# Steroidal Sulphur Compounds. Part II.[1] Pyrolysis, Absolute Configuration, and Optical Rotatory Dispersion of Steroidal Methyl Sulphoxides

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Chirality at sulphur in (*R*)- and (*S*)-4β-methylsulphinyl-5α-cholestane, (*R*)- and (*S*)-5α-methylsulphinylcholestane, and 3β-acetoxy-(*R*)- and (*S*)-5α-methylsulphinylcholestane has been determined by the pyrolytic method. Base-catalysed epimerization of the 4β-sulphoxides gave (*R*)- and (*S*)-4α-methylsulphinyl-5α-cholestane. Chirality at sulphur in 3β-acetoxy-(*R*)- and (*S*)-5α-methylsulphinylcholestane was also determined by an interpretation of intramolecular reactions involving the sulphoxide group. Two Cotton effects of opposite sign near 210 and 230 mμ occur in the o.r.d. spectra of the sulphoxides. Their relevance to chirality at sulphur and to restricted rotation about a C–S bond is discussed.

CORRELATION of the absolute configurations of (+)-*S*-methyl-L-cysteine *S*-oxide, (−)-3-methylsulphinylpropyl isothiocyanate, and (*S*)-methylsulphinylbutane with their optical rotatory dispersion (o.r.d.) characteristics led to the suggestion that alkyl methyl sulphoxides of (*R*)-configuration at sulphur exhibit a negative Cotton effect near 210 mμ.[2] The absolute configurations were determined by *X*-ray analysis,[3,4] or by asymmetric synthesis.[2] Substantiation of the proposed relationship is important in view of the potential utility of the o.r.d. method in determining the chirality of sulphoxides,[2,5] and we have investigated its validity, particularly in relation to the influence of neighbouring chiral centres, by use of the pyrolytic method [1] to determine the absolute configuration of steroidal methyl sulphoxides.

*Preparation of Methylsulphinyl Steroids.*—Evidence for the absolute configurations of the compounds described in this section is presented later in the text. 4α-Methanesulphonyloxy-5α-cholestane (I) with methanethiolate ion in a boiling mixture of propan-2-ol and toluene gave 4β-methylthio-5α-cholestane (II), which was oxidised by peroxylauric acid in light petroleum to a mixture of (*R*)- and (*S*)-4β-methylsulphinyl-5α-cholestanes, (III) and (IV), separated by chromatography. Further oxidation of both sulphoxides (III) and (IV) gave the same sulphone (V). Treatment of (*R*)- and (*S*)-4β-methylsulphinyl-5α-cholestanes (III) and (IV) separately with potassium t-butoxide in dimethyl sulphoxide gave the (*R*)- and (*S*)-4α-methylsulphinyl-5α-cholestanes (VI) and (VII) respectively. These transformations are rational only in terms of the conver-

[1] Part I, D. N. Jones and M. J. Green, *J. Chem. Soc.* (*C*), 1967, 532. Preliminary communications (*a*) D. N. Jones and M. A. Saeed, *Proc. Chem. Soc.*, 1964, 81; (*b*) D. N. Jones, M. J. Green, M. A. Saeed, and R. D. Whitehouse, *Chem. Comm.*, 1967, 1003.

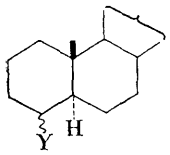
[2] K. Mislow, M. M. Green, P. Laur, J. T. Melillo, T. Simmons, and A. L. Ternay, *J. Amer. Chem. Soc.*, 1965, **87**, 1958.

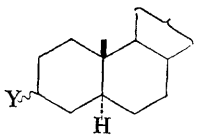
[3] R. Hine, *Acta Cryst.*, 1962, **15**, 635.

[4] K. K. Cheung, A. Kjaer, and G. A. Sim, *Chem. Comm.*, 1965, 100.

[5] W. Klyne, J. Day, and A. Kjaer, *Acta Chem. Scand.*, 1960, **14**, 215.

sion of the methylsulphinyl group from an axial into an equatorial orientation, and so establish the configurations at C-4. Each 4β-sulphoxide gave only one 4α-sulphoxide under these conditions, so equilibration at carbon is not





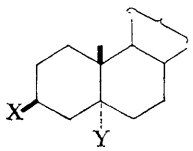
| | Y |
|---|---|
| (I) | 4α-$MeSO_2$·O |
| (II) | 4β-MeS |
| (III) | (*R*)-4β-MeSO |
| (IV) | (*S*)-4β-MeSO |
| (V) | 4β-$MeSO_2$ |
| (VI) | (*R*)-4α-MeSO |
| (VII) | (*S*)-4α-MeSO |
| (VIII) | 4α-$MeSO_2$ |

| | Y |
|---|---|
| (IX) | 3β-*p*-Me·$C_6H_4$·$SO_2$·O |
| (X) | 3α-MeS |
| (XI) | (*S*)-3α-MeSO |
| (XII) | 3α-$MeSO_2$ |
| (XIII) | (*S*)-3β-MeSO |

accompanied by inversion at sulphur, in accord with previous observations.[1,6] The 4α-sulphoxides (VI) and (VII) gave the same sulphone (VIII) on further oxidation.

Treatment of 3β-toluene-*p*-sulphonyloxy-5α-cholestane (IX) with methanethiolate ion in propan-2-ol under reflux gave 3α-methylthio-5α-cholestane (X), which on oxidation with peroxylauric acid in light petroleum gave a mixture of (*R*)- and (*S*)-3α-methylsulphinyl-5α-cholestanes. The (*S*)-3α-sulphoxide (XI) was obtained from the mixture by repeated t.l.c., or by crystallization from methanol, but the (*R*)-3α-sulphoxide could not be obtained pure. Oxidation of the (*S*)-3α-sulphoxide (XI) or the mixture of diastereomeric sulphoxides gave the 3α-sulphone (XII). Equilibration of the (*S*)-3α-sulphoxide (XI) with potassium t-butoxide in dimethyl sulphoxide gave (*S*)-3β-methylsulphinyl-5α-cholestane (XIII). Retention of configuration at sulphur is assumed by analogy with the behaviour of the 4β-sulphoxides (III) and (IV), and of other sulphoxides [1,6] under these conditions.

3β-Acetoxy-5α-mercaptocholestane [7] (XIV) on treatment with diazomethane gave 3β-acetoxy-5α-methylthiocholestane (XV), which was oxidised by hydrogen peroxide in acetic acid to a mixture of 3β-acetoxy-(*R*)- and -(*S*)-5α-methylsulphinylcholestanes (XVI) and (XVII). The sulphoxides (XVI) and (XVII) were separated chromatographically, and each gave the sulphone (XVIII) on further oxidation. 5α-Mercaptocholestan-3β-ol [7] (XIX) with ethereal diazomethane gave 5α-methylthiocholestan-3β-ol (XX), which was converted into the methanesulphonate (XXI) and then treated with boiling ethereal lithium aluminium hydride. The products, 5α-methylthiocholestane (XXII) and 3α-methylthiocholest-5-ene (XXIII) were separated chromatographically. The position of the double bond in (XXIII) was indicated by Raney nickel desulphurization to cholest-5-ene (XXIV), and the 3α-position of the *S*-methyl group was deduced from a mechanistic interpretation of its formation from the 3β-methanesulphonate (XXI). We consider that intramolecular displacement of the 3β-methanesulphonate group by the 5α-methylthio-group leads to the sulphonium ion (XXV), which collapses to 3α-methylthiocholest-5-ene (XXIII). There are numerous examples of neighbouring-group participation by alkylthio-groups in other systems,[8] and of intramolecular displacement of 3β-orientated leaving groups by other 5α-substituents in steroids.[9] We also found that 3β-methanesulphonyloxy-5α-methylthiocholestane (XXI) reacted with tetrapropylammonium acetate in methyl ethyl ketone to give 3α-methylthiocholest-5-ene (XXIII) (92%) and 3β-acetoxy-5α-methylthiocholestane (XV) (6%). The formation of the acetoxy-sulphide (XV) with retention of configuration at C-3 is a clear indication of participation by the 5α-



| | X | Y | | X | Y |
|---|---|---|---|---|---|
| (XIV) | AcO | HS | (XXII) | H | MeS |
| (XV) | AcO | MeS | (XXVII) | H | (*R*)-MeSO |
| (XVI) | AcO | (*R*)-MeSO | (XXVIII) | H | (*S*)-MeSO |
| (XVII) | AcO | (*S*)-MeSO | (XXIX) | H | $MeSO_2$ |
| (XVIII) | AcO | $MeSO_2$ | (XXXIII) | HO | (*R*)-MeSO |
| (XIX) | HO | HS | (XXXIV) | $MeSO_2$·O | (*R*)-MeSO |
| (XX) | HO | MeS | (XXXVI) | HO | (*S*)-MeSO |
| (XXI) | $MeSO_2$·O | MeS | (XXXVII) | $MeSO_2$·O | (*S*)-MeSO |

methylthio-group in heterolysis of the 3β-methanesulphonate group; under the same reaction conditions 3β-toluene-*p*-sulphonyloxy-5α-cholestane gives only 3α-acetoxy-5α-cholestane (85%) and 5α-cholest-2-ene (14%).[10] The n.m.r. spectrum and molecular rotation of the unsaturated sulphide (XXIII) were consistent with the structure allocated. The structure allocated to the saturated sulphide (XXII) was consistent with its n.m.r. spectrum and molecular rotation, and with the pyrolytic decomposition of the derived sulphoxides to give mixtures of cholest-5-ene (XXIV) and cholest-4-ene (XXVI) (see later). Oxidation of the methyl sulphide (XXII) with peroxylauric acid in light petroleum gave a mixture of (*R*)- and (*S*)-5α-methylsulphinylcholestanes, (XXVII) and (XXVIII), which were separated chromatographically. The sulphoxides (XXVII) and (XXVIII) gave the same sulphone (XXIX) on further oxidation.

The n.m.r. spectra of the sulphides, sulphoxides, and sulphones (Table 1) substantiated the above assignments of configuration. The 19-methyl group resonates at lower field in the 4β-sulphoxides and sulphones than in the corresponding 4α-sulphoxides and sulphones, which is consistent with the closer proximity of the methylsulphinyl or methylsulphonyl group to the 19-methyl group in the axial 4β-compounds than in the equatorial

[6] D. J. Cram and S. H. Pine, *J. Amer. Chem. Soc.*, 1963, **85**, 1096.
[7] T. Komeno, *Chem. and Pharm. Bull. (Japan)*, 1960, **18**, 672.
[8] K. D. Gundermann, *Angew. Chem. Internat. Edn.*, 1963, **2**, 674; B. Capon, *Quart. Rev.*, 1964, 45.
[9] P. A. Plattner and W. Lang, *Helv. Chim. Acta*, 1944, **27**, 1872; R. B. Clayton, H. B. Henbest, and M. Smith, *J. Chem. Soc.*, 1957, 1982.
[10] H. B. Henbest and W. R. Jackson, *J. Chem. Soc.*, 1962, 954.

4α-compounds.[11] It also resonated 8 c./sec. to lower field in the (*R*)-4β-sulphoxide (III) than in the (*S*)-4β-sulphoxide (IV), and 4 c./sec. to lower field in the (*S*)-4α-sulphoxide (VII) than in the (*R*)-4α-sulphoxide (VI), which indicates restricted rotation about the C(4)–S bond; the difference in deshielding of the 19-methyl group due to magnetic anisotropy of the S=O bond [12,13] in these pairs of compounds diastereomeric at sulphur is consistent with a difference in geometrical relationship between the sulphoxide and the C(19)-groups. The pronounced deshielding of the 19-methyl group in the 5α-sulphides, sulphoxides, and sulphones is in accord with that observed for other 5α-substituted steroids.[11]

TABLE 1

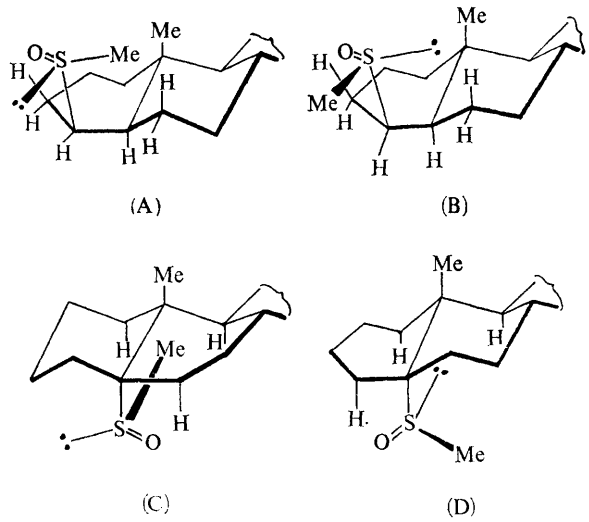
N.m.r. data (τ) of steroidal methyl sulphides, sulphoxides, and sulphones

| | Compound | Geminal H * | | | *S*-Me | 19-Me | | 18-Me | |
|---|---|---|---|---|---|---|---|---|---|
| | | | τ | $W_{\frac{1}{2}}$ | τ | τ | Δ | τ | Δ |
| (II) | 4β-MeS | 4α(e) | 7·32 | 7 | 7·97 | 9·07 | +9·5 | 9·35 | −0·5 |
| (III) | (*R*)-4β-MeSO | 4α(e) | 7·25 | | 7·43 | 8·82 | +24·5 | 9·33 | 0 |
| (IV) | (*S*)-4β-MeSO | 4α(e) | | | 7·48 | 8·95 | +16·5 | 9·33 | 0 |
| (VI) | (*R*)-4α-MeSO | 4β(a) | | | 7·56 | 9·16 | +4·0 | 9·33 | 0 |
| (VII) | (*S*)-4α-MeSO | 4β(a) | 7·07 | 18 | 7·65 | 9·08 | +8·5 | 9·33 | 0 |
| (V) | 4β-$MeSO_2$ | 4α(e) | 6·88 | 9 | 7·14 | 8·9 | +19·5 | 9·35 | −0·5 |
| (VIII) | 4α-$MeSO_2$ | 4β(a) | | | 7·19 | 9·13 | +5·5 | 9·33 | 0 |
| (X) | 3α-MeS | 3β(e) | 7·06 | 7 | 8·01 | 9·21 | +1·0 | 9·35 | −0·5 |
| (XI) | (*S*)-3α-MeSO | 3β(e) | 7·25 | 8 | 7·45 | 9·16 | +4·0 | 9·35 | −0·5 |
| (XIII) | (*S*)-3β-MeSO | 3α(a) | | | 7·48 | 9·17 | +3·5 | 9·33 | 0 |
| (XII) | 3α-$MeSO_2$ | 3β(e) | 6·94 | 8 | 7·11 | 9·17 | +6·5 | 9·33 | 0 |
| (XXII) | 5α-MeS | | | | 8·24 | 8·93 | +17·5 | 9·35 | −0·5 |
| (XXVII) | (*R*)-5α-MeSO | | | | 7·40 | 8·82 | +24·5 | 9·30 | +2·0 |
| (XXVIII) | (*S*)-5α-MeSO | | | | 7·39 | 8·83 | +23·5 | 9·32 | +1·5 |
| (XXIX) | 5α-$MeSO_2$ | | | | 7·15 | 8·88 | +20·5 | 9·34 | −0·5 |

* e = Equatorial, a = axial; $W_{\frac{1}{2}}$ band width at half height in c./sec.; Δ chemical shift from cholestane value in c./sec. (positive value denotes downfield shift).

*Pyrolysis of the Sulphoxides.*—(*S*)-4β-Methylsulphinyl-5α-cholestane (IV) gave only 5α-cholest-3-ene (XXX) after 100 hr. in boiling benzene. The yield was 95% based on starting material consumed; starting material (50%) was recovered. (*R*)-4β-Methylsulphinyl-5α-cholestane (III) was inert under these conditions, and was unchanged after 72 hr. in boiling toluene. Rationalization of this difference in reactivity in terms of the non-bonded interactions of the methylsulphinyl group in the transition state leading to 5α-cholest-3-ene reveals the configuration about sulphur.[1,14] The pyrolysis of sulphoxides proceeds predominantly by a cyclic intramolecular mechanism leading to stereospecific *cis*-elimination.[15] Models show that the (*S*)-4β-sulphoxide (IV) should be the more reactive in pyrolytic elimination, since the transition state from the (*R*)-4β-sulphoxide (III) is destabilized by non-bonded interactions involving the *S*-methyl group, the 19-methyl group, and the 6β-hydrogen (A), whereas that from the (*S*)-4β-sulphoxide (IV) is unhindered (B).† Since the absolute configuration of the steroid skeleton is known,[16] the absolute configurations of the two 4β-sulphoxides (III) and (IV) were established. This leads to an assignment of configuration for the two 4α-sulphoxides (VI) and (VII) formed from the 4β-sulphoxides by isomerization about C-4.

(*R*)-5α-Methylsulphinylcholestane (XXVII) decomposed after 2 hr. in boiling benzene to give cholest-4-ene (XXVI) and cholest-5-ene (XXIV) in the ratio 83 : 17

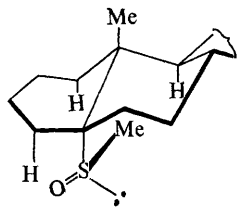



(65% combined yield). (*S*)-5α-Methylsulphinylcholestane (XXVIII) under the same conditions gave the

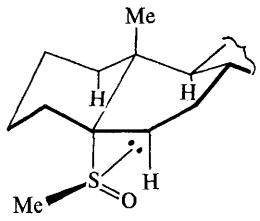
† Since it is impossible to depict these transition states accurately, the configurations of the reacting molecules which approximate to the configurations of the transition state are drawn.

[11] K. Tori and T. Komeno, *Tetrahedron*, 1965, **21**, 309.
[12] K. W. Buck, A. B. Foster, W. D. Pardoe, M. H. Qadir, and J. M. Webber, *Chem. Comm.*, 1966, 759; A. B. Foster, J. M. Duxbury, T. D. Inch, and J. M. Webber, *ibid.*, 1967, 881.
[13] R. Nagarajan, B. H. Chollar, and R. M. Dodson, *Chem. Comm.*, 1967, 550; P. B. Sollman, R. Nagarajaran, and R. M. Dodson, *ibid.*, p. 552.
[14] Cf. ref. 1, and S. I. Goldberg and M. S. Sahli, *J. Org. Chem.*, 1967, **32**, 2059.
[15] C. A. Kingsbury and D. J. Cram, *J. Amer. Chem. Soc.*, 1960, **82**, 1810.
[16] J. A. Mills, *J. Chem. Soc.*, 1952, 4976; V. Prelog and H. L. Meier, *Helv. Chim. Acta*, 1953, **36**, 320; B. Riniker, D. Arigoni, and O. Jeger, *ibid.*, 1954, **37**, 546; J. W. Cornforth, I. Youhotsky, and G. Popjak, *Nature*, 1954, **173**, 536.

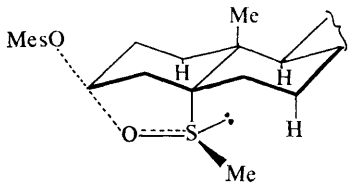
same two olefins (XXVI) and (XXIV) in the ratio 56 : 44 (89% combined yield). These results permitted assignment of configuration about sulphur. Models show that steric interactions between the *S*-methyl group and the 1α- and 9α-hydrogens in the transition state (C) leading from the (*R*)-5α-sulphoxide to cholest-5-ene render it less favourable than the transition state (D) leading to cholest-4-ene. Similarly the transition state (E) from the (*S*)-5α-sulphoxide to cholest-4-ene is destabilized by steric interactions between the *S*-methyl group and the 1α- and 9α-hydrogens, whereas the transition state (F) leading to cholest-5-ene is unhindered. The (*R*)-5α-sulphoxide should therefore give the greater proportion of cholest-4-ene, and the relative configurations of the two sulphoxides were assigned on this basis. Since the absolute configuration of cholestane is known,[16] in a manner analogous to that used for the 5α-sulphoxides (XXVII) and (XXVIII) to allocate configuration at sulphur. In contrast to the 5α-sulphoxides (XXVII) and (XXVIII), the 3β-acetoxy-5α-sulphoxides (XVI) and (XVII) eliminated methane sulphenic acid predominantly in the predicted direction. The compositions of the mixtures of olefins obtained from the four 5α-sulphoxides were determined polarimetrically; application of the method to synthetic mixtures of the olefins confirmed that it was accurate to ±2%. The 3α-hydrogens in the (*R*)-5α-sulphoxides (XVI) and (XXVII) and the 7α-hydrogens in the (*S*)-5α-sulphoxides (XVII) and (XXVIII) were suitably orientated for 1,3-elimination, but we found no evidence for the products of such reactions. Base-catalysed 1,3-eliminations of sulphoxides have been reported.[18]



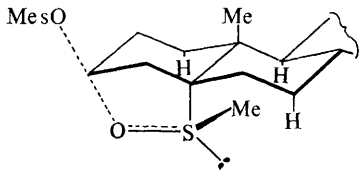

(E)




(F)




(G)




(H)

and the 5α-configuration of the methylthio-group has been unambiguously assigned by synthesis,[7] the absolute configurations of the two 5α-sulphoxides (XXVII) and (XXVIII) were established. The slight preponderance of cholest-4-ene (instead of a preponderance of cholest-5-ene, expected according to the above steric arguments) obtained from the (*S*)-5α-sulphoxide (XXVIII) may be associated with the greater ease of bringing the 4α-H and 5α-S bonds (compared with the 6α-H and 5α-S bonds) into the required *syn*-periplanar arrangement for elimination, because of the greater flexibility of ring A compared with that of the doubly fused ring B. This explanation is analogous to that used to account for the reluctance of (*R*)-4α-phenylsulphinyl-5α-cholestane to give cholest-4-ene,[1] and 6α-dimethylamino-5α-cholestane *N*-oxide to give cholest-5-ene on pyrolysis.[17]

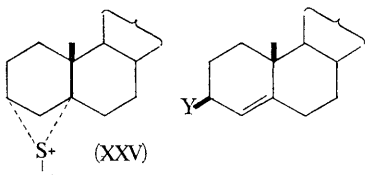
3β-Acetoxy-(*R*)-5α-methylsulphinylcholestane (XVI) after 3·5 hr. in boiling benzene gave only 3β-acetoxycholest-4-ene (XXXI) (89%), whereas under the same conditions 3β-acetoxy-(*S*)-5α-methylsulphinylcholestane (XVII) gave a mixture (36 : 64) of 3β-acetoxycholest-4-ene (XXXI) and 3β-acetoxycholest-5-ene (XXXII) (combined yield 95%). These results were interpreted

Chirality at sulphur in the 3α- and 3β-methyl sulphoxides (XI) and (XIII) was not established by pyrolysis, because they decomposed extremely slowly at 110°; higher temperatures were not employed because of the incursion of non-stereospecific elimination mechanisms.[15] Furthermore the procedure would be unreliable since only one diastereoisomer at sulphur was available for each orientation at C-3, and the method depends essentially upon a comparison of the pyrolytic behaviour of both diastereoisomers at sulphur. They were tentatively assigned the (*S*)-configuration on the basis of their o.r.d. behaviour.

*Intramolecular Reactions of the 5α-Sulphoxides.*—The allocation of chirality at sulphur in the 3β-acetoxy-5α-sulphoxides (XVI) and (XVII) was substantiated in the following manner.[1a] Hydrolysis of 3β-acetoxy-(*R*)-5α-methylsulphinylcholestane (XVI) gave the corresponding hydroxy-sulphoxide (XXXIII) which on treatment with methanesulphonyl chloride in pyridine at 0° did not give the expected methanesulphonate (XXXIV), but the

[17] R. Ledger, A. J. Smith, and J. McKenna, *Tetrahedron*, 1964, **20**, 2413.
[18] R. Baker and M. J. Spillet, *Chem. Comm.*, 1966, 757.

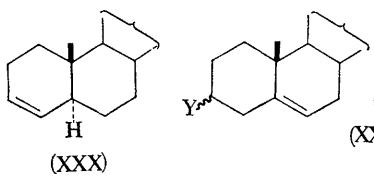
sulphoxonium salt (XXXV) (90%) instead. A similar sequence of reactions under identical conditions to the above starting from 3β-acetoxy-(*S*)-5α-methylsulphinylcholestane (XVII), by way of the hydroxy-sulphoxide (XXXVI), led to 3β-methanesulphonyloxy-(*S*)-5α-methylsulphinylcholestane (XXXVII); no salt analogous to (XXXV) was obtained. The methanesulphonate (XXXVII) decomposed on brief treatment with boiling methanol to give 3α-hydroxycholest-5-ene (XXXVIII). An interpretation of these reactions revealed the chirality about sulphur in these sulphoxides. The probable configurations of the transition states for intramolecular nucleophilic displacement of the methanesulphonyl group by sulphoxide oxygen in the methanesulphonates (XXXIV) and (XXXVII) are depicted in (G) and (H) respectively. It is apparent that the transition state (H) from the (*S*)-5α-sulphoxide (XXXVII) is of higher energy than that (G) from the (*R*)-5α-sulphoxide (XXXIV), because there are non-bonded interactions between the *S*-methyl group and the 1α-, 7α-, and 9α-hydrogens in the former transition state which are absent in the latter. This accounts for the reactivity







| | Y |
|---|---|
| (XXVI) | H |
| (XXXI) | AcO |
| (XL) | $MeSO_2·O$ |

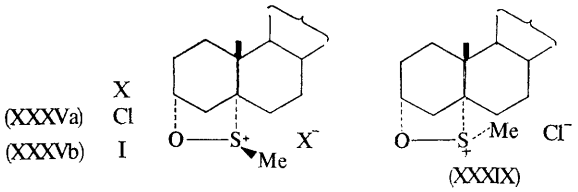






| | Y |
|---|---|
| (XXIII) | 3α-MeS |
| (XXIV) | H |
| (XXXII) | 3β-AcO |
| (XXXVIII) | 3α-HO |
| (XLI) | $3β-MeSO_2·O$ |

of the methanesulphonate (XXXIV) being greater than that of (XXXVII); the methanesulphonate (XXXIV) reacted so readily to give the salt (XXXV) that it could not be isolated. The conversion of the methanesulphonate (XXXVII) into 3α-hydroxycholest-5-ene (XXXVIII) in boiling methanol is consistent with the intermediate formation of the sulphoxonium salt (XXXIX), which being destabilised by non-bonded interactions of the methyl group analogous to those described in (H) undergoes elimination at C-5 very readily, with concomitant or subsequent fission of the S–O bond. The result is transfer of the sulphoxide oxygen to C-3. A sulphoxonium salt analogous to (XXXV), formed by an intramolecular displacement reaction, has been isolated by Montanari and his co-workers,[19] who also found that the rate of intramolecular displacement by sulphinyl oxygen was markedly dependent upon the chirality of the sulphoxide. There are numerous examples of neighbouring group participation by a sulphoxide group.[19,20] Minor products in the reaction of methanesulphonyl chloride with the hydroxy-sulphoxides (XXXIII) and (XXXVI) were substances chromatographically identical with 3β-methanesulphonyloxycholest-5-ene (XLI) and 3β-methanesulphonyloxy-5α-methylthiocholestane (XXI). 3β-Methanesulphonyloxycholest-4-ene (XL), expected as a product by analogy with the behaviour of 3β-




acetoxy-5α-sulphoxides with methanesulphonyl chloride,[21] may also be present, but this was not established, since 3β-substituted cholest-4- and 5-enes are usually identical chromatographically. 3β-Acetoxy-(*R*)- and (*S*)-5α-methylsulphinylcholestanes (XVI) and (XVII) reacted with methanesulphonyl chloride to give only 3β-acetoxycholest-4-ene (XXXI), 3β-acetoxycholest-5-ene (XXXII), and 3β-acetoxy-5α-methylthiocholestane (XV),[21] which suggests that the methanesulphonates (XLI) and (XXI) were not formed by way of sulphoxonium salts such as (XXXV) and (XXXIX).

TABLE 2

U.v. data * for steroidal methyl sulphoxides

| | Compound | λ (mμ) | ε |
|---|---|---|---|
| (III) | (*R*)-4β-MeSO | 210 | 3500 |
| (IV) | (*S*)-4β-MeSO | 212 | 4000 |
| (VI) | (*R*)-4α-MeSO | 210 | 3350 |
| (VII) | (*S*)-4α-MeSO | 212 | 2650 |
| (XI) | (*S*)-3α-MeSO | 210 | 4000 |
| (XIII) | (*S*)-3β-MeSO | 211 | 4200 |
| (XVI) | 3β-OAc-(*R*)-5α-MeSO | 217 | 2600 |
| (XVII) | 3β-OAc-(*S*)-5α-MeSO | 215 | 5800 |
| (XXVIII) | (*S*)-5α-MeSO | 221 | 3500 |

* Solvent hexane.

U.v. spectral data of the sulphoxides in hexane are recorded in Table 2. As for aryl alkyl sulphoxides,[1,22] it appears that steric compression of the sulphinyl chromophore causes a red shift in the main absorption band, which occurred between 210 and 212 mμ for the C(3)- and C(4)-sulphoxides, and between 215 and 221 mμ in the C(5)-sulphoxides. All the sulphoxides except (*S*)-4α-methylsulphinylcholestane (VII) and 3β-acetoxy-(*S*)-5α-methylsulphinylcholestane (XVII) also displayed a shoulder at *ca.* 230 mμ, and the presence of this transition (hidden in the tail of the adjacent band) in (VII) and (XVII) was revealed by their o.r.d. curves. These two bands correlate with those at 206 and 215 mμ

[19] H. Hogeveen, G. Maccagnani, and F. Montanari, *J. Chem. Soc.* (*C*), 1966, 1585.

[20] N. J. Leonard and C. R. Johnson, *J. Amer. Chem. Soc.*, 1962, **84**, 3701; J. D. Loudon and D. M. Smith, *J. Chem. Soc.*, 1964, 2801; N. J. Leonard and W. L. Rippie, *J. Org. Chem.*, 1963, **28**, 1957; J. C. Martin and J. J. Uebel, *J. Amer. Chem. Soc.*, 1964, **86**, 2936; K. W. Buck, A. B. Foster, A. R. Perry, and J. M. Webber, *Chem. Comm.*, 1965, 433.

[21] D. N. Jones, M. J. Green, and M. A. Saeed, *Chem. Comm.*, 1967, 674.

[22] A. Cerniani, G. Modena, and P. E. Todesco, *Gazzetta*, 1960, **90**, 3; G. M. Gasperini, G. Modena, and P. E. Todesco, *ibid.*, p. 12; I. V. Baliah and R. Varadachari, *J. Indian Chem. Soc.*, 1960, **37**, 321.

(shoulder) given by (*S*)-methylsulphinylbutane,[2] and at 200 and 220 mμ (shoulder) for some cyclic sulphoxides.[13] The o.r.d. curves of the C(4)- (Figure 1) and C(5)-sulphoxides (Figure 2) show that both transitions are optically active. Interpretation of the curves was complicated by overlapping and variation in the relative intensities of the two Cotton effects, which may be better investigated by circular dichroism techniques.[23] However the following general features were apparent in the o.r.d. curves. Sulphoxides of (*S*)-configuration at sulphur show a first extremum near 220 mμ of a positive Cotton effect, and a Cotton effect of opposite sign near 230 mμ. Conversely, the (*R*)-sulphoxides had a first extremum of a negative Cotton effect near

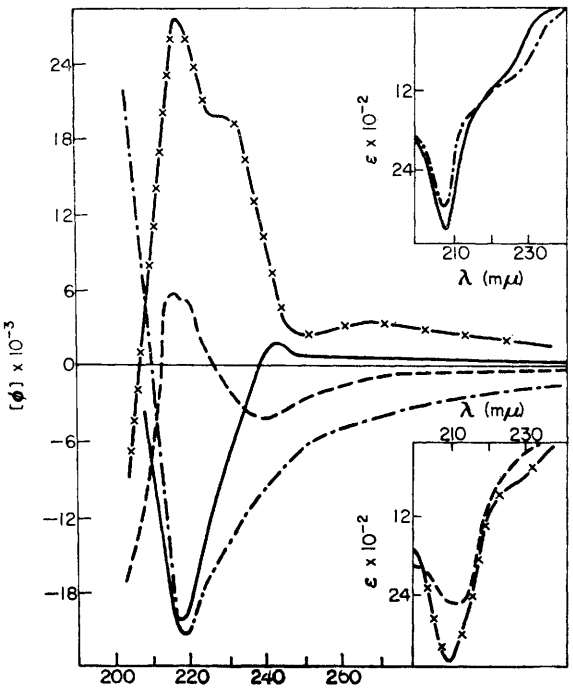



FIGURE 1 O.r.d. curves of C(4)-sulphoxides; (——) (*R*)-4β-methylsulphinyl-5α-cholestane (III), (—×—×—) (*S*)-4β-methylsulphinyl-5α-cholestane (IV), (—·—·—) (*R*)-4α-methylsulphinyl-5α-cholestane (VI), (– – – –) (*S*)-4α-methylsulphinyl-5α-cholestane (VII)

220 mμ, and a Cotton effect of opposite sign near 230 mμ. The longer wavelength Cotton effect was weak for the C(4)-sulphoxides [it was completely obscured for the (*R*)-4α-sulphoxide (VI)] and strong for the C(5)-sulphoxides, where its second extremum possibly obscured the first extremum of the shorter wavelength Cotton effect. The behaviour of the shorter wavelength Cotton effect is in accord with Mislow's generalization relating Cotton effect sign to sulphoxide chirality,[2] but the extremum near 220 mμ, positive for (*S*)-sulphoxides and negative for (*R*)-sulphoxides, is a more readily identified feature for allocating sulphoxide configuration when complicating Cotton effects occur at longer wavelengths.

[23] P. Crabbé, 'Optical Rotatory Dispersion and Circular Dichroism in Organic Chemistry,' Holden-Day, San Francisco, 1965, p. 50.

The presence of the 3β-acetoxy-group does not influence the sign and shape of the o.r.d. curves of the C(5)-sulphoxides, although the amplitude is decreased. The (*R*)-5α-sulphoxide (XXVII) decomposed before an

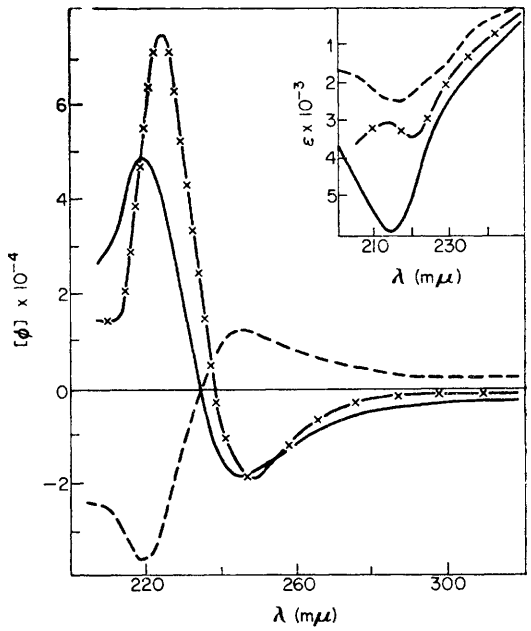



FIGURE 2 O.r.d. curves of C(5)-sulphoxides; (——) 3β-acetoxy-(*S*)-5α-methylsulphinylcholestane (XVII), (– – – –) 3β-acetoxy-(*R*)-5α-methylsulphinylcholestane (XVI), (—×—×—) (*S*)-5α-methylsulphinylcholestane (XXVIII)

accurate spectrum was obtained, but gave a curve qualitatively the mirror image of that of the (*S*)-5α-sulphoxide (XXVIII).

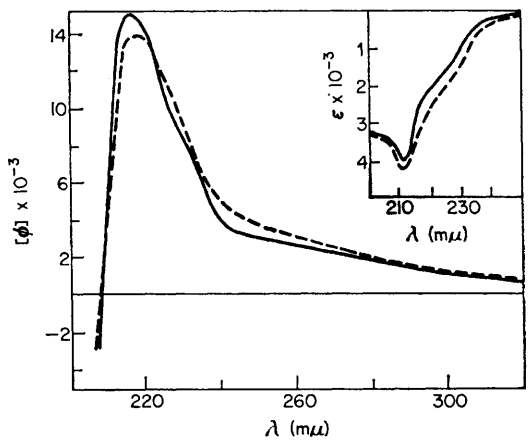



FIGURE 3 O.r.d. curves of C(3)-sulphoxides; (——) 3α-methylsulphinyl-5α-cholestane (XI), (– – – –) 3β-methylsulphinyl-5α-cholestane (XIII)

The o.r.d. curves (Figure 3) of the 3α- and 3β-methyl sulphoxides (XI) and (XIII) showed first extrema near 220 mμ of a positive Cotton effect, and they were therefore assigned the (*S*)-configuration. The 3α-sulphoxide showed a slight inflexion near 230 mμ, possibly due to an underlying Cotton effect.

Above 300 mμ the (*R*)- and (*S*)-4β-sulphoxides (III) and (IV) showed positive, and the (*R*)- and (*S*)-4α-sulphoxides (VI) and (VII) negative plain curves, so that these are not indicative of sulphoxide chirality. The (*R*)-5α-sulphoxide (XVI) had a positive, and the (*S*)-5α-sulphoxides (XVII) and (XXVIII) negative plain curves above 260 mμ. This contrasts with the negative plain curves above 300 mμ of thiourea derivatives of a series of naturally occurring (*R*)-methylsulphinyl isothiocyanates, $MeSO\cdot[CH_2]_n\cdot NCS$ ($n = 3$—5, 8—10).[5] Comparison of plain curves above 300 mμ is probably a valid method of determining the configuration of sulphoxides if sulphur is the sole chiral centre, but the present work shows that the method is inapplicable to methyl alkyl sulphoxides containing a dissymmetric alkyl group.

All the methylsulphinyl steroids behave like (*S*)-methylsulphinylbutane,[2] (—)-3-methylsulphinylpropyl isothiocyanate,[2,4] and four methylsulphinyl amino-acids,[24] in that the (*R*)-sulphoxides gave negative Cotton effects near 210 mμ. Among all these methyl alkyl sulphoxides only the teroidal C(4)- and C(5)-methyl sulphoxides display Cotton effects near 230 mμ, which appear to be associated with the presence of a dissymmetric alkyl group, and with restricted rotation about a C–S bond and consequent adoption of a preferred orientation by the methylsulphinyl group with respect to the steroid nucleus. The optical rotatory power of the carbonyl group in 17-acetyl steroids [25] and steroidal acetates [26] has been explained in an analogous fashion. Preferred conformations of the methylsulphinyl group in the four C(4)-sulphoxides are highly populated, according to n.m.r. evidence, and the dominance of the o.r.d. spectra of the 5α-sulphoxides by the 230 mμ Cotton effect is rational if each sulphoxide exists largely in one conformation (reasonable from Dreiding models) so maximising the perturbing effect of the steroid nucleus. The mirror-image relationship of the curves from 3β-acetoxy-(*R*)- and -(*S*)-5α-methylsulphinylcholestanes (XVI) and (XVII) is consistent with severely restricted rotation about the C(5)-sulphur bonds, since in their least hindered conformations the sulphoxides are pseudo-enantiomeric.

The large amplitude of the Cotton effect near 210 mμ, together with the consistent relationship between its sign and sulphoxide chirality, are properties usually associated with an inherently dissymmetric chromophore,[27] but the incursion of another Cotton effect of widely varying amplitude at longer wavelengths renders attempts at classification of the methylsulphinyl group as an inherently dissymmetric or asymmetrically perturbed symmetric chromophore of doubtful utility.

Some sulphoxides associate in solution,[2,28] but the o.r.d. behaviour of the steroidal methyl sulphoxides cannot be attributed to varying degrees of dimerization since osmometry indicated that they are monomeric in hexane over the range of concentrations used for o.r.d. measurements.

## EXPERIMENTAL

M.p.s were determined with a Kofler hot-stage apparatus. Preparative t.l.c. was performed with glass plates 25 cm. square and a layer of Silica Gel G (Merck) 1 mm. thick. The silica gel was mixed with 6% aqueous silver nitrate solution to make silver-nitrate-impregnated plates for separation of olefins.[29] I.r. spectra were measured with a Unicam SP 100 spectrophotometer, and u.v. spectra were determined for solutions in hexane with a Perkin-Elmer Ultracord spectrophotometer and a Unicam SP 500 spectrophotometer. Rotations cited are for chloroform solutions. Optical rotatory dispersions were measured with hexane as solvent with a Bendix Polarmatic 62 automatic recording instrument. N.m.r. spectra were determined with a Varian A 60 spectrometer for deuteriochloroform solutions, and are recorded on the τ scale. Light petroleum refers to the fraction b.p. 40—60°.

4β-*Methylthio-5α-cholestane* (II).—4α-Methanesulphonyloxy-5α-cholestane (I) (2·2 g.) was added to a solution of sodium (1 g.) in a mixture of propan-2-ol (20 ml.), toluene (40 ml.), and methanethiol (10 ml.). After 3 days at 100° the product was extracted with ether and worked up in the usual way to give a yellow solid (1·75 g.) which was chromatographed on alumina (60 g.). Elution with light petroleum (100 ml.) gave a mixture of 5α-cholest-3-ene and cholest-4-ene (0·4 g.); further elution (25 ml.) gave a mixture (0·5 g.), and final elution (175 ml.) gave the *product* (II) (0·8 g.), m.p. 121—122° (from ether–methanol), $[\alpha]_D$ +57° (*c* 1·9), (Found: C, 80·1; H, 12·0; S, 7·9. $C_{28}H_{50}S$ requires C, 80·3; H, 12·0; S, 7·7%). Re-chromatography of the mixture gave more sulphide (188 mg.; total yield 988 mg., 50%).

(R)-4β- *and* (S)-4β-*Methylsulphinyl-5α-cholestane* (III) *and* (IV).—Peroxylauric acid (95% pure, 320 mg., 1·5 mmole) in light petroleum (30 ml.) was added to 4β-methylthio-5α-cholestane (II) (600 mg., 1·4 mmoles). After 15 min. at 20° the solution was diluted with ether (300 ml.) and filtered through alumina (15 g.). Evaporation left a solid (800 mg.) which was chromatographed on six silica plates developed in chloroform–ether (1 : 1). The two bands were extracted individually with ether, to give (R)-4β-*methylsulphinyl-5α-cholestane* (III) (250 mg., 40%) as needles, m.p. 162—164° (from methanol), $[\alpha]_D$ +15° (*c* 1·7), $\nu_{max.}$ (KBr) 1023 and 1038, $\nu_{max.}$ ($CCl_4$) 1052 $cm.^{-1}$, $\lambda_{max.}$ 210 mμ (ε 3500), o.r.d. $[\Phi]_{244}$ +1200°, $[\Phi]_{238}$ 0, $[\Phi]_{218}$ −20,800° (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%), and (S)-4β-*methylsulphinyl-5α-cholestane* (IV) (250 mg., 40%) as needles, double m.p. 155—156/160—163° (from methanol), $[\alpha]_D$ +83° (*c* 2·1), $\nu_{max.}$ (KBr) 1027 and 1034, $\nu_{max.}$ ($CCl_4$) 1059 $cm.^{-1}$, $\lambda_{max.}$ 212 mμ (ε 4000), o.r.d. $[\Phi]_{265}$ +3000°, $[\Phi]_{250}$ +1900°, $[\Phi]_{216}$ +27,500°, $[\Phi]_{205}$ 0° (Found: C, 77·1; H, 11·5; S, 7·6%).

4β-*Methylsulphonyl-5α-cholestane* (V).—(*a*) (*S*)-4β-Methyl-

[24] W. Gaffield, F. F. Wong, and J. F. Carson, *J. Org. Chem.*, 1965, **30**, 951.
[25] K. M. Wellman and C. Djerassi, *J. Amer. Chem. Soc.*, 1965, **87**, 60.
[26] J. P. Jennings, W. P. Mose, and P. M. Scopes, *J. Chem. Soc.* (*C*), 1967, 1102.
[27] A. Moscowitz in ch. 12 of C. Djerassi, 'Optical Rotatory Dispersion,' McGraw-Hill, New York, 1960; A. Moscowitz, K. Mislow, M. A. W. Glass, and C. Djerassi, *J. Amer. Chem. Soc.*, 1962, **84**, 1945.
[28] R. F. Watson and J. F. Eastham, *J. Amer. Chem. Soc.*, 1965, **87**, 664.
[29] L. J. Morris, *Chem. and Ind.*, 1962, 1238.

sulphinyl-5α-cholestane (IV) (50 mg., 0·12 mmole) was treated with peroxylauric acid (95% pure, 50 mg., 0·09 mmole) in light petroleum (20 ml.) for 20 min. at room temperature. The solution was diluted with ether (20 ml.) and filtered through alumina (1 g.). Evaporation and crystallization from ether–methanol gave the *product* (V) (45 mg., 90%), m.p. 220—223°, $[\alpha]_D$ +65° (*c* 1·3) (Found: C, 74·4; H, 11·1; S, 7·3. $C_{28}H_{50}O_2S$ requires C, 74·6; H, 11·2; S, 7·1%).

(*b*) Oxidation of (*R*)-4β-methylsulphinyl-5α-cholestane (III) (60 mg.) with peroxylauric acid (60 mg.) in the above manner gave the same sulphone (55 mg.), m.p. and mixed m.p. 219—222°, i.r. and t.l.c. behaviour identical with those of the previous sample.

(R)-4α-*Methylsulphinyl-5α-cholestane* (VI).— (*R*)-4β-Methylsulphinyl-5α-cholestane (III) (35 mg.) and potassium t-butoxide (80 mg.) in dimethyl sulphoxide (4 ml.) were kept at 65° for 4 hr. and poured into water. Isolation by ether extraction and crystallisation from methanol gave the *product* (VI) (29 mg., 83%) as needles, m.p. 191—193°, $[\alpha]_D$ −50° (*c* 1·3), $\nu_{max.}$ (KBr) 1026, $\nu_{max.}$ ($CCl_4$) 1056 cm.$^{-1}$, $\lambda_{max.}$ 210 mμ (ε 3300), o.r.d. $[\Phi]_{220}$ −21,400, $[\Phi]_{210}$ 0° (Found: C, 77·4; H, 11·4; S, 7·4%).

(S)-4α-*Methylsulphinyl-5α-cholestane* (VII).— (*S*)-4β-Methylsulphinyl-5α-cholestane (IV) (70 mg.) was equilibrated in the above manner to give the *product* (VII) (59 mg., 85%), m.p. 117—120° (from ether–methanol), $[\alpha]_D$ −42° (*c* 1·5), $\nu_{max.}$ (KBr) 1036, $\nu_{max.}$ ($CCl_4$) 1050 and 1058 cm.$^{-1}$, $\lambda_{max.}$ 212 mμ (ε 2600), o.r.d. $[\Phi]_{239}$ −4200°, $[\Phi]_{226}$ 0°, $[\Phi]_{215}$ +5400°, $[\Phi]_{212}$ 0° (Found: C, 77·1; H, 11·3; S, 7·3%).

4α-*Methylsulphonyl-5α-cholestane* (VIII).— Peroxylauric acid (95% pure, 150 mg., 0·7 mmole) was added to (*R*)-4α-methylsulphinyl-5α-cholestane (VI) (106 mg., 0·25 mmole) in light petroleum (40 ml.) at 20°. After 15 min. the solution was diluted with ether (100 ml.) and filtered through alumina (3 g.). Evaporation of the filtrate and crystallisation from ether–methanol gave the *product* (94 mg., 88%) as plates, m.p. 210—212°, $[\alpha]_D$ +12° (*c* 1·7), (Found; C, 74·8; H, 11·5; S, 7·3%). Oxidation of (*S*)-4α-methylsulphinyl-5α-cholestane (VII) in the above manner gave the same sulphone (VIII), m.p. and mixed m.p. 210—212°; the i.r. spectra and t.l.c. behaviour of the two samples were identical.

3α-*Methylthio-5α-cholestane* (X).—3β-Toluene-*p*-sulphonyloxy-5α-cholestane (IX) [30] (10 g.) was added to a solution of sodium (5 g.) in a mixture of propan-2-ol (150 ml.), toluene (200 ml.), and methanethiol (25 ml.). After 12 hr. under reflux the product was extracted with ether and worked up in the usual way to give a yellow gum (8·3 g.). Crystallisation from ether–methanol gave the *product* (X) (6·3 g., 67%) as needles, double m.p. 80—81/89—90°, $[\alpha]_D$ +30° (*c* 1·1) (Found: C, 80·2; H, 11·7; S, 7·5%).

(S)-3α-*Methylsulphinyl-5α-cholestane* (XI).—Peroxylauric acid (83% pure, 1·3 g., 6 mmoles) in light petroleum (100 ml.) was added to 3α-methylthio-5α-cholestane (X) (6·3 g., 15 mmoles) at 20°, and after 30 min. the solution was passed on to alumina (180 g.). Elution with light petroleum (2 l.) gave 3α-methylthio-5α-cholestane (X) (4·178 g., 66%), double m.p. 80—81/89—90°, and elution with ether (1 l.) gave a mixture of the sulphoxides. This oxidation procedure was repeated twice with the recovered sulphide, to give finally 3α-methylthio-5α-cholestane (X) (0·88 g., 14%) and a mixture of the sulphoxides (5·5 g., 85%). Crystallisation of the mixture of sulphoxides from methanol gave (S)-3α-*methylsulphinyl-5α-cholestane* (XI) (1·46 g., 23%) as needles, m.p. 196—198°, $[\alpha]_D$ +38° (*c* 1·4), $\nu_{max.}$ (KBr) 1025, $\nu_{max.}$ ($CCl_4$) 1054 cm.$^{-1}$, $\lambda_{max.}$ 210 mμ (ε 4000) (Found: C, 77·1; H, 11·8; S, 7·3%). The m.p., spectroscopic properties, and chromatographic behaviour of this sample were unchanged after repeated re-crystallisation. Repeated chromatography of the mixture of sulphoxides (600 mg.) on 20 thin-layer silica plates with chloroform as eluant gave the sulphoxide (XI) (88 mg.) identical in all respects with the sample obtained above.

3α-*Methylsulphonyl-5α-cholestane* (XII).— Peroxylauric acid (95% pure, 200 mg., 1 mmole) in light petroleum (30 ml.) was added to 3α-methylthio-5α-cholestane (200 mg., 0·46 mmoles). After 15 min. at room temperature the solution was diluted with ether (30 ml.) and filtered through alumina (3 g.). Evaporation of the filtrate and crystallisation from methanol gave the *product* (XII) (188 mg., 94%) as needles, m.p. 235—236°, $[\alpha]_D$ +26° (*c* 1·2), (Found: C, 74·6; H, 11·2; S, 7·1%). Oxidation of the mixture of the 3α-methylsulphinyl-5α-cholestanes, and of pure (*S*)-3α-methylsulphinyl-5α-cholestane with peroxylauric acid in the above manner furnished the same sulphone, m.p. and mixed m.p. 234—236°.

(S)-3β-*Methylsulphinyl-5α-cholestane* (XIII).— (*S*)-3α-Methylsulphinyl-5α-cholestane (XI) (515 mg.) and potassium t-butoxide (1 g.) in dimethyl sulphoxide (10 ml.) were kept at 65° for 4 hr., and poured into water. Isolation by ether extraction and crystallisation from methanol gave the *product* (XIII) (262 mg., 51%) as plates, m.p. 146—149°, $[\alpha]_D$ +47° (*c* 1·4), $\nu_{max.}$ (KBr) 1038, $\nu_{max.}$ ($CCl_4$) 1054 cm.$^{-1}$, $\lambda_{max.}$ 211 mμ (ε 4200) (Found: C, 77·4; H, 11·9; S, 7·6%).

3β-*Acetoxy-5α-methylthiocholestane* (XV).—3β-Acetoxy-5α-mercaptocholestane (XIV) [7] (3·8 g.) in dry ether was treated with an ethereal solution of diazomethane. After 12 hr. at room temperature the excess of diazomethane was decomposed with water, and the ethereal solution was dried, filtered, and evaporated. Crystallisation from chloroform–methanol gave the *product* (XV) (3·3 g.) as plates, m.p. 135—137°, $[\alpha]_D$ —12° (*c* 1·1) (Found: C, 75·3; H, 10·6. $C_{30}H_{52}SO_2$ requires C, 75·25; H, 11·0%).

3β-*Acetoxy*-(R)-*and* (S)-5α-*methylsulphinylcholestane* (XVI) *and* (XVII).—3β-Acetoxy-5α-methylthiocholestane (XV) (2·3 g.) in acetic acid (100 ml.) was treated with hydrogen peroxide (30%) (0·7 ml.) in acetic acid (10 ml.). The mixture was left overnight at room temperature and worked up in the usual manner to give a solid (2·4 g.) which was chromatographed on silica (thin-layer). Development with ether–benzene (3 : 7) gave two bands which were severally extracted with methanol–dichloromethane (1 : 1). The faster-moving gave 3β-*acetoxy*-(S)-5α-*methylsulphinylcholestane* (XVII) (720 mg.) as plates, m.p. 135—137° (from di-isopropyl ether), $[\alpha]_D$ −39° (*c* 1·9) $\nu_{max.}$ (KBr) 1728, 1270, and 1032 cm.$^{-1}$, $\lambda_{max.}$ 215 mμ (ε 5800), o.r.d. $[\Phi]_{245}$ −18,800°, $[\Phi]_{235}$ 0°, $[\Phi]_{220}$ +43,000°, (Found: C, 72·8; H, 10·4. $C_{30}H_{52}SO_3$ requires C, 73·1; H, 10·6%), whilst the slower-moving gave 3β-*acetoxy*-(R)-5α-*methylsulphinylcholestane* (XVI) (1·45 g.) as needles, m.p. 141° (from ether–methanol), $[\alpha]_D$ −11° (*c* 1·9), $\nu_{max.}$ (KBr) 1732, 1250, and 1042 cm.$^{-1}$, $\lambda_{max.}$ 217 mμ (ε 2600), o.r.d. $[\Phi]_{243}$ +12,300°, $[\Phi]_{235}$ 0°, $[\Phi]_{219}$ −35,400° (Found: C, 72·6; H, 10·5%).

3β-*Acetoxy-5α-methylsulphonylcholestane* (XVIII).—(*a*) 3β-Acetoxy-(*R*)-5α-methylsulphinylcholestane (XVI) (164 mg.) was treated with hydrogen peroxide (30%; 2 ml.) in acetic acid (10 ml.) overnight at room temperature. The usual

[30] H. R. Nace, *J. Amer. Chem. Soc.*, 1952, **74**, 5937.

work-up gave the *product* (XVIII) as plates, m.p. 190—192° (decomp.) (from methanol), $[\alpha]_D$ −34° (*c* 0·9), $\nu_{max.}$ (KBr) 1755, 1720, 1245, 1309, 1280, 1025, and 955 cm.$^{-1}$ (Found: C, 70·6; H, 10·3. $C_{30}H_{52}SO_4$ requires C, 70·6; H, 10·3%).

(*b*) Oxidation of the acetoxy-sulphoxide (XVII) in the above manner furnished the sulphone (XVIII), m.p. and mixed m.p. 189—190°, $[\alpha]_D$ −34° (*c* 1·1). The two samples were identical (i.r. spectra and chromatographically).

*5α-Methylthiocholestan-3β-ol* (XX).— (*a*) 5α-Mercaptocholestan-3β-ol (XIX) [7] (4·8 g.) in ether (500 ml.) was treated with an ethereal solution of diazomethane and set aside overnight at room temperature. More ethereal diazomethane was then added. This procedure was repeated once more to give, after filtration and evaporation of the ether, the *product* (XX) (4·6 g.), m.p. 181—183° (from ether), $[\alpha]_D$ +8° (*c* 2·1) (Found: C, 77·4; H, 11·6. $C_{28}H_{50}SO$ requires C, 77·1; H, 11·3%).

(*b*) 3β-Acetoxy-5α-methylthiocholestane (XV) (770 mg.) was treated with ethereal lithium aluminium hydride at 0° for 20 min. The residue (600 mg.) obtained after the usual work-up crystallised from ether to give 5α-methylthiocholestan-3β-ol, m.p. and mixed m.p. 181—183°, identical in all respects with the sample obtained before.

*3β-Methanesulphonyloxy-5α-methylthiocholestane* (XXI).— 5α-Methylthiocholestan-3β-ol (XX) (500 mg.) in pyridine (2 ml.) was treated with methanesulphonyl chloride (0·3 ml.) at 0° overnight. The mixture was poured into ice-cold 2N-hydrochloric acid and extracted with ether, and the ethereal extract was washed successively with ice-cold aqueous sodium hydrogen carbonate solution and ice-cold water, dried ($Na_2SO_4$), and evaporated under reduced pressure at room temperature. Crystallisation from ether—light petroleum gave the *product* (XXI), m.p. 111—115° (decomp.), $[\alpha]_D$ −4° (*c* 1·3) (Found: C, 67·3; H, 10·45. $C_{29}H_{52}S_2O_3$ requires C, 67·1; H, 10·45%).

*5α-Methylthiocholestane* (XXII) *and 3α-Methylthiocholest-5-ene* (XXIII).— 3β-Methylsulphonyloxy-5α-methylthiocholestane (XXI) [the crude product from 5α-methylthiocholestane-3β-ol (600 mg.)] was treated with lithium aluminium hydride (500 mg.) in boiling ether for 4 hr. The excess of hydride was destroyed by careful addition of water, and the ethereal solution was decanted and evaporated to leave a solid (573 mg.). Chromatography on silica (thin-layer technique) developed with light petroleum gave two bands which were individually extracted with ether, to give *5α-methylthiocholestane* (XXII) (143 mg., 25%) as needles, m.p. 95—97° (from ether–methanol), $[\alpha]_D$ +12° (*c* 1·4) (Found: C, 80·4; H, 11·9; S, 7·6%), and *3α-methylthiocholest-5-ene* (XXIII) (370 mg., 60%) as needles, m.p. 92—95° (from ether–methanol), $[\alpha]_D$ −28° (*c* 1·6) [$M_D$ is −116, in accord with the calculated $M_D$ for 3α-methylthiocholest-5-ene (−173) and not with that (+202) for 5α-methylthiocholest -2-ene. The following known $M_D$ values were used; 5α-cholestane +90; cholest-5-ene −298; 5α-cholest-2-ene +259; 3α-methylthio-5α-cholestane +125; 5α-methylthiocholestane +50], τ 8·05 (s, SMe), 4·75 (1H, m, $W_{\frac{1}{2}}$ 10 c./sec., vinyl 6-H) (cholest-5-ene shows a one proton signal at τ 4·74, $W_{\frac{1}{2}}$ 9 c./sec., of similar shape to the above, whereas cholest-2-ene gives a two proton singlet, $W_{\frac{1}{2}}$ 2·5 c./sec., at τ 4·46) (Found: C, 80·4; H, 11·4. $C_{28}H_{48}S$ requires C, 80·7; H, 11·6%).

*Raney Nickel Desulphurisation of 3α-Methylthiocholest-5-ene* (XXIII).—3α-Methylthiocholest-5-ene (XXIII) (250 mg.) in benzene (50 ml.) was treated with freshly prepared Raney nickel (2 ml. of settled sludge). The mixture was boiled overnight and filtered through Hyflosupercel, and the filtrate was evaporated to leave an oil (220 mg.) which solidified. The product was chiefly cholest-5-ene, with *ca.* 10% of a saturated hydrocarbon (probably cholestane); it contained no 5α-cholest-2-ene. Crystallisation from ether–methanol gave cholest-5-ene (XXIV) (140 mg.), m.p. and mixed m.p. 92—95°, spectroscopic properties identical with those of an authentic specimen.

*Treatment of 3β-Methanesulphonyloxy-5α-methylthiocholestane* (XXI) *with Tetrapropylammonium acetate.*—The methanesulphonate (XXI) (350 mg.) was treated with tetrapropylammonium acetate (300 mg.) in boiling ethyl methyl ketone (50 ml.) overnight. The oily product (317 mg.) obtained after the usual work-up was chromatographed on two silica plates, developed with light petroleum. The two bands were extracted individually with ether to give 3α-methylthiocholest-5-ene (XXIII) (268 mg., 92%) as needles, m.p. and mixed m.p. 92—95° (from acetone), and 3β-acetoxy-5α-methylthiocholestane (XV) (20 mg., 6%), m.p. and mixed m.p. 132—135° (from chloroform–methanol). The two samples were spectroscopically identical with authentic specimens.

(R)- *and* (S)-*5α-Methylsulphinylcholestane* (XXVII) *and* (XXVIII).—Peroxylauric acid (90% pure, 400 mg., 1·85 mmole) in light petroleum (30 ml.) was added to 5α-methylthiocholestane (XXII) (740 mg., 1·77 mmole) at room temperature. After 15 min. the solution was diluted with ether (1 l.) and filtered through alumina (30 g.). The solvent was evaporated off to leave the mixture of sulphoxides, which was chromatographed on eight silica plates developed with benzene–ether (4 : 1). The two layers were separately extracted with ether to give (R)-*5α-methylsulphinylcholestane* (XXVII) (202 mg., 27%) as plates, m.p. 95—97° (from di-isopropyl ether), $[\alpha]_D$ +8° (*c* 2·2), $\nu_{max.}$ (KBr) 1021, $\nu_{max.}$ ($CCl_4$) 1040 and 1052 cm.$^{-1}$ (Found: C, 76·9; H, 11·5; S, 7·4%), and (S)-*5α-methylsulphinylcholestane* (XXVIII) (406 mg., 55%) as needles, m.p. 118—120° (from di-isopropyl ether), $[\alpha]_D$ −12° (*c* 2·3), $\nu_{max.}$ (KBr) 1037, $\nu_{max.}$ ($CCl_4$) 1042 and 1052 cm.$^{-1}$ (Found: C, 77·3; H, 11·7; S, 7·5%).

*5α-Methylsulphonylcholestane* (XXIX).— (*S*)-5α-Methylsulphinylcholestane (XXVIII) (106 mg., 0·244 mmole) was treated with peroxylauric acid (90% pure, 150 mg., 0·7 mmole) in light petroleum (10 ml.) for 15 min. at room temperature. The solution was diluted with ether (40 ml.) and filtered through alumina (3 g.). Evaporation and crystallisation from methanol gave the *product* (XXIX) (81 mg., 76%) as needles, m.p. 134°, $[\alpha]_D$ −10° (*c* 1·4) (Found: C, 74·7; H, 10·9; S, 7·3%). Oxidation of (*R*)-5α-methylsulphinylcholestane (XXVII) (18 mg.) with peroxylauric acid in the same way gave the same sulphone (XXIX) (16 mg., 86%), m.p. 127°, mixed m.p. 127—128°, spectroscopic and t.l.c. behaviour identical with those of the previous sample.

(R)-*5α-Methylsulphinylcholestan-3β-ol* (XXXIII).— 3β-Acetoxy-(*R*)-5α-methylsulphinylcholestane (XVI) (390 mg.) was treated with potassium hydrogen carbonate (400 mg.) in a boiling mixture of methanol (50 ml.) and water (2 ml.) for 1 hr. The usual work-up gave the *product* (XXXIII) as plates, m.p. 155° (decomp.) (from ether), $[\alpha]_D$ +2° (*c* 1·4), $\nu_{max.}$ (KBr) 3480, 1040, and 1023 cm.$^{-1}$ (Found: C, 74·6; H, 11·2. $C_{28}H_{50}SO_2$ requires C, 74·6; H, 11·2%).

(S)-*5α-Methylsulphinylcholestane-3β-ol* (XXXVI).— 3β-Acetoxy-(*S*)-5α-methylsulphinylcholestane (XVII) (164 mg.) was treated with aqueous methanolic potassium hydrogen

carbonate in the above manner to give the *product* (XXXVI) as needles, m.p. 149° (from ether), $[\alpha]_D$ −8° (*c* 1·6), $\nu_{max.}$ (KBr) 3350, 1050, 1008, and 960 cm.$^{-1}$ (Found: C, 74·45; H, 11·55%).

*Reaction of* (R)-5α-*Methylsulphinylcholestane*-3β-*ol* (XXXIII) *with Methanesulphonyl Chloride.*—(*a*) The hydroxy-sulphoxide (XXXIII) (2·4 g.) was treated with methanesulphonyl chloride (1·5 ml.) in pyridine (40 ml.) containing dichloromethane (20 ml.) at 0° for 12 hr. The mixture was poured into ice-cold 2N-hydrochloric acid, and the white precipitate was collected and dried. The solid (1·135 g.) was dissolved in methanol and precipitated with ether to give the *sulphoxonium chloride* (XXXVa), m.p. 179—182° (Found: C, 71·8; H, 10·2. $C_{28}H_{49}ClOS$ requires C, 71·7; H, 10·5%). The original aqueous hydrochloric acid solution was extracted several times with dichloromethane, and the extract was washed with water and dried. Evaporation furnished more (1·13 g.) sulphoxonium chloride (XXXVa), m.p. 177—180°.

(*b*) (*R*)-5α-Methylsulphinylcholestane-3β-ol (XXXIII) (230 mg.) was treated with methanesulphonyl chloride (0·11 ml.) in a mixture of dichloromethane (2 ml.) and pyridine (2 ml.) at 0° overnight. The mixture was poured into ice-cold 2N-hydrochloric acid to give a solution 'S' which was extracted with ether. The extract was washed with ice-cold water, dried ($Na_2SO_4$), and evaporated, to give a gum (50 mg.) which contained substances chromatographically (thin-layer) identical with 3β-methanesulphonyloxycholest-5-ene (XLI) and 3β-methanesulphonyloxy-5α-methylthiocholestane (XXI). The solution 'S' was extracted three times with dichloromethane, and the combined extracts were washed with water, dried, and evaporated. The solid residue (185 mg.) was dissolved in warm water and cooled, and a concentrated solution of potassium iodide was added dropwise. The precipitate was washed with cold water, triturated with ether, dissolved in chloroform, and precipitated with ether to give the *sulphoxonium iodide* (XXXVb), m.p. 134—138°, $[\alpha]_D$ +19° (*c* 1·3), $\nu_{max.}$ (KBr) 1630, 1205, 808, 740, and 680 cm.$^{-1}$ (Found: C, 60·1; H, 8·7. $C_{28}H_{49}IOS$ requires C, 60·0; H, 8·8%).

3β-*Methanesulphonyloxy*-(S)-5α-*methylsulphinylcholestane* (XXXVII).—(*S*)-5α-Methylsulphinylcholestan-3β-ol (XXXVI) (1·3 g.) was treated with methanesulphonyl chloride (0·62 ml.) in a mixture of dichloromethane (15 ml.) and pyridine (15 ml.) at 0° for 12 hr. The mixture was poured into ice-cold 2N-hydrochloric acid and extracted with ether; the extract was then washed with ice-cold sodium hydrogen carbonate solution, ice-cold water, dried, and evaporated at room temperature under reduced pressure. The solid product (1·13 g.) was a mixture of three substances (t.l.c.). Crystallisation from ether furnished the *product* (XXXVII) (439 mg., 36%) as plates, m.p. 112—114°, $[\alpha]_D$ −27° (*c* 1·4) (Found: C, 65·7; H, 10·0. $C_{29}H_{52}O_4S$ requires C, 65·9; H, 9·9%). The mother liquor contained the product (XXXVII), 3β-methanesulphonyloxycholest-5-ene (XLI) and 3β-methanesulphonyloxy-5α-methylthiocholestane (XXI) in approximately equal quantities (t.l.c.). (The mother liquor may have contained 3β-methanesulphonyloxycholest-4-ene, since most 3β-substituted cholest-4- and 5-enes are chromatographically identical.)

*Solvolysis of* 3β-*Methanesulphonyloxy*-(S)-5α-*methylsulphinylcholestane* (XXXVII).—The methanesulphonate (XXXVII) (136 mg.) was treated with boiling methanol (25 ml.) for 15 min. The usual work-up gave a gum (92 mg.), which was chromatographed on silica (thin-layer technique). Only one band was obtained on development with ether–benzene (1 : 9); this was extracted with ether and gave a crystalline solid (71 mg., 72%), m.p. 134—138°. Crystallisation from acetone gave 3α-hydroxycholest-5-ene, m.p. and mixed m.p. 140—141°, identical spectroscopically and chromatographically with an authentic specimen.

*Pyrolysis of the Sulphoxides.*—Pyrolyses at 80° were performed in boiling benzene, and at 110° in boiling toluene. Each pyrolysis was performed at least twice, and reproducible results were obtained in each case. The procedures described below are typical.

(*a*) (*S*)-4β-Methylsulphinyl-5α-cholestane (IV) (42 mg.) was treated with boiling benzene (10 ml.) for 100 hr. The mixture was diluted with ether, washed with water, and dried ($Na_2SO_4$). The solvent was evaporated off to leave a gum (39·5 mg.) which was chromatographed on one silica plate. Development with light petroleum gave a band at the solvent front and another at the origin; these were individually extracted with ether. The band at the origin gave (*S*)-4β-methylsulphinyl-5α-cholestane (IV) (22·1 mg., 50%), m.p. and mixed m.p. 160—163° (from ether–methanol), whilst the band at the solvent front gave 5α-cholest-3-ene (XXX) (17·2 mg., 45%), m.p. and mixed m.p. 72—74°. Both substances were identical, chromatographically and spectroscopically, with authentic specimens.

(*b*) (*R*)-4β-Methylsulphinyl-5α-cholestane (III) (103 mg.) was treated with boiling toluene (5 ml.) for 72 hr. The work-up described above gave only starting material (III) (92 mg., 90%), m.p. and mixed m.p. 161—163° (from ether–methanol), i.r. and t.l.c. behaviour identical with those of an authentic specimen.

(*c*) (*R*)-5α-Methylsulphinylcholestane (XXVII) (51 mg.)

TABLE 3

| Sample | | Wt.* (mg.) | $[\alpha]_D$ | Mean $[\alpha]_D$ | $\Delta^4$ (%) determined |
|---|---|---|---|---|---|
| Cholest-4-ene | | 31·04 | +70·0 | +70·4 | |
| | | 29·21 | +68·6 | | |
| | | 23·55 | +73·0 | | |
| | | 20·45 | +72·3 | | |
| Cholest-5-ene | | 35·40 | −60·0 | −60·0 | |
| | | 35·69 | −60·0 | | |
| | | 26·67 | −60·0 | | |
| Synthetic mixtures | | | | | |
| $\Delta^4$ | $\Delta^5$ | | | | |
| 63 | 37 | 33·4 | +25·6 | +24·7 | 65 |
| | | 31·61 | +24·7 | | |
| | | 31·58 | +23·8 | | |
| 50 | 50 | 29·91 | +7·7 | +7·7 | 52 |
| | | 29·29 | +8·5 | | |
| | | 29·33 | +6·8 | | |
| 32 | 68 | 37·47 | −17·4 | −18·2 | 32 |
| | | 36·74 | −19·6 | | |
| | | 36·33 | −17·6 | | |
| 62 | 38 | 36·5 | +22·4 | +22·9 | 62 |
| | | 33·34 | +22·4 | | |
| | | 30·47 | +23·8 | | |
| 34 | 62 | 33·90 | −14·0 | −14·7 | 33 |
| | | 32·91 | −15·7 | | |
| | | 32·22 | −14·3 | | |
| Pyrolysis product from | | | | | |
| (XXVII) | | 28·23 | +55 | +50 | 83 |
| | | 28·20 | +50 | | |
| | | 26·92 | +46 | | |
| (XXVIII) | | 37·97 | +15·1 | +14·5 | 56 |
| | | 38·04 | +14·8 | | |
| | | 37·58 | +13·5 | | |

* In chloroform (2·2 ml.); path length 2 cm.

was treated with boiling benzene (5 ml.) for 2 hr. The work-up described above gave an oil (28 mg.) which was chromatographed on one silver-nitrate-impregnated silica plate. Development with light petroleum gave one band, $R_F$ 0·1, which was extracted with ether. Evaporation of the extract afforded a gum (28 mg., 65%) which was a mixture of cholest-4-ene (XXVI) and cholest-5-ene (XXIV) in the ratio 83 : 17 (analysed by the method described below).

(*d*) (*S*)-5α-Methylsulphinylcholestane (XXVIII) (50 mg.) treated in the above manner gave a mixture (38 mg., 89%) of cholest-4-ene (XXVI) and cholest-5-ene (XXIV) in the ratio 56 : 44, analysed by the method described below.

(*e*) 3β-Acetoxy-(*R*)-5α-methylsulphinylcholestane (XVI) (115 mg.) was treated with boiling benzene for 7 hr. Chromatography of the product on silica (thin-layer) developed with benzene–light petroleum (1 : 1) gave only one band which was extracted with ether to give pure 3β-acetoxycholest-4-ene (XXXI) (89 mg., 89%), $[\alpha]_D$ +9° (3β-acetoxycholest-4-ene obtained by acetylation of cholest-4-ene-3β-ol prepared by the method of Burgstahler and Nordin [31] had $[\alpha]_D$ +6°). The product was identical spectroscopically and chromatographically with authentic 3β-acetoxycholest-4-ene, and crystallisation from acetone–methanol gave 3β-acetoxycholest-4-ene, m.p. and mixed m.p. 82—83° (lit.,[30] m.p. 85°).

(*f*) 3β-Acetoxy-(*S*)-5α-methylsulphinylcholestane (XVII) (113 mg.) was treated with boiling benzene for 7 hr. Chromatography of the product on silica (thin-layer) developed with benzene–light petroleum (1 : 1) gave only one band of the same $R_F$ as 3β-acetoxycholest-4-ene and 3β-acetoxycholest-5-ene, which was extracted with ether. The white crystalline residue (93 mg., 95%) had $[\alpha]_D$ −28° (*c* 1·2). Since 3β-acetoxycholest-5-ene has $[\alpha]_D$ −48°, and 3β-acetoxycholest-4-ene has $[\alpha]_D$ +6°, the product contained 3β-acetoxycholest-5-ene and 3β-acetoxycholest-4-ene in the ratio 64 : 36. Application of the method to synthetic mixtures of the two compounds showed that it was accurate to ±2%; there was an excellent linear relationship between $[\alpha]_D$ and percentage composition in a series of synthetic mixtures of the two acetoxy-olefins. A synthetic mixture of 3β-acetoxy-5- and 4-enes in the ratio 64 : 36 was identical spectroscopically and chromatographically with the product obtained above.

*Analysis of Mixtures of Cholest-4-ene* (XXVI) *and Cholest-5-ene* (XXIV).—The percentage compositions of the mixtures of olefins obtained by pyrolysis of (*R*)- and (*S*)-5α-methylsulphinylcholestanes were determined polarimetrically. The data are collected in Table 3

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