170. *Steroids. Part XX.* The Stereochemistry of the Homolytic Addition of Thioacetic Acid to Olefins of the Cholestane Series.*

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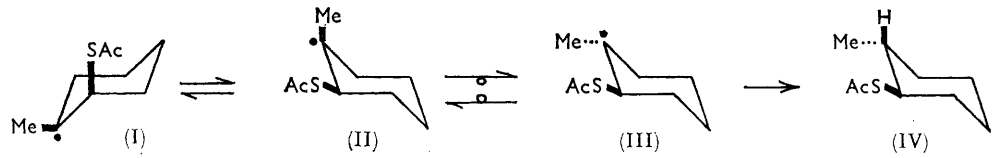
The homolytic addition of thioacetic acid to cholest-5-ene and cholesteryl acetate gives only the product of *trans*-diaxial 5α,6β-addition. Cholest-4-ene gives mainly the *trans*-diaxial 4β,5α-addition product, together with a second isomer which may be the 4β,5β-product of radical inversion.

The free-radical addition of hydrogen bromide to 1-methylcyclohexene [1] and 1-bromocyclohexene [2] gives only the *trans*-diaxial addition product. Although a number of workers [3] have found that decrease in ring size causes an increase of *cis*-addition owing to steric inhibition, Abell and Bohm [4] obtained predominantly the *trans*-addition product when 1-methylcycloheptene was treated with hydrogen bromide in the presence of oxygen. The homolytic addition of thioacetic acid to 1-methylcyclohexene [5] gives predominantly the *trans*-addition product but also affords the *cis*-addition product in yields which decrease with increasing concentration of thioacetic acid.

The intermediate in the free-radical addition of hydrogen bromide to olefins has been formulated by Goering *et al.*[1] as a bridged brominium radical which maintains conformation until hydrogen-transfer completes the process from the side opposite to the bromine bridge. Abell and Piette [6] have shown that this type of intermediate is supported by the electron paramagnetic resonance spectrum of the radical formed by the addition, catalysed by ultraviolet light, of hydrogen bromide to cyclohexene.

The differences between the free-radical addition of hydrogen bromide and thioacetic acid to cycloalkenes and their simple derivatives appear to arise from (*a*) the formation, by participation of the bromine atom, of bridged free radicals with consequent *trans*-addition, and (*b*) the non-formation, by the sulphur atom, of analogous bridged radicals; this and the lesser reactivity of thioacetic acid as a hydrogen-transfer reagent will permit the proposed [7] thioacetate radicals to undergo conformational (*e.g.*, I ⟶ II) and radical inversions (II ⟶ III), to give the *cis*-addition product (IV).



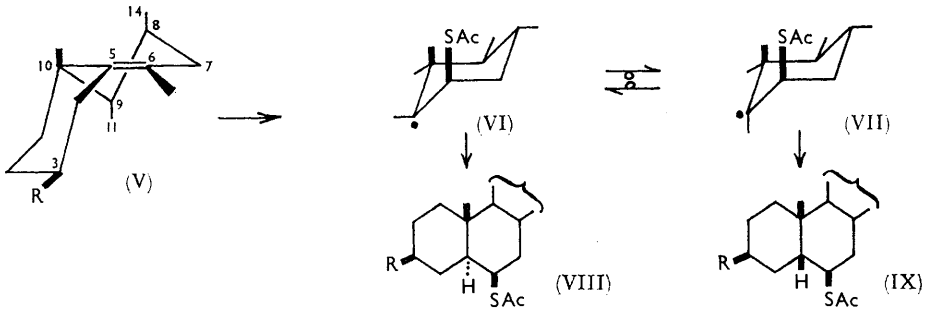
The polycyclic steroid nucleus is immune to, or subject only to limited conformational inversion, but radical inversion is possible. Thus, if ring A is a chair form, cholest-5-ene has the unique conformation (V) because ring B is held in one of the two half-chair forms by *trans*-fusion with ring C. By contrast, cholest-4-ene can exist in two conformations (XIIa and b) involving the two possible half-chair forms of ring A. We have found that the free-radical addition of hydrogen bromide to cholesteryl acetate gives only 6β-bromo-5α-cholestanyl acetate by *trans*-diaxial addition; [8,9] it therefore seemed of interest to

* Part XIX, *J.*, 1963, 3281.

[1] Goering, Abell, and Aycock, *J. Amer. Chem. Soc.*, 1952, **74**, 3588.
[2] Goering and Sims, *J. Amer. Chem. Soc.*, 1955, **77**, 3465.
[3] Howe, Ph.D. Thesis, University of Wisconsin, 1957; Abell and Chiao, *J. Amer. Chem. Soc.*, 1960, **82**, 3610.
[4] Abell and Bohm, *J. Org. Chem.*, 1961, **26**, 252.
[5] Bordwell and Hewett, *J. Amer. Chem. Soc.*, 1957, **79**, 3493; Goering, Relyea, and Larsen, *J. Amer. Chem. Soc.*, 1956, **78**, 348.
[6] Abell and Piette, *J. Amer. Chem. Soc.*, 1962, **84**, 916.
[7] Brand and Stevens, *J.*, 1958, 629.
[8] Shoppee and Lack, *J.*, 1960, 4864.
[9] Urushibara and Mori, *J. Chem. Soc. Japan*, 1943, **64**, 1285; cf. *Chem. Abs.*, 1947, **41**, 3807.

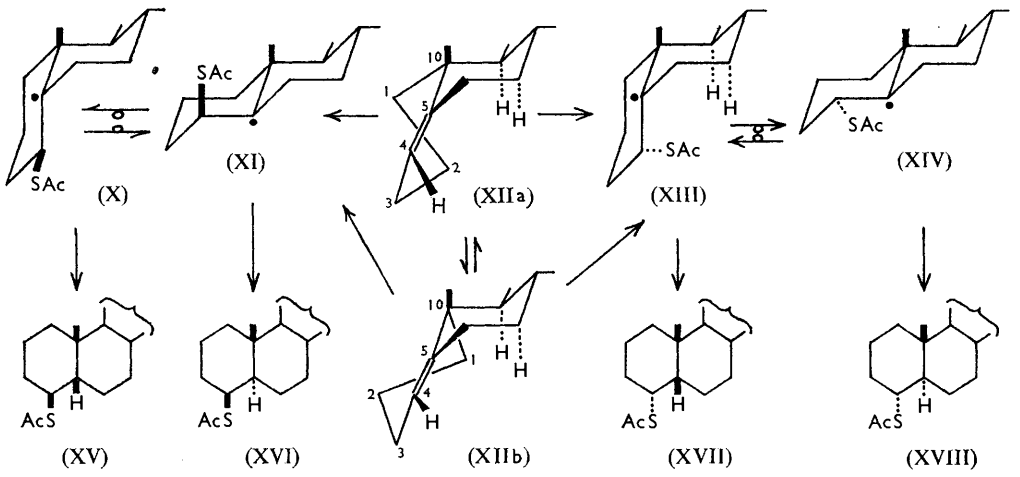
examine the free-radical addition of thioacetic acid to cholest-5-ene and cholesteryl acetate, and to cholest-4-ene. The only analogous work known to us was the reported [10] *trans*-diaxial addition of thioacetic acid to the 6-double bond of a 17-substituted derivative of 6-methylandrosta-4,6-diene-3,17-dione.

Addition of thioacetic acid to cholest-5-ene (V; R = H) or cholesteryl acetate (V; R = OAc) should furnish, by axial radical attack, the thioacetate radicals (VI); radical inversion of these to give (VII) should be unlikely, since it would not relieve the 1,3-diaxial interactions between the 6β-thioacetate and the 10β-methyl groups, and a 3β-substituent



if present would become axially oriented, so that the expected result should be the *trans*-diaxial addition products 5α-cholestan-6β-yl thioacetate (VIII; R = H) and 3β-acetoxy-5α-cholestan-6β-yl thioacetate (VIII; R = OAc), and not their 5β-isomers (IX; R = H or OAc).

Axial approach of the thioacetate radical to the 4-position in cholest-4-ene (XIIa or b) may be α- or β-orientated. Both reaction paths are equally subject to hindrance by the geometrical features (quasiaxial 5,10α-ring B, quasiaxial 10β-Me) common to the two conformations (XIIa and b); α-attack in (XIIa) to give (XIII) should be slightly favoured



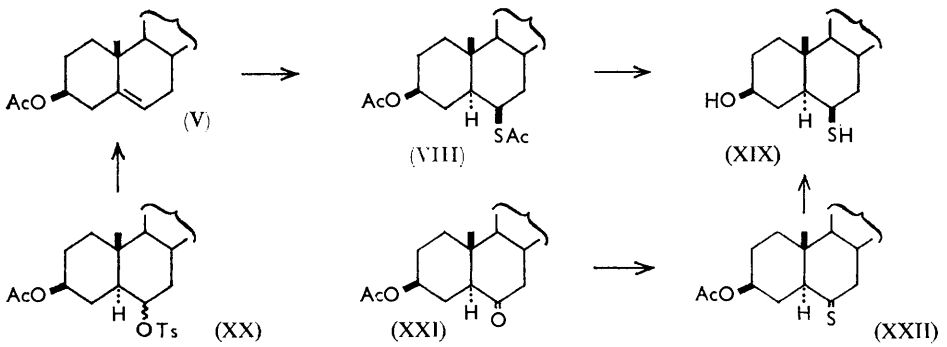
(axial 2α-H< axial 1β-H + quasiaxial 3β-H), whilst β-attack in (XIIb) to furnish (XI) should likewise be slightly favoured (axial 2β-H< axial 1α-H + quasiaxial 3α-H). Some radical inversion might be expected to occur with both (XI) and (XIII) to yield (X) and (XIV), respectively, in which steric repulsions would be relieved, so that formation of all four possible addition products (XV—XVIII) might be expected. The most probable products

[10] Tweit, Colton, McNiven, and Klyne, *J. Org. Chem.*, 1962, **27**, 3325.

appear to be 5α-cholestan-4β-yl thioacetate (XVI), 5β-cholestan-4β-yl thioacetate (XV), and 5α-cholestan-4α-yl thioacetate (XVIII).

Cholesteryl acetate (V; R = OAc) was inactive to thioacetic acid under the conditions employed by Bordwell and Hewett,[5] but on prolonged exposure to sunlight with a slight excess of thioacetic acid gave a quantitative yield of 3β-acetoxy-5α-cholestan-6β-yl thioacetate (VIII; R = OAc), converted into 3β-hydroxy-5α-cholestane-6β-thiol (XIX) by hydrogenolysis with lithium aluminium hydride [11] or by hydrolysis with alcoholic sodium hydroxide at 20°; at 80°, diaxial elimination of thioacetic acid occurred, to give cholesterol (V; R = OH).

To facilitate the identification of the addition product (VIII; R = Ac) attempts were made to prepare the 6β-thiol (XIX) and its 6α-epimer by alternative methods. Treatment of the 6α- and 6β-toluene-*p*-sulphonates as (XX) with thiourea or potassium thiocyanate, successfully employed by Bourdon [12] in the preparation of epimeric 3-thiols, resulted in elimination of the toluene-*p*-sulphonate group to give cholesteryl acetate (V; R = OAc). The same result was obtained when 3β-acetoxy-5α-cholestan-6β-yl bromide [8] was treated with sodium hydrogen sulphide. Attempted preparation of 3β-acetoxy-5α-cholestane-



6-thione (XXII) by treatment of the ketone (XXI) with hydrogen sulphide and hydrochloric acid,[13] followed by acetylation, gave a low yield of a colourless product, having the correct analysis for the thione (XXII), but the plain rotatory dispersion curve [14] probably indicates the dimer. This was unchanged by treatment with sodium and ethanol at 80° for 7 days but was partially reduced to the corresponding thiol (XIX) on prolonged treatment with lithium aluminium hydride in ether to give, after acetylation, the thioacetate (VIII; R = OAc), identical with the product from the addition of thioacetic acid to cholesteryl acetate. Lithium aluminium hydride was found by Bourdon [15] to reduce polymeric 3-thiones to the monomeric 3-thiols.

Cholest-5-ene (V; R = H) and thioacetic acid gave the *trans*-diaxial addition product 5α-cholestan-6β-yl thioacetate (VIII; R = H), which readily eliminated thioacetic acid to regenerate cholest-5-ene; formation of the isomeric 5β-cholestan-6β-yl thioacetate (IX; R = H) could not be detected. Attempts to prepare the 6β-thiol corresponding to (VIII; R = H) and its 6α-epimer from the appropriate 6α- and 6β-toluene-*p*-sulphonates resulted in elimination of toluene-*p*-sulphonic acid to give cholest-5-ene.

Cholest-4-ene (XIIa or b) and thioacetic acid gave 5α-cholestan-4β-yl thioacetate (XVI) as the main addition product, whose nuclear magnetic resonance (n.m.r.) spectrum showed a sharp peak (τ 7·75) for the methyl group of the thioacetate moiety.[10] The

[11] Bobbio, *J. Org. Chem.*, 1961, **26**, 3023.
[12] Bourdon, *Bull. Soc. chim. France*, 1962, 844.
[13] Dodson and Sollman, U.S. Pat. 2,837,538 (1958); cf. *Chem. Abs.*, 1959, **53**, 3282.
[14] Djerassi and Herbst, *J. Org. Chem.*, 1961, **26**, 4675.
[15] Bourdon, *Bull. Soc. chim. France*, 1958, 722.

n.m.r. spectrum of the mother-liquors however disclosed the presence of a second product by showing two peaks, τ 7·78 and 7·75. Thin-layer chromatography on silica gel of the same sample also disclosed the presence of a minor product which could not be isolated by recrystallisation or by column chromatography on silica gel or alumina. Attempts to prepare for comparison the 4β-thiol corresponding to (XVI) and the 4α-thiol corresponding to (XVIII), from the 5α-cholestan-4α- and -4β-yl toluene-*p*-sulphonates resulted in elimination of toluene-*p*-sulphonic acid to give cholest-4-ene.

The minor product must be a thioacetate [τ 7·78 (·S·COMe)]; we have attempted to distinguish between the structures (XV), (XVII), and (XVIII) by reference to the n.m.r. spectra of 5α- and 5β-cholestane, 3β-acetoxy-5α- and -5β-cholestane, and 3β-acetoxy-5α-cholestan-6β-yl thioacetate (VIII; R = OAc), whose structure is established by partial synthesis. The significant peaks in the n.m.r. spectra are collected in the Table.

Nuclear magnetic resonance spectra.

	18-Methyl	19-Methyl	4- or 6-S·CO·CH_3	4- or 6-protons	Methylene protons
5α-Cholestane	9·30	9·17			8·8
5β-Cholestane	9·38	9·10			8·7
5α-Cholestan-3-β-yl acetate	9·32	9·17			8·8
5β-Cholestan-3β-yl acetate	9·34	9·04			8·7
5α-Cholestan-6β-yl thioacetate (VIII; R = H)	9·33	9·12	7·72	6·2	8·8
3β-Acetoxy-5α-cholestan-6β-yl thioacetate (VIII; R = OAc)	9·33	9·10	7·75	6·2	8·8
5α-Cholestan-4β-yl thioacetate (XVI)	9·35	9·16	7·75	6·2	8·8
Mixture of 5α-cholestan-4β-yl (XVI) and 5β-cholestan-4β-yl thioacetate? (XV)	9·33	9·16	7·75	—	8·8
	9·36	9·10	7·78	—	8·8
3β,6β-Diacetoxy-5α-cholestane [16]	—	8·99			—
6β-Bromo-5α-cholestan-3β-yl acetate	9·29	8·89			8·8

The presence of a thioacetate group in (VIII; R = H and OAc) and in (XVI) is confirmed by the sharp singlet at τ 7·75 for the three protons of the methyl group, and by the multiplet at τ 6·2 for the single proton associated with the carbon atom bearing the thioacetate group. The axial 6β-thioacetate group causes the signal for the 19-methyl group at τ 9·10 in (VIII; R = OAc) and at τ 9·12 in (VIII; R = H) to show a paramagnetic shift of 0·07 and 0·05 p.p.m. by comparison with 3β-acetoxy-5α-cholestane and 5α-cholestane, respectively; larger shifts are caused by the axial 6β-acetoxyl group in 3β,6β-diacetoxy-5α-cholestane (0·18 p.p.m.) and the axial 6β-bromine atom in 3β-acetoxy-5α-cholestan-6β-yl bromide (0·28 p.p.m.).

The axial 4β-thioacetate group in (XVI), by comparison with 5α-cholestane, exhibits a paramagnetic shift of only 0·01 p.p.m. in the signal for the 19-methyl group, but the alternative 5β-structures (XV and XVII) are excluded by comparison with 5β-cholestane, whilst the 5α-structure (XVI) is consistent with the molecular rotation data (see below).

The minor product formed in the radical addition of thioacetic acid to cholest-4-ene gives rise to a 19-methyl signal at τ 9·10; this, by comparison with the value τ 9·17 for 5α-cholestane, appears to exclude 5α-cholestan-4α-yl thioacetate (XVIII), and to be consistent with the value τ 9·10 for 5β-cholestane; the minor constituent is tentatively regarded as the product of radical inversion, 5β-cholestan-4β-yl thioacetate (XV), or, less probably, 5β-cholestan-4α-yl thioacetate (XVII).

The molecular rotatory contributions of the 6β-thioacetate group in 5α-cholestan-6β-yl thioacetate (VIII; R = H) [−112], and in the 3β-acetoxy-analogue (VIII; R = OAc) [−190], are in agreement with the large negative contributions observed for the 6β-acetoxyl group [−110],[17] the 6β-hydroxyl group [−60],[17] and the 6β-bromine atom [−163] [8] in the 5α-cholestane series. The sign of the molecular rotatory contribution of the 4β-thioacetate group [+100] in 5α-cholestan-4β-yl thioacetate (XVI) is consistent with that

[16] Zurcher, *Helv. Chim. Acta*, 1961, **44**, 1380.
[17] Shoppee and Summers, *J.*, 1952, 3361.

found for the 4β-hydroxyl group [+22) [18] but not with that observed for the 4α-hydroxyl group [−75] [18] in the 5α-cholestane series.

Recently, Tweit *et al.*[10] reported the production of a small amount of 7β-thioacetate together with the main 7α-isomer in the addition of thioacetic acid to the 4,6-dien-3-one system. Since the reaction was carried out at 100°, epimerisation of the first formed axial product may have occurred. We treated cholest-4-ene with thioacetic acid at 100° for 1 hr., but recovered only unchanged material, possibly on account of the instability of the addition product under these conditions.

Experimental

For general directions see *J.*, 1959, 345. $[\alpha]_D$'s refer to chloroform solutions at room temperature. Infrared spectra were determined in a Perkin-Elmer model 221 double-beam instrument. Analysis samples were dried at 70°/0·5 mm. for 4 hr. Nuclear magnetic resonance spectra were determined on a Varian D.P. 60 instrument at 60 Mc./sec., with deuterochloroform as solvent and tetramethylsilane as internal reference; the charts were calibrated by the audio side-band technique.

3β-*Acetoxy*-5α-*cholestan*-6β-*yl Thioacetate*.—Cholesteryl acetate (1·07 g.) in carbon tetrachloride (2 ml.) was treated with freshly distilled thioacetic acid (250 mg.) at 20° in bright sunlight for 24 hr. Sodium hydrogen carbonate solution was added, and extraction with ether gave the *thioacetate* (1·18 g.), m. p. 111°, $[\alpha]_D$ −25° (*c* 1·2), $\nu_{max.}$ ($CHCl_3$) 1735, 1690, 1240 cm.$^{-1}$ (Found: C, 73·9; H, 10·25. $C_{31}H_{52}O_3S$ requires C, 73·75; H, 10·35%).

3β-*Hydroxy*-5α-*cholestane*-6β-*thiol*.—(*a*) 3β-Acetoxy-5α-cholestan-6β-yl thioacetate (1 g.) in ether (10 ml.) was treated with sodium hydroxide (1 g.), dissolved in water (5 ml.) and ethanol (5 ml.), at 20° for 18 hr. Evaporation of the ether at 20° and neutralisation with acetic acid gave the *thiol* (850 mg.), m. p. after recrystallisation from ethanol as plates, 96°, forming needles, m. p. 104°, $\nu_{max.}$ ($CHCl_3$) 3400, 1050 cm.$^{-1}$ (Found: C, 76·9; H, 11·4. $C_{27}H_{48}OS$ requires C, 77·1; H, 11·5%). Attempts to hydrolyse 3β-acetoxy-5α-cholestan-6β-yl thioacetate at higher temperatures resulted in elimination of the 6β-thiol group to give cholesterol.

(*b*) 3β-Acetoxy-5α-cholestan-6β-yl thioacetate (100 mg.) in dry ether (15 ml.) was treated with lithium aluminium hydride [11] (500 mg.) at 35° for 2 hr. The colourless oil obtained after the usual isolation procedure gave the *thiol* (75 mg.), m. p. and mixed m. p. 96° (from acetone), with the same infrared spectrum as the product prepared in (*a*).

3β-*Acetoxy*-5α-*cholestane*-6-*thione*.—3β-Acetoxy-5α-cholestan-6-one [19] (500 mg.) in benzene–ethanol (30 ml.; 3 : 7) was treated simultaneously with dry streams of hydrogen sulphide and hydrogen chloride [15] at 20° for 32 hr. The reaction mixture was allowed to stand overnight and then extracted with ether and chromatographed on alumina (15 g.). Elution with ether–benzene (1 : 50) gave 3β-chloro-5α-cholestan-6-one (20 mg.), m. p. 125—127° (from methanol), $\nu_{max.}$ (Nujol) 760 cm.$^{-1}$ (Found: C, 77·5; H, 10·5. Calc. for $C_{27}H_{45}ClO$: C, 77·1; H, 10·7%). Elution with chloroform–ether (1 : 1) gave 3β-hydroxy-5α-cholestan-6-one (417 mg.), m. p. 142° and 151—153° (from methanol), $\nu_{max.}$ ($CHCl_3$) 1705 cm.$^{-1}$. Further elution with chloroform gave polymeric 3β-*hydroxy*-5α-*cholestane*-6-*thione* (50 mg.), $\nu_{max.}$ (Nujol) 3400, 1060 cm.$^{-1}$, which was treated with acetic anhydride (1 ml.) for 10 min. at 130°. Crystallisation from methanol gave polymeric 3β-*acetoxy*-5α-*cholestane*-6-*thione*, m. p. 98—100°, $\nu_{max.}$ (Nujol) 1740, 1240 cm.$^{-1}$ (Found: C, 75·1; H, 10·35; S, 7·6. $C_{29}H_{48}O_2S$ requires C, 75·65; H, 10·4; S, 6·95%).

Reduction of Polymeric 3β-*Acetoxy*-5α-*cholestane*-6-*thione*.—(*a*) The polymeric thione (100 mg.) was treated with sodium (2 g.) in pentyl alcohol at 133° for 7 days, with further additions of sodium (1 g.) and pentyl alcohol (10 ml.) each 24 hr. The product was treated with acetic anhydride (1·5 ml.) in pyridine (5 ml.) at 20° for 24 hr. Polymeric 3β-acetoxy-5α-cholestane-6-thione was recovered.

(*b*) Polymeric 3β-hydroxy-5α-cholestane-6-thione (200 mg.) in dry ether (50 ml.) was refluxed with lithium aluminium hydride (500 mg.) for 24 hr. The crude product was treated

[18] Barton and Klyne, *Chem. and Ind.*, 1948, 755; Stokes and Bergmann, *J. Org. Chem.*, 1952, **17**, 1194.

[19] Dodson and Riegel, *J. Org. Chem.*, 1948, **13**, 424.

with acetic anhydride (2 ml.) in pyridine (10 ml.) at 20° for 24 hr. and the product was chromatographed on silica gel (12 g.) in pentane. Elution with ether–pentane (1 : 10) gave 3β-acetoxy-5α-cholestan-6β-yl thioacetate (65 mg.), m. p. and mixed m. p. 109—111° (from methanol).

5α-Cholestan-6β-yl Thioacetate.—Cholest-5-ene (1 g.) in dry carbon tetrachloride (3 ml.) was treated with freshly distilled thioacetic acid (216 mg.) at 20° in bright sunlight for 14 days. The usual isolation gave a yellow oil which was chromatographed on silica gel (60 g.) in pentane. Elution with pentane gave unchanged cholest-5-ene (150 mg.), while the use of ether–pentane (1 : 50) gave the *thioacetate* (990 mg.), m. p. 70—72° (from ether–methanol), $[\alpha]_D$ −4·6° (*c* 1·1), $\nu_{max.}$ (Nujol) 1680, 1110, 950 cm.$^{-1}$ (Found: C, 77·7; H, 11·15. $C_{29}H_{50}OS$ requires C, 78·0; H, 11·3%).

5α-Cholestan-4β-yl Thioacetate.—Cholest-4-ene (1 g.) in dry carbon tetrachloride (3 ml.) was treated with freshly distilled thioacetic acid (215 mg.) at 20° in bright sunlight for 14 days. The product, isolated in the usual way, was chromatographed on silica gel (60 g.) in pentane. Elution with pentane gave unchanged cholest-4-ene (300 mg.), and elution with ether–pentane (1 : 50) gave the *thioacetate* (870 mg.), m. p. 131—133° after two crystallisations from ether–methanol, $[\alpha]_D$ +45° (*c* 1·0), $\gamma_{max.}$ (Nujol) 1680, 1110, 950 cm.$^{-1}$ (Found: C, 77·6; H, 11·1%). Thin-layer chromatography of the mother-liquors on silica gel showed two spots of similar R_F value, and the n.m.r. spectrum also showed the presence of two isomers.

*5α-Cholestan-6α-yl Toluene-*p*-sulphonate.*—6α-Hydroxy-5α-cholestane (1 g.) in dry pyridine (20 ml.) was treated with toluene-*p*-sulphonyl chloride (5 g.) at 20° for 48 hr. Isolation as usual gave an oil (1·2 g.) which crystallised from light petroleum at 0° to give the toluene-*p*-sulphonate as needles, m. p. 109—111°, [α] +67° (*c* 1·31),[17,20] $\gamma_{max.}$ (Nujol) 1175, 1160 cm.$^{-1}$ (Found: C, 75·4; H, 10·1. Calc. for $C_{34}H_{54}O_3S$: C, 75·2; H, 10·0%).

*5α-Cholestan-4α-yl Toluene-*p*-sulphonate.*—4α-Hydroxy-5α-Cholestane (900 mg.) in dry pyridine (20 ml.) was treated with toluene-*p*-sulphonyl chloride (4·5 g.) at 20° for 48 hr. The oil (1·1 g.) obtained after the usual isolation process gave the *product* as needles (from light petroleum), m. p. 136·5—138°, $[\alpha]_D$ +24° (*c* 1·02), $\nu_{max.}$ (Nujol) 1175, 1160 cm.$^{-1}$ (Found: C, 75·5; H, 10·2%).

Attempts to prepare 5α-cholestan-6β-yl thiocyanate and 5α-cholestan-4β-yl thiocyanate, by treatment of the above toluene-*p*-sulphonates with potassium thiocyanate in ether–methanol at 20° for 21 days, yielded unchanged material, whilst at 65° elimination of the tosylate group occurred, to give cholest-5-ene and cholest-4-ene, respectively.

*3β-Acetoxy-5α-cholestan-6β-yl Toluene-*p*-sulphonate.*—3β-Acetoxy-5α-cholestan-6β-ol (1 g.) in dry pyridine (20 ml.) was treated with toluene-*p*-sulphonyl chloride (6 g.) at 0° for 10 days. Extraction with ether and evaporation of the solvent under vacuum at 20° gave a yellow oil (1·26 g.). Three crystallisations from light petroleum gave the *product* as needles, m. p. 136—138°, $[\alpha]_D$ −18° (*c* 0·9), $\nu_{max.}$ (Nujol) 1735, 1250, 1190, 1180 cm.$^{-1}$ (Found: C, 72·0; H, 9·3. $C_{36}H_{56}O_5S$ requires C, 72·0; H, 9·4%).

Treatment of the tosylate with potassium thiocyanate in ether–methanol at 20° for 15 days gave only unchanged material, while at 65° elimination of the tosylate group occurred to give cholesteryl acetate.

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[20] Karrer, Asmis, Sareen, and Schwyzer, *Helv. Chim. Acta*, 1951, **34**, 1022.