whilst examination of the transition states (J) and (K) derived from the 4α-sulphoxides indicated that (*S*)-4α-methylsulphinylcholest-5-ene rearranged faster than its isomer at sulphur.



(E) a = Me, b = lone electron pair
(F) b = Me, a = lone electron pair



(G) b = Me, a = lone electron pair
(H) a = Me, b = lone electron pair



(J) a = lone electron pair, b = Me
(K) b = lone electron pair, a = Me

It should be noted that in the ground-state conformation of the 6α-sulphoxides the bottom and top lobes of a potential *p* orbital at C-4 are equally accessible for 'sideways' overlap with an appropriate orbital on sulphinyl oxygen, so that if maximal continuous orbital overlap were not a requirement for the sigmatropic rearrangement significant conformational distortion of the molecules would not be necessary and both the symmetry-allowed suprafacial and antarafacial modes would have been observed. This also applies to the rearrangement of the 4α-sulphoxides. That only suprafacial rearrangement occurred provides evidence additional to that already presented [31] for the importance of good orbital overlap in such processes.

EXPERIMENTAL

M.p.s were determined on a Kofler hot-stage apparatus. I.r. spectra were determined with a Unicam SP 100 spectrophotometer, and n.m.r. spectra with a Varian HA 100

[31] S. Magaswaran, W. D. Ollis, I. O. Sutherland, and Y. Thebtaranonth, *Chem. Comm.*, 1971, 1494; C. J. Dixie and I. O. Sutherland, *J.C.S. Chem. Comm.*, 1972, 646.

spectrometer. U.v. spectral data and chiroptical properties will be reported in Part X of this series. Optical rotations were determined with a Perkin-Elmer 141 automatic polarimeter for chloroform solutions. The identity of the known compounds which were isolated was established by comparison of their t.l.c., i.r., and n.m.r. properties with those of authentic samples, and by mixed m.p. determinations in appropriate cases. Preparative thick-layer chromatography (p.l.c.) was performed with a layer of silica gel G (Merck) 1 mm thick. Light petroleum refers to the fraction b.p. 40—60°.

Preparation of the Hydroxy-sulphides (XXV)—(XXVIII).—A solution of sodium (2 g) in dry ethanol (75 ml) was cooled to 0° under nitrogen, and methanethiol (2 ml), previously cooled to 0°, was added slowly, with the temperature kept at 0°. (CAUTION: other procedures resulted in violent conflagrations, especially when use of nitrogen and thorough cooling were omitted). After the addition of 5α-cholestane 5,6α-epoxide [32] (500 mg), the solution was boiled for 24 h, poured into ice-cold 2N-sodium hydroxide, and extracted with ether. After washing twice with water and drying (Na_2SO_4), evaporation of the extract gave 6β-*methylthiocholestan-5α-ol* (XXV) (0·47 g, 84%) as an oil, $[\alpha]_D$ −44° (*c* 0·2) (Found: C, 77·6; H, 11·4; S, 7·6. $C_{28}H_{50}OS$ requires C, 77·3; H, 11·6; S, 7·4%). Treatment of 5α-cholestane 4α,5-epoxide [5] (0·64 g) in the same way gave 4β-*methylthiocholestan-5α-ol* (XXVII) (0·68 g, 95%), m.p. 116—118° (plates from acetone–methanol), $[\alpha]_D$ +55° (*c* 1·3) (Found: C, 77·6; H, 11·5; S, 7·4%); 5β-cholestane 5,6β-epoxide [32] (5 g) gave 6α-*methylthiocholestan-5β-ol* (XXVI) (4·7 g, 86%) as an oil, $[\alpha]_D$ +41° (*c* 0·6) (Found: C, 77·5; H, 11·3; S, 7·3%), and 5β-cholestane 4β,5-epoxide [33] (5·7 g) gave 4α-*methylthiocholestan-5β-ol* (XXVIII) (5·95 g, 91%), m.p. 89—90° (from acetone), $[\alpha]_D$ −52° (*c* 0·5) (Found: C, 77·2; H, 11·4; S, 7·4%).

Dehydration of the Hydroxy-sulphides (XXV)—(XXVIII).—(*a*) 6β-Methylthiocholestan-5α-ol (XXV) (0·9 g) in dry pyridine (2 ml) at 0° was treated with thionyl chloride (0·2 ml), and after a further 1 h at 0° the mixture was poured into cold 2N-hydrochloric acid and extracted with ether. After washing and drying in the usual way evaporation of the extract gave 6β-*methylthiocholest-4-ene* (IX) (0·85 g, 98%), m.p. 90—92° (from acetone–methanol), $[\alpha]_D$ +74° (*c* 0·7) (Found: C, 80·6; H, 11·6; S, 7·9. $C_{28}H_{48}S$ requires C, 80·7; H, 11·6; S, 7·7%).

(*b*) Dehydration of 6α-methylthiocholestan-5β-ol (XXVI) (2·48 g) in the same way gave 6α-*methylthiocholest-4-ene* (X) (2 g, 84%), m.p. 91—93° (plates from ether–methanol), $[\alpha]_D$ +56° (*c* 1·3) (Found: C, 80·4; H, 11·5; S, 7·8%).

(*c*) The oily mixture obtained when 4β-methylthiocholestan-5α-ol (XXVII) (0·84 g) was dehydrated in the above manner was chromatographed on a column of alumina (40 g). Elution with light petroleum first gave cholest-4-ene (0·275 g, 38%) and then 4β-*methylthiocholest-5-ene* (XVII) (0·39 g, 49%), m.p. 61—64° (from acetone–methanol), $[\alpha]_D$ −67° (*c* 0·7) (Found: C, 80·8; H, 11·65; S, 7·5%). Elution with benzene gave starting material (XXVII) (0·05 g, 6%).

(*d*) Treatment of 4α-methylthiocholestan-5β-ol (XXVIII) (2·87 g) with thionyl chloride in the above manner and p.l.c. of the oily product with light petroleum–benzene (4 : 1) as developer gave cholest-4-ene (1·2 g, 45%) and 4α-*methylthiocholest-5-ene* (XVIII) (1·22 g, 45%), m.p. 84—85° (from ether–methanol), $[\alpha]_D$ −38° (*c* 0·7) (Found: C, 80·8; H, 11·4; S, 8·0%).

(*e*) 4β-Methylthiocholestan-5α-ol (XXVII) (500 mg) and (methoxycarbonylsulphamoyl)triethylammonium hydroxide inner salt[12] (500 mg) in dry benzene (10 ml) were stirred at room temperature for 48 h, and the solution was poured onto a column of neutral alumina (20 g). Elution with light petroleum gave successively cholest-4-ene (76 mg, 18%) and 4β-methylthiocholest-5-ene (300 mg, 63%), identical with the sample prepared above. Elution with benzene gave starting material (XXVII) (25 mg, 5%). Analogous results were obtained when 4α-methylthiocholest-5β-ol was dehydrated with this reagent.

(R)- *and* (S)-6β-*Methylsulphinylcholest-4-ene* [(I) *and* (II)].—Peroxydodecanoic acid (70% pure; 370 mg, 1·19 mmol) was added to 6β-methylthiocholest-4-ene (IX) (0·5 g, 1·20 mmol) in light petroleum (40 ml). After 10 min the solution was poured onto a column of neutral alumina, and elution with light petroleum gave starting material (IX) (98 mg, 20%). Elution with chloroform gave a mixture of sulphoxides which were separated by p.l.c. [ether–chloroform (2 : 1)]. Extraction of a band at R_F *ca.* 0·4 gave (R)-6β-*methylsulphinylcholest-4-ene* (I) (0·18 g, 35%), m.p. 152—154° (from ether–methanol), $[\alpha]_D$ +105° (*c* 0·4), $\nu_{max.}$ 1022 cm^{-1} ($CHCl_3$) (Found: C, 77·7; H, 11·0; S, 7·5. $C_{28}H_{48}OS$ requires C, 77·7; H, 11·2; S, 7·4%); extraction of the band at R_F *ca.* 0·35 gave the (S)-*isomer* (II) (0·075 g, 15%) as an oil, $[\alpha]_D$ +79° (*c* 0·4), $\nu_{max.}$ 1020 cm^{-1} ($CHCl_3$) (Found: C, 75·8; H, 10·9; S, 7·3. $C_{28}H_{48}OS$ requires C, 77·7: H, 11·2; S, 7·4%). Combustion analysis of this compound repeatedly gave consistently low (by 1—2%) values for carbon, even after prolonged drying in a high vacuum at room temperature. The use of elevated temperature for drying caused partial equilibration of the sulphoxide with its isomer at sulphur. The discrepancy is presumably due to the presence of traces of solvent in the oily compound, but it could not be detected by spectroscopic means. Careful chromatographic and spectroscopic analysis of the compound failed to indicate the presence of any impurity. The clean first-order kinetic data (see later) for the reaction of the sulphoxide in chlorobenzene–piperidine also suggested that reactive optically active impurities were absent.

(R)- *and* (S)-6α-*Methylsulphinylcholest-4-ene* [(III) and (IV)].—(*a*) Peroxydodecanoic acid (90% pure; 0·96 mmol) was added to 6α-methylthiocholest-4-ene (X) (435 mg, 1·04 mmol) in light petroleum (50 ml) at room temperature, and after 1 h the solution was poured onto a column of alumina (25 g) prepared in light petroleum. Elution with light petroleum gave the starting material (X) (90 mg, 20%), and elution with chloroform gave (S)-6α-*methylsulphinylcholest-4-ene* (IV) (285 mg, 80%), m.p. 140—141° (from acetone), $[\alpha]_D$ +83° (*c* 0·8), $\nu_{max.}$ 1055 cm^{-1} ($CHCl_3$) (Found: C, 77·8; H, 11·1; S, 7·5. $C_{28}H_{48}OS$ requires C, 77·7; H, 11·2; S, 7·4%).

(*b*) Hydrogen peroxide (0·26 ml of 30% w/v solution; 2·3 mmol) was added to 6α-methylthiocholest-4-ene (X) (1·0 g, 2·4 mmol) in glacial acetic acid (150 ml) at room temperature, and after 24 h the mixture was poured onto ice and worked up with ether in the usual manner. P.l.c. with ether–chloroform (4 : 1) as developer gave a band at the solvent front, extraction of which gave starting material (XI) (200 mg, 20%), and a band at R_F *ca.* 0·25 was extracted to give a mixture of (R)- *and* (S)-6α-*methylsulphinylcholest-4-ene*

[32] H. B. Henbest and T. I. Wrigley, *J. Chem. Soc.*, 1957, 4596.

[33] C. W. Shoppee, M. E. H. Howden, R. W. Killick, and G. H. R. Summers, *J. Chem. Soc.*, 1959, 630.

[(III) and (IV), respectively] (710 mg. 68%), $[\alpha]_D$ +91° (*c* 1·1) (Found: C, 77·5; H, 11·1. $C_{28}H_{48}OS$ requires C, 77·7; H, 11·2%). The sulphoxides were chromatographically identical (t.l.c.) in a wide variety of solvent systems, and could not be separated by fractional crystallisation. The presence of both isomers was clearly revealed by the n.m.r. spectrum. Whereas pure (*S*)-6α-methylsulphinylcholest-4-ene (IV) displayed bands at τ 4·56 (C-4 vinyl H), 6·90 (d, *J* 12 Hz, 6β-H) and 7·38 (SMe), the mixture showed additional bands at τ 4·70 (C-4 vinyl H), 6·49 (d, *J* 12 Hz, 6β-H), and 7·44 (SMe). The ratio of sulphoxides in the mixture was 63 : 37 according to planimetric measurement (average of 10 readings) of the areas of the signals due to the vinyl protons in the n.m.r. spectra of 100 mg samples.

(R)- *and* (S)-4β-*Methylsulphinylcholest-5-ene* [(V) *and* (VI)].—3-Chloroperbenzoic acid (0·251 g, 1·46 mmol) was added to 4β-methylthiocholest-5-ene (XVII) (610 mg, 1·47 mmol) in dry ether (36 ml) at room temperature. After 30 min the ether was evaporated off under reduced pressure and the residue was chromatographed on a column of alumina (15 g). Elution with light petroleum gave starting material (XVII) (78 mg, 13%) and elution with chloroform gave a mixture of the (*R*)- and (*S*)-4β-sulphoxides which was subjected to p.l.c., the plates being developed twice with ether–chloroform (2 : 1). Extraction of a band at R_F *ca.* 0·4 gave (S)-4β-*methylsulphinylcholest-5-ene* (VI) (410 mg, 62%), m.p. 153—154° (from ether–methanol), $[\alpha]_D$ −125° (*c* 0·4), $\nu_{max.}$ 1015 cm^{-1} ($CHCl_3$) (Found: C, 77·6; H, 11·05; S, 7·4. $C_{28}H_{48}OS$ requires C, 77·7; H, 11·2; S, 7·4%); extraction of a band at R_F *ca.* 0·35 gave (R)-4β-*methylsulphinylcholest-5-ene* (V) (73 mg, 12%) as an oil, $[\alpha]_D$ −99° (*c* 0·4), $\nu_{max.}$ 1020 cm^{-1} ($CHCl_3$), which was pure according to t.l.c. and spectroscopic (i.r., n.m.r.) analysis. Elemental analysis by combustion of the compound gave unsatisfactory figures for the elemental composition, presumably because traces of solvent could not be removed from the oil even by prolonged drying at room temperature in a high vacuum. Drying at elevated temperatures caused partial isomerisation to the (*S*)-4β-sulphoxide (VI).

(R)- *and* (S)-4α-*Methylsulphinylcholest-5-ene* [(VII) *and* (VIII)].—(*a*) Peroxydodecanoic acid (78% pure; 108 mg, 0·39 mmol) was added to 4α-methylthiocholest-5-ene (XVIII) (170 mg, 0·41 mmol) in light petroleum (20 ml) at room temperature. After 30 min the solution was poured onto a column of alumina (1·5 g) prepared in light petroleum, and elution with chloroform gave a mixture which was subjected to p.l.c. [ether–chloroform (4 : 1)]. The sole band (at R_F *ca.* 0·25) was extracted with ether to give (R)-4α-*methylsulphinylcholest-5-ene* (VII) (151 mg, 90%), m.p. 147—148° (from acetone), $[\alpha]_D$ −62° (*c* 0·4), $\nu_{max.}$ 1052 cm^{-1} (CCl_4) (Found: C, 77·5; H, 11·0; S, 7·5. $C_{28}H_{48}OS$ requires C, 77·7; H, 11·2; S, 7·4%).

(*b*) Hydrogen peroxide (0·05 ml of 30% w/v; 0·44 mmol) solution was added to a solution of 4α-methylthiocholest-5-ene (XVIII) (200 mg, 0·49 mmol) in glacial acetic acid (40 ml) at room temperature, and after 2 days the mixture was poured into ice–water and worked up with ether in the usual manner. P.l.c. [ether–chloroform (4 : 1)] gave only one band at R_F *ca.* 0·25, which on extraction gave a mixture of (R)- *and* (S)-4α-*methylsulphinylcholest-5-ene*, [(VII) and (VIII)], m.p. 144—145°, $[\alpha]_D$ −69° (*c* 0·5) (Found: C, 77·5; H, 11·0; S, 7·6. $C_{28}H_{48}OS$ requires C, 77·7; H, 11·2; S, 7·4%), τ 4·52 and 4·73 (C-6 vinyl H), 6·46 and 6·86 (both d, *J* 12 and 11 Hz, respectively, 4β-H), and 7·40 and 7·50 (SMe); the pure (*R*)-4α-sulphoxide (VII) displayed bands at τ 4·52, 6·86, and 7·40. The relative intensities of the signals due to the C-6 vinyl protons in the n.m.r. spectrum of the mixture (determined for a 100 mg sample) measured by planimetry and by the ' cut and weight ' method indicated that the mixture contained 60 ± 3% of the (*R*)-4α-sulphoxide (VII). The mixture could not be separated into its components either by crystallisation or by chromatography.

Preparation of the Sulphoxides (I), (II), (V), *and* (VI) *from* 6β-*Chlorocholest-4-ene*.—6β-Chlorocholest-4-ene [5] (2·5 g) was treated with methanethiol (30 ml) in a sealed tube at room temperature for 24 h. Evaporation gave an oily mixture of 6β-methylthiocholest-4-ene (IX) and 4β-methylthiocholest-5-ene (XVII) which could not be separated by crystallisation or chromatography. The mixture (2·5 g, 6 mmol) of unsaturated sulphides was treated with peroxydodecanoic acid (69% pure; 0·8 g, 7·26 mmol) in light petroleum for 30 min at room temperature, and the solution was passed onto a column of alumina (90 g) prepared in light petroleum. Elution with light petroleum (1 l) gave a mixture of unsaturated sulphides (IX) and (XVII) (1·4 g); elution with chloroform (1 l) gave a crude mixture of sulphoxides (1·09 g) which was subjected to p.l.c. [developed twice with ether–chloroform (1 : 2)]. The four bands, after extraction with chloroform gave, in increasing order of polarity, (*R*)-6β-methylsulphinylcholest-4-ene (I) (148 mg, 14%), (*S*)-4β-methylsulphinylcholest-5-ene (V) (313 mg, 29%), (*S*)-6β-methylsulphinylcholest-4-ene (II) (74 mg, 7%), and a mixture (20 mg, 2%) of the (*S*)-6β-sulphoxide (II) and (*R*)-4β-methylsulphinylcholest-5-ene (VI).

6β-*Methylsulphonylcholest-4-ene* (XI).—6β-Methylthiocholest-4-ene (IX) (500 mg, 1·2 mmol) was treated with peroxydodecanoic acid (70% pure; 970 mg, 3·1 mmol) in light petroleum (50 ml) at room temperature, and after 30 min the mixture was poured onto a column of neutral alumina (15 g) prepared in light petroleum. Elution with benzene gave 6β-*methylsulphonylcholest-4-ene* (XVII) (0·45 g, 84%), m.p. 155—157° (needles from ether–methanol), $[\alpha]_D$ +5° (*c* 0·4), $\nu_{max.}$ 1300 and 1125 cm^{-1} ($CHCl_3$) (Found: C, 74·9; H, 10·55; S, 7·0. $C_{28}H_{48}O_2S$ requires C, 74·9; H, 10·8; S, 7·15%).

Oxidation of (*R*)- and (*S*)-6β-methylsulphinylcholest-4-ene (I) and (II) individually in the above manner gave only the 6β-sulphone (XVII) quantitatively.

4β-*Methylsulphonylcholest-5-ene* (XIX).—3-Chloroperbenzoic acid (200 mg, 1·2 mmol) was added to 4β-methylthiocholest-5-ene (X) (210 mg, 0·5 mmol) in ether (18 ml) at room temperature. After 1 h the ether was removed under reduced pressure and the residue was chromatographed on a column of alumina (8 g) prepared in light petroleum. Elution with benzene gave 4β-*methylsulphonylcholest-5-ene* (XIX) (180 mg, 83%) m.p. 177—179° (from acetone), $[\alpha]_D$ −6° (*c* 0·5), $\nu_{max.}$ 1138 and 1311 cm^{-1} ($CHCl_3$) (Found: C, 75·1; H, 10·5; S, 7·15. $C_{28}H_{48}O_2S$ requires C, 74·9; H, 10·8; S, 7·15%).

Oxidation of the (*R*)- and (*S*)-4β-sulphoxides (V) and (VI) separately under the above conditions gave only the sulphone (XIX) almost quantitatively.

6α-*Methylsulphonylcholest-4-ene* (XII).—6α-Methylthiocholest-4-ene (X) (200 mg, 0·48 mmol) in light petroleum (30 ml) was treated with peroxydodecanoic acid (69% pure; 330 mg, 1·05 mmol). After 2 h at 20° the mixture was poured onto a column of alumina (10 g) prepared in light petroleum; elution with ether gave the *sulphone* (XII) (176 mg, 81%), m.p. 171—174° (from ether–methanol), $[\alpha]_D$ +36° (*c* 0·8), $\nu_{max.}$ 1144 and 1318 cm^{-1} (CCl_4) (Found: C,

74·7; H, 10·95; S, 7·3. $C_{28}H_{48}O_2S$ requires C, 74·9; H, 10·8; S, 7·1%).

Oxidation of (*S*)-6α-methylsulphinylcholest-4-ene (IV), and of a mixture of the (*R*)- and (*S*)-6α-sulphoxides (III) and (IV) [obtained by oxidation of the 6α-sulphide (XI) with hydrogen peroxide] with peroxydodecanoic acid in the above manner gave the sulphone (XII) almost quantitatively.

4α-Methylsulphonylcholest-5-ene (XX).—Peroxydodecanoic acid (78% pure; 170 mg, 0·61 mmol) was added to 4α-methylthiocholest-5-ene (XVIII) (120 mg, 0·29 mmol) in light petroleum (25 ml) at 20°, and after 2 h the mixture was poured onto a column of alumina (5 g) prepared in light petroleum. Elution with ether gave the *sulphone* (XX) (113 mg, 88%), m.p. 151—152° (from methanol), $[\alpha]_D$ −34° (*c* 0·4), $\nu_{max.}$ 1132, 1140, and 1314 cm^{-1} (CCl_4) (Found: C, 75·2; H, 10·6; S, 7·4. $C_{28}H_{48}O_2S$ requires C, 74·9; H, 10·8; S, 7·1%).

Oxidation of (*R*)-4α-methylsulphinylcholest-5-ene (VII), and of a mixture of the (*R*)- and (*S*)-4α-sulphoxides (VII) and (VIII) [obtained by oxidation of the 4α-sulphide (XII) with hydrogen peroxide] with peroxydodecanoic acid in the above manner gave only the sulphone (XX) almost quantitatively.

Thermolysis and Equilibration of the Sulphoxides (I)—(VIII) *in Benzene.*—(*a*) A solution of (*R*)-6β-methylsulphinylcholest-4-ene (I) (112 mg) in dry benzene (30 ml) was boiled for 16 h, then evaporated. The residue was chromatographed (p.l.c.) with ether–chloroform (2 : 1) as developer. Two bands at R_F *ca.* 0·4 and 0·35 were extracted together to give a mixture of the (*R*)- and (*S*)-6β-sulphoxides (I) and (II) (71 mg, 64%) containing at least 80% of the (*R*)-6β-isomer (I) according to t.l.c. comparisons with synthetic mixtures, and a band at the solvent front was extracted to give cholesta-4,6-diene (XXIX) (40 mg, 24%), $[\alpha]_D$ (before crystallisation) +4° (*c* 1·0) (lit.[34] $[\alpha]_D$ +4°; cholest-3,5-diene has $[\alpha]_D$ −123°). T.l.c. of the diene on silver-nitrate-impregnated silica [35] developed with light petroleum, conditions under which cholest-4,6-diene and cholesta-3,5-diene have slightly different R_F values, confirmed that detectable amounts of cholesta-3,5-diene were absent.

(*b*) Treatment of (*S*)-6β-methylsulphinylcholest-4-ene (II) (64 mg) in boiling benzene (15 ml) for 28 h, and chromatography in the above manner gave a mixture of the (*R*)- and (*S*)-6β-sulphoxides (I) and (II) (24 mg, 33%) containing at least 80% of the (*R*)-6β-sulphoxide (I), and cholesta-4,6-diene (XXIX) (35 mg, 64%), $[\alpha]_D$ +4°.

(*c*) (*S*)-4β-Methylsulphinylcholest-5-ene (VI) (49 mg) in boiling benzene (15 ml) for 53 h gave, after chromatography in the above manner, a mixture of (*R*)- and (*S*)-4β-methylsulphinylcholest-5-ene (V) and (VI) (17 mg, 35%), containing at least 80% of the (*S*)-4β-isomer (VI) according to t.l.c., together with cholesta-3,5-diene (XXX) (25 mg, 60%), $[\alpha]_D$ −115° (*c* 1·0) (lit.,[34] −123°), which was pure according to t.l.c. on silica impregnated with silver nitrate.

(*d*) A mixture of (*R*)- and (*S*)-6α-methylsulphinylcholest-4-ene (III) and (IV) (50 mg) in boiling benzene for 17 h gave, after chromatography in the above manner, only a mixture of cholesta-4,6-diene (XXIX) and cholesta-3,5-diene (XXX) (42 mg, 98%) having $[\alpha]_D$ −21° (*c* 1·0) and therefore containing the dienes in the ratio 4 : 1. The mixture was chromatographically (t.l.c. on silver-nitrate-impregnated silica) and spectroscopically identical with a synthetic 4 : 1 mixture of the dienes.

(*e*) (*R*)-4α-Methylsulphinylcholest-5-ene (VII) (60 mg) in boiling benzene (20 ml) under nitrogen for 24 h gave, after p.l.c. on silica impregnated with silver nitrate and development with light petroleum, cholesta-3,5-diene (41 mg, 80%), identical with an authentic specimen.

(*f*) Equilibration of the (*R*)- and (*S*)-6β-sulphoxides (I) and (II) in benzene at 56° was monitored by withdrawing samples at intervals, evaporating the solvent rapidly under reduced pressure, and determining the n.m.r. spectrum of the residue in [^{2}H]chloroform. The relative intensities of the signals due to the *S*-methyl groups provided the best measure of the relative proportions of the sulphoxides, although they partially overlapped with the ' methylene envelope '. The equilibration of the (*R*)- and (*S*)-4β-sulphoxides (V) and (VI) was followed in the same way.

(*g*) Equilibration of (*R*)- and (*S*)-6α-methylsulphinylcholest-4-ene (III) and (IV) in [$^2H_6$]benzene at 56° in an n.m.r. tube [starting from the pure (*S*)-6α-isomer (IV) and from the mixture of (III) and (IV) obtained by oxidation of the unsaturated sulphide (X) with hydrogen peroxide] was followed by measuring the relative intensities of the n.m.r. signals due to the C-4 vinyl protons at intervals. Equilibration was complete within 2 h, after which time decomposition to diene was not significant. The equilibration of (*R*)-4α-methylsulphinylcholest-5-ene (V) with its (*S*)-4α-isomer (VI) in [$^2H_6$]benzene at 56° was followed in the same way, equilibration being complete within 2·5 h. First-order rate constants were determined graphically in the usual manner.[30c,d]

Rearrangements of the Sulphoxides (I)—(VIII) *in Chlorobenzene–Piperidine.*—(*a*) (*S*)-6β-Methylsulphinylcholest-4-ene (II) (61 mg) in a mixture of chlorobenzene (3 ml) and piperidine (1·4 ml) was heated at 56° for 2·5 h, and then poured into 2M-hydrochloric acid. After extraction with ether, washing with water, and drying (Na_2SO_4) in the usual way, evaporation gave 4β-hydroxycholest-5-ene (XXI) (55 mg, 97%) identical with an authentic sample.[36]

(*b*) (*R*)-6β-Methylsulphinylcholest-4-ene (I) (105 mg), after heating in a mixture of chlorobenzene (5 ml) and piperidine (2·5 ml) at 56° for 2·5 h, was recovered unchanged (98%). After treatment under the same conditions for 92 h, the mixture was worked up in the above manner and chromatographed (p.l.c.) with benzene as developer. Extraction of a band at R_F *ca.* 0·5 gave 4β-hydroxycholest-5-ene (XXI) (89 mg, 95%); extraction of the band at the origin gave starting material (I) (4 mg, 4%).

(*c*) (*S*)-4β-Methylsulphinylcholest-5-ene (VI) (150 mg) in a mixture of chlorobenzene (7·5 ml) and piperidine (3·5 ml) was kept at 95° for 3 h. Work-up and chromatography in the above manner gave 6β-hydroxycholest-4-ene (86 mg, 91% based on sulphoxide consumed) identical with an authentic sample,[36] and the starting sulphoxide (VI) (44 mg, 30%).

(*d*) (*S*)-6α-Methylsulphinylcholest-4-ene (IV) (101 mg) in chlorobenzene (4 ml) containing piperidine (250 mg) was heated on a steam-bath for 2 h. The mixture was poured into water and worked up with ether in the usual manner to give 4α-hydroxycholest-5-ene (XXII) (80 mg, 92%), identical with an authentic specimen.[36]

(*e*) A mixture of (*R*)- and (*S*)-6α-methylsulphinylcholest-4-

[34] L. F. Fieser and M. Fieser, ' Steroids,' Rheinhold, New York, 1959, p. 265.
[35] L. J. Morris, *Chem. and Ind.*, 1962, 1238.
[36] D. N. Jones, J. R. Lewis, C. W. Shoppee, and G. H. R. Summers, *J. Chem. Soc.*, 1955, 2876; D. Lavie, S. Greenfield, Y. Kashman, and E. Glotter, *Israel J. Chem.*, 1967, **5**, 151.

ene [(III) and (IV) in the ratio of 35 : 65)] (101 mg) in chlorobenzene (4 ml) containing piperidine (250 mg) was heated at 56° for 4 h. After work-up with ether in the usual way the products were chromatographed (p.l.c.) with ether–benzene (2 : 3) as developer. Extraction of the band at R_F *ca.* 0·7 gave 4α-hydroxycholest-5-ene (XXII) (50 mg, 93% based on sulphoxide consumed); extraction of the band at R_F *ca.* 0·2 gave pure (*S*)-6α-methylsulphinylcholest-4-ene (IV) (41 mg, 42%).

(*f*) A mixture of (*R*)- and (*S*)-4α-methylsulphinylcholest-5-ene [(VII) and (VIII)] (320 mg) in a mixture of chlorobenzene (28 ml) and piperidine (6 ml) was kept at 56° for 42 min, and then worked up in the usual manner with ether. P.l.c. with ether–benzene (2 : 3) as developer gave two bands. Extraction of the band at R_F *ca.* 0·85 gave 6α-hydroxycholest-4-ene (XIV) (127 mg, 92% based on sulphoxide consumed), identical with an authentic specimen; extraction of the band at R_F *ca.* 0·25 gave pure (*R*)-4α-methylsulphinylcholest-5-ene (VII) (166 mg, 52%).

Kinetics of Rearrangement of the Sulphoxides.—The rearrangements were followed polarimetrically (Perkin-Elmer 141 polarimeter). Solutions (*ca.* 8 mg ml^{-1}) of the sulphoxides in chlorobenzene–piperidine (70 : 16 v/v), prepared in 2 ml graduated flasks, were immediately introduced into a temperature-controlled 10 cm polarimeter cell held at the operating temperature. Rotations (α) were recorded continuously as a function of time over a period of at least three half-lives, except in the case of the (*R*)-6β-sulphoxide which reacted very slowly, and the first-order rate constants were obtained from the slope ($-k/2{\cdot}303$) of the plot of $\ln(\alpha_t - \alpha_\infty)$ *vs.* time (*t*),[30c] which were good straight lines for the (*R*)-6β-sulphoxide (I) and the (*S*)-6β-sulphoxide (II). The plots for mixtures of the (*R*)- and (*S*)-6α-sulphoxides (III) and (IV) (Figure 1), and for mixtures of the (*R*)- and (*S*)-4α-sulphoxides (VII) and (VIII) (Figure 2) were typical of those for two parallel first-order reactions producing a common product,[30a] and on analysis furnished good first-order plots for the separate isomers. Since the difference between the specific rotations of the (*R*)- and (*S*)-6α-sulphoxides (III) and (IV) was small compared with the overall change in specific rotation during the rearrangements, the relative values of the initial rotation of each isomer (determined for each kinetic run by extrapolation of the first-order plot line to zero time) indicated the approximate relative proportions of the isomers in the mixture. The relative proportions of the (*R*)- and (*S*)-4α-sulphoxides (VII) and (VIII) in the mixtures were determined in the same way from the kinetic data. The Arrhenius activation energy (E_a) was calculated from the slope ($-E_a/R$) of the best straight line plot of ln *k* *vs.* T^{-1}, and the pre-exponential factor A from the Arrhenius equation $k = Ae^{-E_a/RT}$. The transition state parameters $\Delta H^\ddagger$ and $\Delta S^\ddagger$ were calculated from the Arrhenius activation parameters by using the relationships [37] $\Delta H^\ddagger = E_a - RT$, $\Delta S^\ddagger = 4{\cdot}574 \log (A/T) - 49{\cdot}203$, and $\Delta G^\ddagger = \Delta H^\ddagger - T\Delta S.^\ddagger$ The best straight lines were determined in all cases by the linear least-squares method, by using a Hewlett–Packard 9100B Calculator with 9125 B Plotter.

We thank the S.R.C. for Postgraduate Training Awards (to J. B. and R. J. K. T.).

[3/1293 *Received*, 19*th June*, 1973]

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