Steroidal Sulphur Compounds. Part VIII.[1] Pummerer Reactions of Steroidal Sulphoxides induced by Acetic Anhydride

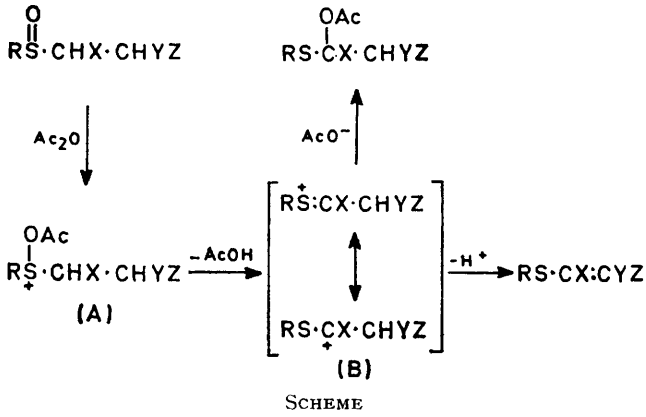
By **D. Neville Jones,* E. Helmy,** and **R. D. Whitehouse,** The Chemistry Department, The University, Sheffield S3 7HF

Regioselection in the acetic anhydride-induced Pummerer reactions of steroidal sulphoxides was influenced by steric factors associated with the axial or equatorial orientation of the sulphoxide groups and the degree of steric compression in the axial orientation. The axial 6β-alkylsulphinyl-5α-cholestanes gave only the corresponding 6-alkylthiocholest-5-enes (and in one case the Δ^6-isomer), providing the first examples of predominant oxidation of the more substituted α-carbon atom in acetic anhydride-induced Pummerer reactions of sulphoxides, whereas the equatorial 6α-alkylsulphinyl-5α-cholestanes gave products derived mainly from oxidation of the alkyl groups. Oxidation at C-3 occurred to a larger extent for the axial 3α-methylsulphinyl-5α-cholestane than for its equatorial 3β-isomer, although both isomers gave predominantly the corresponding 3-acetoxymethylthio-5α-cholestane with retention of configuration at C-3. The reactions were not influenced by the configuration at the sulphur atom. The mechanistic implications of these observations are discussed.

THE most common examples of the Pummerer reaction, a term suggested [2,3] for a class of reactions involving concomitant reduction of a sulphonium sulphur atom with oxidation of the α-carbon atom, involve the reaction of sulphoxides with acetic anhydride to give α-acetoxysulphides and αβ-unsaturated sulphides.[4] Many mechanisms have been suggested for these reactions,[5] but there is good evidence that they proceed by initial formation of an acetoxysulphonium ion [2] which collapses to a sulphur-stabilised carbonium ion [2,4] and thence to products (Scheme). Three pathways have been considered for the elimination of acetic acid from the acetoxysulphonium ion (A) to give the sulphur-stabilised carbonium ion (B). The first involves a base-catalysed non-concerted elimination *via* an ylide intermediate (pathway *a*), the second a base-catalysed concerted elimination (pathway *b*), and the third a concerted cyclic elimination (pathway *c*). Pathway *a* is consistent with observations that acetic anhydride-induced Pummerer reactions of unsymmetrical sulphoxides proceeded regioselectively with preferential oxidation of the least substituted α-carbon atom,[2,4] the site of the more stable carbanion, and these results were also considered [4] to accord with pathway *c*, with the assumption that the more acidic α-hydrogen atom was most susceptible to intramolecular abstraction. Pathway *b* was considered unlikely because it was thought to imply the development of partial carbonium ion character at the α-carbon atom,[2] and hence would prescribe migration towards the more substituted α-carbon atom, but the possibility that this concerted

[1] Part VII, D. N. Jones, E. Helmy, and A. C. F. Edmonds, *J. Chem. Soc.* (*C*), 1970, 833.
[2] C. R. Johnson and W. G. Phillips, *J. Amer. Chem. Soc.*, 1969, **91**, 682.
[3] T. Durst, *Adv. Org. Chem.*, 1969, **6**, 285.
[4] W. E. Parham and L. D. Edwards, *J. Org. Chem.*, 1968, **33**, 4150, and references cited therein.
[5] Reviewed in refs. 2 and 3.

elimination could involve the development of partial negative charge at the α-carbon atom was neglected. Pathway *a* found analogy in the securely established



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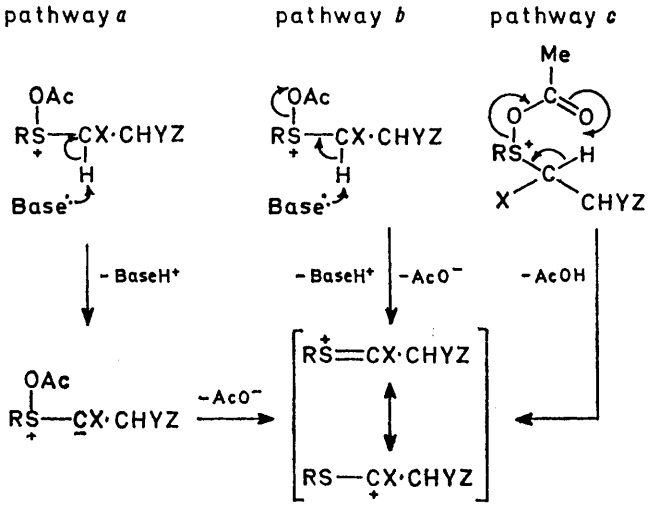
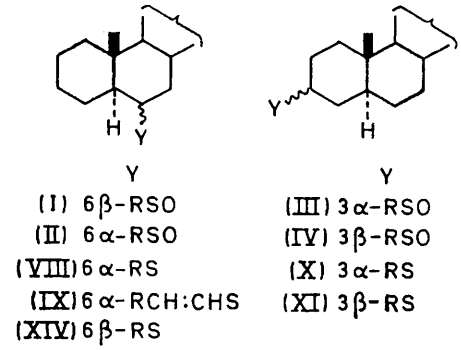
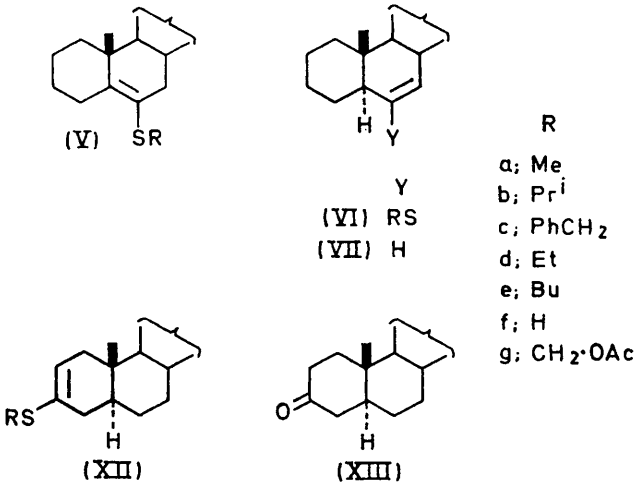
mode of base-catalysed rearrangement of alkoxysulphonium ions,[2,6] and was consequently favoured by Johnson,[2] whereas Parham [4] favoured pathway *c* while



recognising that 'the mechanism of the Pummerer reaction may vary markedly with subtle changes in structure of starting sulphoxide'. Little evidence is available concerning the possible influence of steric factors upon the course of the reaction, which might further illuminate the mechanism. This forms the subject of the present investigation, performed with steroidal sulphoxides (Ia—e), (IIa—e), (IIIa—c), and (IVa) in which the sulphoxide groups were subject to varying degrees of steric compression.

The sulphoxides were treated at 80° with neat acetic anhydride or with acetic anhydride in benzene, which gave cleaner products. The same major products in virtually the same yields were obtained with both sets of conditions. Like other sulphoxides,[7] the 6β-steroidal sulphoxides (Ia—e) underwent racemisation at the sulphur atom under the conditions of the reaction, and no differences were detected in the behaviour with acetic anhydride of the (*R*)- and (*S*)-isomers (configurations at the sulphur atom). The (*R*)-6α-sulphoxides also behaved identically with their (*S*)-isomers, although we did





not examine for racemisation at the sulphur atom in these cases because of the chromatographic and polarimetric similarities of the isomers. This insensitivity to chirality at the sulphur atom was assumed also to apply for the 3-sulphoxides (IIIa—c) and (IVa), where only mixtures diastereoisomeric at the sulphur atom were employed. The products are recorded in the Table, in which the column headed 'Direction 1' refers to products derived from Pummerer reactions involving the α-carbon atom most capable of supporting a negative charge, as defined by the sequence: benzyl CH_2 > primary > secondary > tertiary, and 'Direction 2' refers to products obtained from rearrangement in the alternative direction. The initial products of rearrangement (vinyl sulphides or α-acetoxy-sulphides) were usually isolated, but some of those derived from the isopropyl sulphoxides (IIb) and (IIIb) and benzyl sulphoxides (IIc) and (IIIc) we hydrolysed very readily and the corresponding steroidal thiols were obtained after chromatography. For 3α-benzylsulphinyl-5α-cholestane (IIIc) isolation of identifiable materials was simplified by acid-catalysed hydrolysis of the crude products prior to chromatography. The

[6] C. R. Johnson and W. G. Phillips, *J. Org. Chem.*, 1967, **32**, 1926.

[7] M. Kise and S. Oae, *Bull. Chem. Soc. Japan*, 1970, **43**, 1426.

thiols (VIIIf) and (Xf) were characterised as the corresponding disulphides. The poor yield of identifiable products from 6α-ethylsulphinyl-5α-cholestane (IId) was not improved upon in repeated experiments.

Products derived from the reactions of steroidal sulphoxides with acetic anhydride [a]

Sulphoxide	Products derived from Pummerer reactions [b] Direction 1	Direction 2	Other products
(Ia)		(Va) (73)	
(Ib)		(Vb) + (VIb) (58) [c]	(VII) (16)
(Ic)		(Vc) (69)	
(Id)		(Vd) (81)	
(Ie)		(Ve) (79)	
(IIa)	(VIIIg) (68)	(Va) (15)	
(IIb)	(VIIIf) (59)	(Vb) + (VIb) (30)	
(IIc)	(VIIIf) (73)	(Vc) (9)	
(IId)	(IXf) (23)		
(IIe)	(IXd) (90) [d]		
(IIIa)	(Xg) (56)	(XIIa) (26) [e]	
(IIIb)	(Xf) (27)	(XIIb) (40)	
(IIIc)	(Xf) (35) [f]	(XIII) (28) [f]	
(IVa)	(XIg) (70)	(XIIa) (4) [e]	

[a] Yields (%) in parentheses. [b] See text for the meaning of Direction 1 and Direction 2. These cannot apply to the sulphoxides (Ib), (IIb), and (IIIb). [c] In the ratio 1 : 2. [d] Mixture of *E*- and *Z*-isomers. [e] The crude product contains <10% of the Δ^3-isomer. [f] After hydrolysis of the crude product.

The structures of the products were established by chemical and spectroscopic methods. Acid-catalysed hydrolysis of the 6-alkylthiocholest-5-enes (Va) and (Vc—e) gave a mixture of 5α- and 5β-cholestan-6-one; 3-methylthiocholest-2-ene (XIIa) and 3-isopropylthiocholest-2-ene (XIIb) similarly gave 5α-cholestan-3-one (XIII), and the compounds (IXf) and (IXd) (*E*- and *Z*-isomers) gave 6α-mercapto-5α-cholestane (VIIIf), characterised as the corresponding disulphide. These reactions established that the above products were enol thioethers, the double bond in (Va), (Vc—e), (XIIa), and (XIIb) was in the steroid skeleton, and that (IXf) and (IXd) were 6α-alkenylthio-5α-cholestanes. The positions of the nuclear double bonds were revealed by Raney nickel desulphurisation, (Va) and (Vc—e) giving cholest-5-ene, whereas (XIIa) and (XIIb) gave 5α-cholest-2-ene. The location of the double bonds in the unsaturated sulphides is probably a reflection of the greater thermodynamic stability of cholest-5-ene than 5α-cholest-6-ene, and of 5α-cholest-2-ene than 5α-cholest-3-ene.[8] In accord with their allocated structures the oily (Va) and (Vc—e) displayed no signal attributable to a vinyl proton in their n.m.r. spectra; 6-benzylthiocholest-5-ene (Vc) showed no vinyl proton signal before or after crystallisation, indicating the absence of the Δ^6-isomer as contaminant. A significant feature of the n.m.r. spectra of the unsaturated sulphides (Va) and (Vc—e) was a one-proton doublet in the region τ 6·62—6·86 (*J* 14·0—14·7 Hz) attributed to the 4α-proton, which, because of its closer proximity to the 6-alkylthio-group, was deshielded relative to the 4β-proton.* This behaviour finds analogy in the n.m.r. characteristics of the 6α-proton in 4-ethylthiocholest-4-en-3-one.[9] The oily 6-isopropylthiocholest-5-ene (Vb) and 6-isopropylthiocholest-6-ene (VIb) were identical chromatographically, and the presence of both compounds was revealed by Raney nickel desulphurisation of the mixture to a mixture of cholest-5-ene and 5α-cholest-6-ene, and by n.m.r. spectroscopy, which showed a signal at τ 4·42 attributed to the 7-vinyl proton in (VIb) together with a doublet at τ 6·62 (*J* 14·0 Hz) allocated to the 4α-proton in (Vb); the intensities of these signals were in the ratio 2 : 1. The predominance of 6α-isopropylthio-5α-cholest-6-ene (VIb) over its Δ^5-isomer (Vb), which is contrary to the relative thermodynamic stability of cholest-5-ene and 5α-cholest-6-ene,[8] may possibly be due to the destabilisation of (Vb) relative to (VIb) (and hence of the transition states leading to these unsaturated sulphides) by steric interactions, especially those involving the 6-isopropylthio-group and the 4-methylene group in 6-isopropylthiocholest-5-ene (Vb), which are apparent from Dreiding models. In accord with the structures allocated, acid-catalysed hydrolysis of the mixture of (Vb) and (VIb) gave only a mixture of 5α- and 5β-cholestan-6-one, which are known to equilibrate under these conditions.[10] The n.m.r. spectra of the crystalline 3-methylthiocholest-2-ene (XIIa) and 3-isopropylthiocholest-2-ene (XIIb) displayed one-proton signals at τ 4·70 and 4·28, respectively, assigned to the 2-proton, but the spectra of the chromatographically homogeneous crude samples (before crystallisation) showed weak additional signals at τ 4·97 [in (XIIa)] and τ 4·58 [in (XIIb)] suggesting that each unsaturated sulphide was contaminated with a little (<10%) of the Δ^3-isomer. Acid-catalysed hydrolysis of 3α-acetoxymethyl-5α-cholestane (Xg) gave 3α-mercapto-5α-cholestane (Xf), whereas 3β-acetoxymethyl-5α-cholestane (XIg) gave 3β-mercapto-5α-cholestane (XIf), revealing the orientations at C-3. The thiols (Xf) and (XIf) were characterised as the corresponding disulphides. The n.m.r. spectra of (Xg) and (XIg), respectively, displayed one-proton signals at τ 6·62 ($W_{\frac{1}{2}}$ 9 Hz) and 7·20 ($W_{\frac{1}{2}}$ 24 Hz), attributed to the geminal 3-protons; the relative positions and band-widths of these signals further indicated the axial orientation of the acetoxymethyl group in (Xg) and its equatorial disposition in (XIg).[11] 6α-Acetoxymethylthio-5α-cholestane (VIIIg) underwent acid-catalysed hydrolysis to 6α-mercapto-5α-cholestane (VIIIf), indicating the equatorial 6α-orientation of the acetoxymethyl group; the n.m.r. spectrum of (VIIIg) confirmed this assignment, the width (25 Hz) of the signal at τ 7·34 due to the C-6 proton revealing its axial 6β-orientation. Other spectral data for the products (see Experimental section) were in accord with the structures allocated.

* According to Dreiding models, the non-bonded distances between the sulphur atom at C-6 and the 4α- and 4β-hydrogen atoms respectively are 2·24 and 3·48 Å.

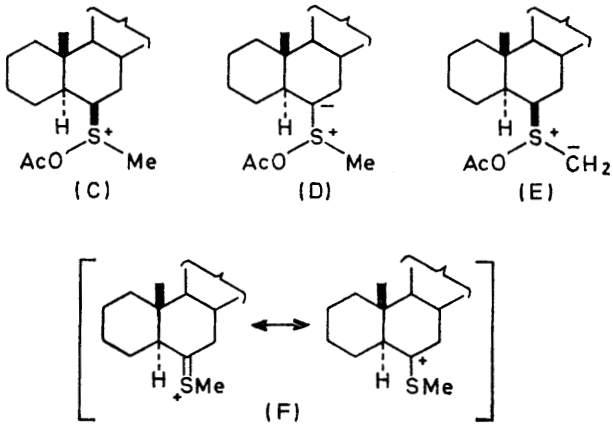
[8] R. B. Turner, W. R. Meador, and R. E. Winkler, *J. Amer. Chem. Soc.*, 1957, **79**, 4122.

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

[10] D. N. Jones and D. E. Kime, *J. Chem. Soc.* (*C*), 1966, 846.

[11] R. U. Lemieux, R. K. Kullnig, H. J. Bernstein, and W. G. Schneider, *J. Amer. Chem. Soc.*, 1958, **80**, 6098; W. Hofman, L. Stefaniak, T. Urbanski, and W. Witanowski, *ibid.*, 1964, **86**, 554.

The major products were consistent with the operation of the mechanism summarised in the Scheme. The predominant products from the 6α-sulphoxides (IIa—e) and the 3-sulphoxides (IIIa) and (IVa) were derived by oxidation at the less substituted α-carbon atom, which suggested the initial abstraction of the more acidic α-hydrogen atom, in accord with the operation of pathway *a*. However, in the case of the more sterically hindered 6β-sulphoxides (Ia—e) oxidation occurred only at the



more substituted α-carbon atom to give the vinyl sulphides (Va—e) and (VIb), behaviour which finds no precedent among the reported reactions of sulphoxides with acetic anhydride. This unusual behaviour is rational in terms of pathway *a* if, taking (*S*)-6β-methylsulphinyl-5α-cholestane (Ia) is an example, the configuration at C-6 in the ylide (D) approaches planarity (Figure 1), and if the transition state connecting the

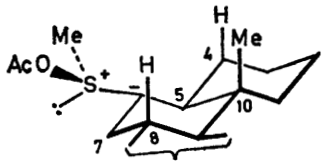


FIGURE 1

acetoxysulphonium ion (C) with the ylide (D) has a great deal of ylide character, so that the conversion of (C) into (D) would be attended by a relief of the steric compression present in (C) by virtue of the syn-axial non-bonded repulsive interactions between the 6β-acetoxysulphonium group, the C-10 methyl group, and the 4β- and 8β-hydrogen atoms (Figure 2). Since similar steric de-

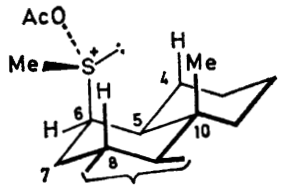


FIGURE 2

compression cannot accompany the conversion of the acetoxysulphonium ion (C) into the alternative ylide (E), in which the axial 6β-orientation is maintained (Figure 3), the transition state leading to (D) could be

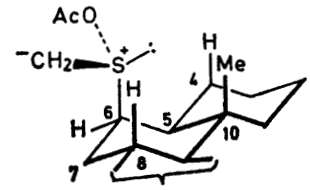


FIGURE 3

favoured energetically over that leading to (E). Similar considerations account for the greater tendency of the axial 3α-methyl sulphoxide (IIIa) than its less sterically hindered equatorial 3β-isomer (IVa) to undergo Pummerer reactions towards C-3. They also provide a reasonable explanation for the fact that a much smaller proportion of Pummerer reaction in Direction 2 to give unsaturated sulphide occurs for the axial 3α-methyl sulphoxide (IIIa), which has two syn-axial hydrogen atoms, than for the axial 6β-methyl sulphoxide (Ia), which has two syn-axial hydrogen atoms and one syn-axial methyl group and is therefore the more sterically compressed. The differences in regioselectivity of the Pummerer reactions of other pairs of sulphoxides, such as the isopropyl sulphoxides (IIb) and (IIIb) and the benzyl sulphoxides (IIc) and (IIIc) may be interpreted in the same way. The marked differences in the behaviour of the 6α- and 6β-sulphoxides, the absence of acetoxymethyl sulphides of inverted configuration at C-3 from the 3α- and 3β-methyl sulphoxides (IIIa) and (IVa), and the observed regioselectivities of the Pummerer reactions are consistent with previous suggestions that ylide formation is the rate- and product-determining step in the acetic anhydride-induced rearrangements of sulphoxides.[2,7] The production of some 5α-cholest-6-ene (VII) from 6β-isopropylsulphinyl-5α-cholestane (Ib) is probably due to pyrolytic elimination of the sulphoxide,[12] which is known to proceed at 80°.

The pattern of products may alternatively be interpreted in terms of the steric factors discussed above and the operation of pathway *b*, but only if the transition state connecting the acetoxysulphonium ion (A) and the sulphur-stabilised carbonium ion (B) has considerable ylide character, and heterolysis of the C–H bond is appreciably more advanced than fission of the S–OAc bond in the transition state. However, the operation of pathway *c* does not satisfactorily account for the observed steric effects upon the regioselectivity of the reaction of the steroidal sulphoxides with acetic anhydride. This may be illustrated by taking 6β-methylsulphinyl-5α-cholestane (Ia) as an example. It would be reasonable to assume that the regioselectivity of reaction by pathway *c* would be controlled largely by statistical factors associated with the number of available α-hydrogen atoms, together with some preference for intramolecular abstraction of the more acidic α-hydrogen atoms. The

[12] D. N. Jones, D. Mundy, and R. D. Whitehouse, *J. Chem. Soc.* (*C*), 1969, 1668.

possible importance of the latter factor is indicated by the predominance of oxidation of the benzyl methylene group of benzyl methyl sulphoxide in its reaction with acetic anhydride.[4] The formation of the unsaturated sulphide (Va) and not the acetoxy-sulphide (XIVg) from the 6β-methyl sulphoxide (Ia) is contrary to expectation if these assumptions are valid. It is not possible to resolve this difficulty by further assuming that elimination involving the 6α-hydrogen atom is facilitated by relief of the steric compression present in the acetoxysulphonium ion (C) (Figure 2), since it is apparent from models that the formation of a cyclic transition state leading to the sulphur-stabilised carbonium ion (F) is attended by an increase of steric compression, irrespective of whether the configuration at C-6 in the transition state is tetrahedral or almost planar, whereas the generation of a cyclic transition state leading to elimination involving the *S*-methyl group does not correspondingly increase the steric compression.

It appears that the acetic anhydride-induced Pummerer reactions of these steroidal sulphoxides are consistent with the mechanism outlined in the Scheme, and that the intermediate acetoxysulphonium ion (A) collapses to a sulphur-stabilised carbonium ion (B) either by way of an ylide (pathway *a*) or by way of a concerted elimination of acetic acid (pathway *b*) in which the transition state possesses appreciable ylide character. In either case the development of partial negative charge at the α-carbon atom is apparently accompanied by a change from a tetrahedral to a more approximately planar configuration at the α-carbon atom.

EXPERIMENTAL

M.p.s were determined on a Kofler hot-stage apparatus. I.r. spectra were measured for carbon tetrachloride solutions with a Unicam SP 100 spectrophotometer, and u.v. spectra for solutions in hexane with a Cary 14 spectrophotometer. Rotations cited are for chloroform solutions. N.m.r. spectra were determined with a Varian A60 or HA100 spectrometer for deuteriochloroform solutions. Mass spectra were determined with an A.E.I. MS9 double-focusing mass spectrometer operating at 70 eV. Samples were introduced through a heated inlet system in the temperature range 100—200°. Preparative thick-layer chromatography (p.l.c.) was performed with a layer of silica gel G (Merck) 1 mm thick. The silica gel was mixed with aqueous 6% silver nitrate solution to make silver nitrate-impregnated plates for separation of olefins.[13] Light petroleum refers to the fraction b.p. 40—60°. The identity of the known compounds which were isolated was established by comparison of their chromatographic (t.l.c.) and spectroscopic (i.r., n.m.r., and mass) properties with those of authentic samples, and by mixed m.p. determinations in appropriate cases.

Reactions of the Sulphoxides with Acetic Anhydride; General Conditions.—In procedure (*A*) a solution of the sulphoxide in acetic anhydride was heated at 80° for 4 h; in procedure (*B*) the sulphoxide in benzene–acetic anhydride (1 : 1) was heated at 80° for 16 h. At least a 100 molar ratio of acetic anhydride to sulphoxide was used in each case. After evaporation of the solvent under reduced pressure the crude products were chromatographed (p.l.c.) with light petroleum development. For isolation of the acetoxymethyl sulphides (VIIIg), (Xg), and (XIg) development with benzene–light petroleum (1 : 1) was required.

Reactions of the 6β-Sulphoxides with Acetic Anhydride.—(*a*) 6β-Butylsulphinyl-5α-cholestane [12] (Ie) (940 mg) [procedure (*A*)] gave only 6-*butylthiocholest-5-ene* (Ve) (717 mg, 79%), as an oil, $[\alpha]_D$ −40° (*c* 0·5), $\lambda_{max.}$ 254 nm (ε 3500), τ 6·68 (d, *J* 14·7 Hz, 4α-H), 7·37 (t, *J* 7·0 Hz, $PrCH_2{\cdot}S$), 8·98 (10-Me), and 9·32 (13-Me), *m/e* 458 (M^+) and 369 ($M - C_4H_9S$) (Found: C, 81·0; H, 11·9; S, 7·2. $C_{31}H_{54}S$ requires C, 81·1; H, 11·9; S, 7·0%).

(*b*) The following 6-alkylthiocholest-5-enes were obtained from the corresponding 6β-alkyl sulphoxides [12,14] by the foregoing method: 6-*methylthiocholest-5-ene* (Va) (73%), oil, τ 6·83 (d, *J* 14·0 Hz, 4α-H), 7·85 (s, $CH_3{\cdot}S$), 8·98 (10-Me), and 9·32 (13-Me), *m/e* 416 (M^+) and 369 ($M - CH_3{\cdot}S$) (Found: C, 80·5; H, 11·6; S, 7·8. $C_{28}H_{48}S$ requires C, 80·7; H, 11·6; S, 7·7%); 6-*ethylthiocholest-5-ene* (Vd) (81%), oil, $[\alpha]_D$ −56° (*c* 0·6), $\lambda_{max.}$ 254 nm (ε 3500), τ 6·68 (d, *J* 14·2 Hz, 4α-H), 7·39 (q, *J* 7 Hz, $CH_3{\cdot}CH_2{\cdot}S$), 8·82 (t, *J* 7 Hz, $CH_3{\cdot}CH_2{\cdot}S$), 8·98 (10-Me), and 9·32 (13-Me), *m/e* 430 (M^+) and 369 ($M - C_2H_5{\cdot}S$) (Found: C, 80·9; H, 11·7; S, 7·7. $C_{29}H_{50}S$ requires C, 80·85; H, 11·7; S, 7·4%); 6-*benzylthiocholest-5-ene* (Vc) (69%), m.p. 91—92° (from acetone), $[\alpha]_D$ −102° (*c* 0·8), $\lambda_{max.}$ 217 (ε 13,000) and 270sh nm (1600), τ 6·26 (s, $PhCH_2{\cdot}S$), 6·86 (d, *J* 14·4 Hz, 4α-H), 9·12 (10-Me), and 9·34 (13-Me), *m/e* 492 (M^+) and 369 ($M - C_7H_7S$) (Found: C, 82·8; H, 10·9; S, 6·9. $C_{34}H_{52}S$ requires C, 82·85; H, 10·6; S, 6·5%).

(*c*) 6β-Isopropylsulphinyl-5α-cholestane [12] (Ib) (131 mg) [procedure (*B*)] gave 5α-cholest-6-ene (VII) (17 mg, 16%), m.p. 86—88°, and a mixture (71 mg, 58%) of the chromatographically identical 6-isopropylthiocholest-5-ene (Vb) and 6-isopropylthio-5α-cholest-6-ene (VIb), τ 4·42 (s, 7-H), 6·62 (d, *J* 14·0 Hz, 4α-H), and 7·0 (m, $Me_2CH{\cdot}S$), *m/e* 444·3789 ($C_{30}H_{52}S$ requires 444·3790). The intensities of the signals at τ 4·42 and 6·62 were in the ratio 2 : 1. Hydrolysis of a mixture (20 mg) of (Vb) and (VIb) in boiling aqueous methanol (15 ml) containing concentrated hydrochloric acid (2 drops) gave a mixture of 5α- and 5β-cholestan-6-one (13·3 mg, 73%). These ketones equilibrate at C-5 under these conditions.

Reactions of the 6α-Sulphoxides with Acetic Anhydride.—(a) 6α-Methylsulphinyl-5α-cholestane [14b] (IIa) (200 mg) [procedure (*A*)] gave 6α-*acetoxymethylthio-5α-cholestane* (VIIIg) (148 mg, 68%), oil, $[\alpha]_D$ +47° (*c* 1·5), $\nu_{max.}$ 1735 cm^{-1}, τ 4·84 (s, $AcO{\cdot}CH_2{\cdot}S$), 7·34 ($W_{\frac{1}{2}}$ 25 Hz, 6β-H), 7·93 (s, $CH_3{\cdot}CO_2$), 9·18 (10-Me), and 9·35 (13-Me), *m/e* 476 (M^+), 416 ($M - C_2H_4O_2$), and 371 ($M - C_3H_5O_2S$) (Found: C, 75·9; H, 11·1; S, 6·9. $C_{30}H_{52}O_2S$ requires C, 75·6; H, 11·0; S, 6·7%); and 6-methylthiocholest-5-ene (Va) (29 mg, 15%), identical with the sample obtained from 6β-methylsulphinyl-5α-cholestane.

(*b*) 6α-Ethylsulphinyl-5α-cholestane [12] (IId) (70 mg) [procedure (*A*)] gave many products (t.l.c.). The major product after p.l.c. was the oily 6α-*vinylthio-5α-cholestane* (IXf) (16 mg, 23%), τ 4·8 (m, vinyl protons), 7·32 ($W_{\frac{1}{2}}$ 25 Hz, 6β-H), 9·15 (10-Me), and 9·35 (13-Me), *m/e* 430 (M^+) and

[13] L. J. Morris, *Chem. and Ind.*, 1962, 1238.

[14] (*a*) D. N. Jones, M. J. Green, M. A. Saeed, and R. D. Whitehouse, *J. Chem. Soc.* (*C*), 1968, 1362; (*b*) D. N. Jones, M. J. Green, and R. D. Whitehouse, *ibid.*, 1969, 1166; (*c*) D. N. Jones and W. Higgins, *ibid.*, p. 2159.

371 (M — C_2H_3S), (Found: C, 80·8; H, 11·4; S, 7·8. $C_{29}H_{50}S$ requires C, 80·85; H, 11·7; S, 7·4%).

(*c*) 6α-Butylsulphinyl-5α-cholestane [12] (IIe) (57 mg) [procedure (*B*)] gave *E*- and *Z*-isomers of 6α-(*but*-1-*enylthio*)-5α-*cholestane* (IXd). One *isomer* (20 mg, 36%) displayed $\lambda_{max.}$ 253 (ε 4200) and 236 nm (3900), τ 4·2 (m, vinyl protons), 7·36 ($W_{\frac{1}{2}}$ 22 Hz, 6β-H), 9·12 (10-Me), and 9·30 (13-Me), *m/e* 458 (M^+) and 371 (M — C_4H_7S) (Found: C, 81·2; H, 12·1; S, 6·85. $C_{31}H_{54}S$ requires C, 81·1; H, 11·9; S, 7·0%); the other *isomer* (30 mg, 54%) displayed $\lambda_{max.}$ 247sh (ε 5000) and 233 nm (7000), τ 4·4 (m, vinyl protons), 7·42 ($W_{\frac{1}{2}}$ 34 Hz, 6β-H), 9·17 (10-Me), and 9·33 (13-Me), *m/e* 458 (M^+) and 371 (M — C_4H_7S) (Found: C, 81·0; H, 11·8; S, 7·2%).

(*d*) 6α-Benzylsulphinyl-5α-cholestane [14c] (IIc) (300 mg) [procedure (*B*)] gave 6-benzylthiocholest-5-ene (20 mg, 9%) and a mixture (139 mg, 73%) of 6α-mercapto-5α-cholestane (VIIIf) and di-5α-cholestan-6α-yl disulphide, *m/e* 806 (M^+ for the disulphide) and 404 [M^+ for (VIIIf)]. This mixture (200 mg; from two experiments) of disulphide and thiol in dichloromethane (5 ml) and ethanol (5 ml) was treated dropwise with a solution of iodine in dichloromethane until a brown colour persisted for longer than 1 min. Evaporation of the solution to small bulk, collection of the precipitate, and crystallisation of this from dichloromethane–acetone gave *di-5α-cholestan-6α-yl disulphide* (191 mg, 95%), m.p. 196°, $[\alpha]_D$ +80° (*c* 0·8), τ 7·48 ($W_{\frac{1}{2}}$ 28 Hz, 6β-H), 9·18 (10-Me), and 9·35 (13-Me), *m/e* 806 (M^+) and 371 (M — $C_{27}H_{47}S_2$) (Found: C, 80·0; H, 11·5; S, 7·9. $C_{54}H_{94}S_2$ requires C, 80·3; H, 11·7; S, 7·9%).

(*e*) 6α-Isopropylsulphinyl-5α-cholestane [12] (IIb) (320 mg) [procedure (*B*)] gave a mixture (57 mg, 30%) of 6-isopropylthiocholest-5-ene (Vb) and 6-isopropylthio-5α-cholest-6-ene (VIb) identical chromatographically and spectroscopically with that obtained from the 6β-isopropyl sulphoxide (Ib), and a mixture (102 mg, 59%) of 6α-mercapto-5α-cholestane (VIIIf) and the corresponding disulphide, characterised by oxidation in the above manner to di-5α-cholestan-6α-yl disulphide, m.p. 195—196°. Starting material (IIb) (12 mg) was recovered.

Reactions of the 3-*Sulphoxides with Acetic Anhydride.*—(*a*) Procedure (*A*) applied to 3α-methylsulphinyl-5α-cholestane [14a] (IIIa) (100 mg) afforded 3α-*acetoxymethyl-5α-cholestane* (Xg) (61 mg, 56%), m.p. 67—69° (from ether–methanol), $\nu_{max.}$ 1750 cm^{-1}, τ 4·85 (s, AcO·CH_2·S), 6·62 ($W_{\frac{1}{2}}$ 9 Hz, 3β-H), 7·93 (s, CH_3·CO$_2$), 9·20 (10-Me), and 9·35 (13-Me), *m/e* 476 (M^+), 416 (M — $C_2H_4O_2$), and 371 (M — $C_3H_5O_2S$) (Found: C, 75·9; H, 10·9; S, 6·8. $C_{30}H_{52}O_2S$ requires C, 75·6; H, 11·0; S, 6·7%); and 3-*methylthiocholest*-2-*ene* (XIIa) (25 mg, 26%), m.p. 87—88° (needles from ether–methanol), $[\alpha]_D$ +78° (*c* 1·5), τ 4·70 (2-H), 7·8 (s, CH_3·S), 9·23 (10-Me), and 9·32 (13-Me) (Found: C, 80·9; H, 11·6; S, 8·0. $C_{28}H_{48}S$ requires C, 80·7; H, 11·6; S, 7·7%).

(*b*) 3β-Methylsulphinyl-5α-cholestane [14a] (IVa) (100 mg) treated in the foregoing manner gave 3β-*acetoxymethyl-5α-cholestane* (XIg) (68 mg, 70%), m.p. 81—83° (from ether–methanol), $[\alpha]_D$ +21° (*c* 2·1) $\nu_{max.}$ 1750 cm^{-1}, τ 4·82 (s, AcO·CH_2·S), 7·20 ($W_{\frac{1}{2}}$ 24 Hz, 3α-H), 7·93 (s, CH_3·CO$_2$), 9·18 (10-Me), and 9·35 (13-Me), *m/e* 476 (M^+), 416 (M — $C_2H_4O_2$), and 371 (M — $C_3H_5O_2S$) (Found: C, 75·2; H, 10·7; S, 6·8. $C_{30}H_{52}O_2S$ requires C, 75·6; H, 11·0; S, 6·7%); and 3-methylthiocholest-2-ene (XIIa) (4 mg, 4%), m.p. 87—88°. Starting material (12 mg.) was recovered.

(*c*) 3α-Isopropylsulphinyl-5α-cholestane [1] (IIIb) (200 mg) [procedure (*B*)] gave 3-*isopropylthio-5α-cholest*-2-*ene* (XIIb) (70 mg, 40%), m.p. 85—86° (from ether–methanol), $[\alpha]_D$ +68° (*c* 0·5), $\lambda_{max.}$ 220 (ε 3800) and 247 nm (3400), τ 4·48 (C-2 vinyl proton), 6·84 (m, Me_2·CH·S), 9·14 (10-Me), and 9·33 (13-Me), *m/e* 444 (M^+), 401 (M — C_3H_7), and 369 (M — C_3H_7S) (Found: C, 81·2; H, 11·7; S, 7·3. $C_{30}H_{52}S$ requires C, 81·0; H, 11·8; S, 7·2%); and 3α-mercapto-5α-cholestane (Xf) (70 mg, 27%), which was characterised by oxidation with iodine in ethanolic dichloromethane to di-5α-cholestan-3α-yl disulphide,[1] m.p. 178—179°. Starting material (18 mg) was recovered.

(*d*) 3α-Benzylsulphinyl-5α-cholestane [14c] (IIIc) (371 mg) was treated according to procedure (*B*) and the crude product was hydrolysed in boiling 10% aqueous acetone (25 ml) containing toluene-*p*-sulphonic acid (10 mg). After 6 h the usual work-up gave an oil which was chromatographed (p.l.c.) using light petroleum as developer to give 5α-cholestan-3-one (XIII) (41 mg, 28%), m.p. 128—130°, and a mixture (103 mg, 35%) of 3α-mercapto-5α-cholestane (Xf) and di-5α-cholestan-3α-yl disulphide, which was characterised by oxidation with iodine to di-5α-cholestan-3α-yl disulphide,[1] m.p. 178—179°.

Hydrolysis of the Unsaturated Sulphides and Acetoxymethyl Sulphides.—(*a*) 3-Methylthio-5α-cholest-2-ene (XIIa) (230 mg) was treated with concentrated hydrochloric acid (2 drops) in boiling 5% aqueous methanol (30 ml) for 3 h. The usual work-up gave only 5α-cholestan-3-one (XIII) (185 mg, 85%), m.p. 129—130°. 3-Isopropylthio-5α-cholest-2-ene (30 mg) (XIIb) on similar treatment also gave only 5α-cholestan-3-one (XIII) (22 mg, 83%), m.p. 129—130°.

(*b*) Hydrolysis of 6-benzylthiocholest-5-ene (Vc) (18·5 mg) in the foregoing manner gave a mixture (15 mg, 100%) of 5α- and 5β-cholestan-6-one, chromatographically and spectroscopically identical with an equilibrium mixture of the ketones. Hydrolysis of the 6-alkylthiocholest-5-enes (Va), (Vd), and (Ve) separately under similar conditions also gave only a mixture of 5α- and 5β-cholestan-6-one in >85% yield.

(*c*) 6α-Vinylthio-5α-cholestane (IXf) and the mixed *E*- and *Z*-isomers of 6α-(but-1-enylthio)-5α-cholestane (IXd) were hydrolysed separately under the foregoing conditions to give only a mixture (t.l.c.) of 6α-mercapto-5α-cholestane (VIIIf) and the corresponding disulphide, which was characterised by oxidation to di-5α-cholestan-6α-yl disulphide, m.p. 194—196°, in the manner described previously (see the Pummerer reaction of 6α-benzylsulphinyl-5α-cholestane). Di-5α-cholestan-6β-yl disulphide [15] has m.p. 141—144°.

(*d*) 3α-Acetoxymethyl-5α-cholestane (Xg) (30 mg) was treated with toluene-*p*-sulphonic acid (10 mg) in boiling aqueous acetone (20 ml) overnight. The usual work-up gave a mixture (t.l.c.) of 5α-cholestan-3α-thiol (Xf) and the corresponding disulphide, and oxidation of the mixture with iodine in ethanolic dichloromethane as described previously [1] gave only di-5α-cholestan-3α-yl disulphide (19 mg, 75%), m.p. 177—179°. 3β-Acetoxymethyl-5α-cholestane (XIg) treated in the same way gave only di-5α-cholestan-3β-yl disulphide [1] (71%), m.p. 142—144°, and 6α-acetoxymethyl-5α-cholestane (VIIIg) gave only di-5α-cholestan-6α-yl disulphide (70%), m.p. 195°. 5α-Cholestane-3α-thiol (Xf) and 5α-cholestane-3β-thiol (XIf) are chromatographically (t.l.c.) identical, as are the corresponding disulphides, and the foregoing chemical evidence does not preclude the

[15] D. N. Jones and W. Higgins, *J. Chem. Soc.* (*C*), 1970, 81.

possibility that each 3-acetoxymethyl sulphide [(Xg) and (XIg)] is contaminated with some of its C-3 epimer. However careful comparison of the n.m.r. spectra of (Xg) and (XIg), particularly with respect to the unique signals due to the C-3 protons at τ 6·62 [in (Xg)] and τ 7·20 [in (XIg)] revealed that neither compound was contaminated with detectable quantities of the other.

Desulphurisation of the Unsaturated Sulphides with Raney Nickel.—(*a*) 3-Methylthio-5α-cholest-2-ene (XIIa) (84 mg) was treated with freshly prepared Raney nickel (1 g of sludge) in boiling dry acetone (10 ml) for 4 h. Filtration through Hyflo Supercel and evaporation of the solvent gave only 5α-cholest-2-ene (55 mg, 74%), m.p. 72—73°, mixed m.p. 69—72°, identical chromatographically and spectroscopically with an authentic specimen. It was not contaminated with 5α-cholest-3-ene (which has a similar m.p. and identical t.l.c. characteristics) according to n.m.r. spectroscopy (Varian A60 spectrometer); the isomers are readily distinguished, the almost isochronous vinyl protons of the 5α-cholest-2-ene resonating as a broad singlet ($W_{\frac{1}{2}}$ 2·5 Hz) at τ 4·46, whereas the vinyl protons of 5α-cholest-3-ene give rise to an AB pattern, τ_A 4·5, τ_B 4·8 (J 10·5 Hz). Desulphurisation of 3-isopropylthio-5α-cholest-2-ene (XIIb) (30 mg) in the same manner also gave only 5α-cholest-2-ene (20 mg, 80%), m.p. 70—72°.

(*b*) Desulphurisation of the 6-alkylthiocholest-5-enes (Va) and (Vc—e) in the foregoing manner gave only cholest-5-ene (70—80% yield), m.p. 91°; similar treatment of the mixture (40 mg) of 6-isopropylthiocholest-5-ene (Vb) and 6-isopropylthio-5α-cholest-6-ene (VIb) gave a mixture (27 mg, 81%) of cholest-5-ene and 5α-cholest-6-ene, the n.m.r. characteristics of which were identical with those of a 1 : 2 mixture of these two olefins. The presence or absence of 5α-cholest-6-ene in the products was also revealed by t.l.c. on silver nitrate-impregnated plates developed with light petroleum; cholest-5-ene and 5α-cholest-6-ene have R_F *ca.* 0·7 and *ca.* 0·4, respectively; 5α-cholest-7-ene has R_F *ca.* 1·0.

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