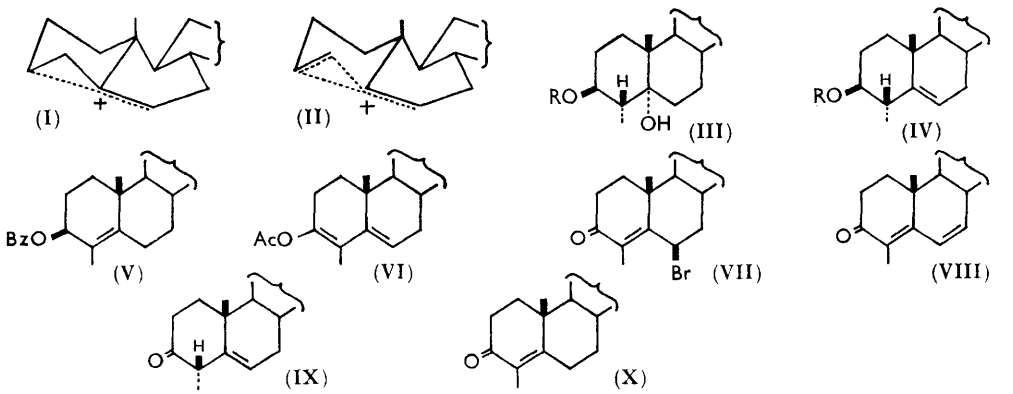
504. *Solvolysis of Sulphonate Esters of 4α- and 4β-Methylcholesterol.*[1]

By S. Julia, J. P. Lavaux, S. R. Pathak, and G. H. Whitham.

Solvolysis of 4α-methylcholesteryl methanesulphonate in buffered aqueous acetone led to products analogous to those derived from cholesteryl methanesulphonate. In contrast 4β-methylcholesteryl methanesulphonate gave largely 4-methylcholesta-3,5-diene and small amounts of the ring-contracted alcohol (XV) under the same conditions. First-order rate constants for the corresponding acetolyses were also measured. Possible interpretations of these results are discussed.

Two forms have been suggested for the cationic intermediate involved in solvolysis reactions of sulphonate esters of cholesterol,[2] namely the non-classical ions (I) and (II), which differ in degree of delocalisation of positive charge. Solvolysis of the toluene-*p*-sulphonate of 3β-hydroxymethyl-A-norcholest-5-ene gives results that have been taken to favour (II).[3] In principle another way of deciding between the two cations is to study the effect of alkylation at C-4 on the outcome of the reaction. This Paper describes results obtained with 4α- and 4β-methylcholesteryl sulphonates.

4α-Methylcholesterol was prepared by the method of Julia and Lavaux[4] with the modification that the glycol (III; R = H) was converted into the monobenzoate (III; R = Bz) instead of the monoacetate (III; R = Ac). Dehydration of the monobenzoate with thionyl chloride–pyridine gave a mixture of unsaturated benzoates (IV; R = Bz) and (V), the former predominating. Straight crystallisation of the mixture gave pure 4α-methylcholesteryl benzoate which was hydrolysed to the parent alcohol (IV; R = H) in high yield.



An alternative method of preparation of 4α-methylcholesterol, involving the sequence (VI)[5] ⟶ (VII) ⟶ (VIII) ⟶ (IX) ⟶ (IV; R = H), was investigated. Although the first two stages to the dienone (VIII) proceeded in good yield (see Experimental section), the lithium–ammonia reduction of (VIII) gave only 10% yield of the pure unconjugated

[1] Preliminary communication: Julia, Lavaux, Pathak, and Whitham, *Compt. rend.*, 1963, **256**, 1537.
[2] Winstein and Kosower, *J. Amer. Chem. Soc.*, 1959, **81**, 4399.
[3] Whitham and Wickramasinghe, *J.*, 1964, 1655.
[4] Julia and Lavaux, *Bull. Soc. chim. France*, 1963, 1231.

ketone (IX).* The structure of the latter follows from (i) its spectral characterisation as an unconjugated ketone; (ii) conversion into the conjugated ketone (X) [5] on treatment with alkali; and (iii) reduction with lithium aluminium hydride to 4α-methylcholesterol identical with that produced above. This preparation serves to confirm the structure of 4α-methylcholesterol.

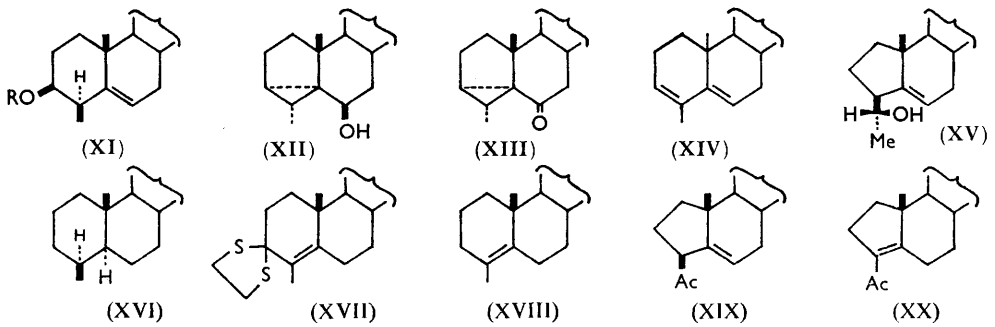
4β-Methylcholesterol (XI) was prepared by the method of Julia and Lavaux.[7]

Results

The 4-methylcholesteryl methanesulphonates could be prepared more conveniently than the toluene-*p*-sulphonates, thus the former were used for most of the work.

Products (% yield) obtained on solvolysis of 4α-methylcholesteryl methanesulphonate in aqueous acetone buffered with potassium acetate are: hydrocarbons, absent; acetates, 8·5; 4α-methyl-3α,5-cyclo-5α-cholestan-6β-ol (XII), 82; and 4α-methylcholesterol, 5. The gross structure of the cyclo-alcohol (XII) follows from (i) its reconversion into 4α-methylcholesterol when heated with mineral acid, and (ii) its conversion on oxidation with chromium trioxide–pyridine into a ketone (XIII) [$\nu_{max.}$ 1710 and 1420 cm.$^{-1}$ (CH_2·CO)], which is unaffected on treatment with aqueous ethanolic potassium hydroxide. The stereochemistry of the cyclo-alcohol (XII) is assigned by analogy with that of the 3α,5-cyclo-5α-cholestan-6β-ol, derived by solvolysis of cholesteryl toluene-*p*-sulphonate.

Products (% yield) obtained from solvolysis of 4β-methylcholesteryl methanesulphonate in buffered aqueous acetone are: 4-methylcholesta-3,5-diene (XIV), 78; acetates, trace; 4β-methylcholesterol, 3; A-nor-alcohol (XV), 7. Similar results were obtained with the toluene-*p*-sulphonate.



(XI) (XII) (XIII) (XIV) (XV)

(XVI) (XVII) (XVIII) (XIX) (XX)

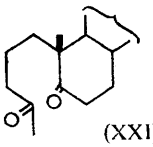
The conjugated diene (XIV), $\lambda_{max.}$ (cyclohexane) 239 (ε, 18,200) with shoulders at 232 (ε, 15,900) and 247 mμ (ε, 11,200), was shown to have an unrearranged skeleton by catalytic hydrogenation to a saturated hydrocarbon, presumably 4β-methyl-5α-cholestane (XVI), identical with that obtained by hydrogenation of 4-methylcholest-4-ene (XVIII). The latter compound was prepared by reduction of the thioketal (XVII) of 4-methylcholest-4-en-3-one.

The alcohol obtained from the solvolysis of 4β-methylcholesteryl methanesulphonate was shown to be a ring-contracted homoallylic alcohol of the gross structure (XV) by oxidation with chromium trioxide–pyridine to an unconjugated ketone (XIX) which was in turn converted into the conjugated ketone (XX) on treatment with ethanolic potassium hydroxide. Authentic samples of the conjugated ketone (XX) were prepared in two ways: (i) by ozonolysis of 4-methylcholest-4-ene (XVIII) followed by base-catalysed cyclisation of the resulting diketone (XXI); (ii) by treatment of the monomethanesulphonate (XXII;

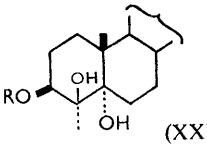
* Attempts to generate (IX) by kinetically controlled protonation of the enolate ion from 4-methylcholest-4-en-3-one were unsuccessful (cf. Ringold and Malhotra [6]).

[5] Atwater, *J. Amer. Chem. Soc.*, 1960, **82**, 2847.
[6] Ringold and Malhotra, *J. Amer. Chem. Soc.*, 1962, **84**, 3402.
[7] Julia and Lavaux, *Bull. Soc. chim. France*, 1963, 1223.

R = $MeSO_2$–) of 4α-methylcholestane-3β,4β,5α-triol [4] (XXII; R = H) with potassium t-butoxide. The latter process involves fragmentation to the diketone (XXI) and concomitant cyclisation (cf. ref. 8 for a related example). The stereochemical assignments indicated in formula (XV) will be discussed below.



(XXI)



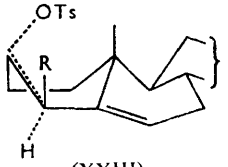
(XXII)

First-order rate constants for acetolysis of the 4α- and 4β-methylcholesteryl methanesulphonates are tabulated. For comparison, values for cholesterol, 4,4-dimethylcholesterol, cholestanol, and 4α-methylcholestanol are also given.

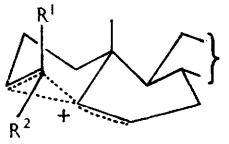
Methanesulphonate	10^4k at 50° (sec.$^{-1}$)	Rel. k	Methanesulphonate	10^4k at 50° (sec.$^{-1}$)	Rel. k
4α-Methylcholesteryl...	37	21	4,4-Dimethylcholesteryl	14·5	8·3
4β-Methylcholesteryl...	6·5	3·7	5α-Cholestan-3β-yl (at 80°)	0·47	—
Cholesteryl	1·75	1	4α-Methyl-5α-cholestan-3β-yl (at 80°)	0·66	—

Discussion

We consider first the results obtained on solvolysis of 4α-methylcholesteryl methanesulphonate. The preparative run shows a strong similarity between this reaction and the corresponding solvolysis of sulphonates of cholesterol, a typical product composition for the latter being: *ca.* 90% of alcohol products [comprising 82% 3α,5-cyclo-5α-cholestanol and 18% cholesterol] together with 1—2% of cholesta-3,5-diene. The complete absence of diene in the 4α-methyl series is indicative that the diene in the cholesteryl series is derived by a route independent of that leading to the alcohol products. It seems possible that this route involves an anti-coplanar elimination process in the ring-A boat of twist conformation, *i.e.* (XXIII; R = H).



(XXIII)



(XXIV)

The rate of acetolysis of 4α-methylcholesteryl methanesulphonate is 21 times that of the cholesteryl compound. As the two reactions follow a similar course, this rate enhancement appears to be a good measure of the effect of a methyl group on the rate-determining step for formation of a homoallylic cholesteryl cation. Two possible explanations for this enhancement are that ionisation leads to (i) a cation of type (II), bearing partial positive charge on C-4, so that the methyl group can inductively stabilise the transition state, or (ii) a cation of type (I), the rate enhancement being due to steric acceleration of ionisation, *i.e.*, the 4α-methyl group raises the free energy of the ground state. The second explanation appears less significant in view of the small effect that the introduction of a 4α-methyl group has on the rate of acetolysis in the 5α-cholestan-3β-yl series, where the steric, but not the electronic, situation is closely similar.* It seems probable, therefore, that one

* The slightly increased rate of acetolysis of 4α-methyl-5α-cholestan-3β-yl over that of cholestanyl methanesulphonate represents an upper limit to the contribution of steric acceleration to ionisation of 4α-methylcholesteryl methanesulphonate since, even in the saturated series, the possibility exists for inductive stabilisation by the methyl group if the rate-determining step leads to a bridged cation.

It is noteworthy that, in the simple monocyclic system, Hückel has found the relatives rates of acetolysis to be cyclohexyl : *trans*-2-methylcyclohexyl : *cis*-2-methylcyclohexyl toluene-*p*-sulphonate = 1 : 0·23 : 21 at 50°.[9] We have not tried to relate his results to ours, as it is difficult to compare the highly mobile cyclohexyl system with the considerably more restricted steroid skeleton.

[8] Thomas, Heusler, and Müller, *Tetrahedron*, 1961, **16**, 254.
[9] Hückel, *Annalen*, 1959, **624**, 142.

of the major cationic species involved in the solvolysis of 4α-methylcholesteryl methanesulphonate is the non-classical cation (XXIV; $R^1 = H$, $R^2 = Me$), and by inference we favour the symmetrical cation (II) for the intermediate cation in the cholesteryl series.

We consider now the results obtained on the solvolysis of 4β-methylcholesteryl methanesulphonate. The product analysis indicates a very different outcome as compared with the 4α-methylcholesteryl and cholesteryl systems. The high yield of 4-methylcholesta-3,5-diene is in line with the interpretation already advanced for the formation of cholesta-3,5-diene in the cholesteryl system. Clearly the transition state leading to a symmetrical cation (XXIV, $R^1 = Me$, $R^2 = H$) would be destabilised relative to a transition state of the type (XXIII; R = Me) as a result of 1,3-diaxial interactions between the 4β-methyl group and the 19-methyl in the former.

The simplest interpretation for the formation of the A-noralcohol (XV) seems to be that it is derived from the symmetrical cation (XXIV; $R^1 = Me$, $R^2 = H$) by co-ordination of solvent at C-4. Such a reaction course for this cation would be favoured since it would relieve the methyl–methyl diaxial interaction by cleavage of the 4—5 partial bond. The stereochemistry of the alcohol (XV) was assigned on the basis of this hypothesis, *i.e.*, attack at C-4 with inversion of configuration.

Owing to the very different outcome of the 4β-methylcholesteryl reaction it is difficult to interpret the rate constant. Apparently introduction of the 4-methyl group considerably enhances the rate of the elimination process (XXIII), presumably through stabilisation of the partial double bond in the transition state (Saytzeff). It would be unprofitable to attempt a dissection into separate rate constants for reaction *via* the boat and chair conformations, particularly since product analyses and rate constants have been determined for different solvent systems.

The dominating effect of the diaxial methyl–methyl interaction on the solvolysis of 4β-methylcholesterol is in agreement with recent findings on the solvolysis of 4,4-dimethylcholesteryl toluene-*p*-sulphonate [10] where a similar interaction occurs. In the latter case, alkyl migration occurs to a significant extent *via* a ring-A boat or twist conformation. Clearly, therefore, the rate of acetolysis of 4,4-dimethylcholesteryl methanesulphonate is a poor measure of the effect of gem-dimethyl substitution at C-4 on the rate of formation of the cholesteryl cation. This is in agreement with the lower rate of acetolysis of 4,4-dimethylcholesteryl methanesulphonate than the 4α-methyl compound.*

Experimental

For general experimental points see ref. 3.

3β-*Benzoyloxy*-4α-*methylcholestan*-5α-*ol*.—Benzoyl chloride (4·8 ml., 1·5 mol.) was added to 4α-methylcholestan-3β,5α-diol [4] (5·9 g.) in pyridine (15 ml.). After 3 hr. at 20° water was added and the product was isolated with ether. Crystallisation from acetone–methanol gave the *monobenzoate* (5·05 g.), m. p. 199—201°, $[\alpha]_D$ +56° (Found: C, 80·5; H, 10·25. $C_{35}H_{54}O_3$ requires C, 80·4; H, 10·4%).

3β-*Benzoyloxy*-4α-*methylcholest*-5-*ene*.—Thionyl chloride (7·9 ml.) was added to a solution of 3β-benzoyloxy-4α-methylcholestan-5α-ol (5·88 g.) in dry pyridine (22 ml.) at −60°. After 30 min. at 0° ice–water was added and the product was isolated with ether. Crystallisation from acetone gave 4α-methylcholesteryl benzoate as plates (3·46 g., 61%), m. p. 136—138°, $[\alpha]_D$ +38° (Found: C, 83·25; H, 10·1. Calc. for $C_{34}H_{52}O_2$: C, 83·3; H, 10·4%).

Concentration of the mother-liquor gave a solid (1·99 g.) which was hydrolysed with ethanolic potassium hydroxide. The resulting alcohol mixture had $[\alpha]_D$ +36° showing it to be a mixture

* While this Paper was being prepared an abstract of a Paper entitled "The Solvolysis of 4α- and 4β-methylcholesteryl *p*-toluenesulphonate" appeared.[11] The authors describe results on the preparative solvolysis of 4β-methylcholesteryl toluene-*p*-sulphonate which are in good agreement with ours on the methanesulphonate; however in their hands the solvolysis of 4α-methylcholesteryl toluene-*p*-sulphonate in buffered aqueous acetone led to the formation of diene along with the cyclo-alcohol (XII; 55%).

[10] Just and Richardson, XIXth Internat. Congr. Pure and Appl. Chem., 1963, Abs. A, p. 151, and personal communication.

[11] Moriarty and de Sousa, Abs. Meeting *Amer. Chem. Soc.*, Sept. 1963, p. 91Q.

of 4α-methylcholesterol (22%) $[\alpha]_D$ −23°, and 4-methylcholest-4-en-3β-ol (78%), $[\alpha]_D$ +52·5°. A pure sample of the latter was obtained by hydrolysis of the acetate.[4]

6β-*Bromo*-4-*methylcholest*-4-*en*-3-*one*.—The two-phase system comprising 4-methylcholesta-3,5-dien-3-yl acetate (1·1 g.) in carbon tetrachloride (12 ml.) and calcium carbonate (500 mg.) in water (100 ml.) was stirred rapidly at 20°. A solution of bromine in carbon tetrachloride (1 mol., 13 ml. of a solution containing 0·5 ml. of bromine in 50 ml. of carbon tetrachloride) was added over 15 min. After filtration, ether was added and the organic phase was isolated and dried. Evaporation at 20° followed by crystallisation from ether gave the *bromo-ketone* as long needles (0·798 g.), m. p. 136—138°, $[\alpha]_D$ −125°, $\lambda_{max.}$ (in EtOH) 262 mμ (ε, 12,400), R_F (in benzene) 0·68 (Found: C, 70·75; H, 9·5. $C_{28}H_{45}OBr$ requires C, 70·4; H, 9·4%).

Other conditions, *e.g.*, bromination in acetic acid buffered with sodium acetate, resulted in formation of the 6α-bromo-isomer presumably by isomerisation of the first formed 6β-bromo-compound.

4-*Methylcholesta*-4,6-*dien*-3-*one*.—A solution of 6β-bromo-4-methylcholest-4-en-3-one (1·19 g.) in dimethylformamide (100 ml.) was added during 30 min. to a refluxing suspension of calcium carbonate (500 mg.) in dimethylformamide.[12] After a further 30 min. the solution was cooled, filtered, and evaporated under reduced pressure. The residue was taken up in ether washed with water and dried. Evaporation gave an oil which slowly crystallised from methanol to give the unsaturated ketone (0·8 g.) as plates, m. p. 74·5—75°, $[\alpha]_D$ +59·7°, $\lambda_{max.}$ (in EtOH) 292 mμ (ε, 23,390), R_F (in benzene–chloroform, 1 : 1) 0·52. (Found: C, 84·5; H, 11·0. $C_{28}H_{44}O$ requires C, 84·8; H, 11·2%).

4α-*Methylcholest*-5-*en*-3-*one*.—Lithium (90 mg.) was added to a solution of 4-methylcholesta-4,6-dien-3-one (495 mg.) in a mixture of ether (15 ml.) and dry ammonia (25 ml.). After 30 min., ammonia and ether were evaporated off and the residue was treated at −60° with a mixture of water, acetic acid, and carbon tetrachloride (30 ml.). The product was isolated with ether and chromatographed on silica gel. Elution with benzene–light petroleum (1 : 1) gave 4α-methylcholest-5-en-3-one (41 mg.). Crystallisation from methanol gave crystals (18 mg.), m. p. 119—122°, $\nu_{max.}$ 1715 cm.$^{-1}$ (in CCl_4), no selective u.v., absorption R_F (in benzene–chloroform, 1 : 1) 0·48. The mother-liquors were treated with ethanolic sodium hydroxide (1%) at 50° for 5 min.; after appropriate dilution the solution had $\lambda_{max.}$ (in EtOH) 251 mμ (ε *ca.* 10,000); *cf.* 4-methylcholest-4-en-3-one has $\lambda_{max.}$ (in EtOH) 251 mμ (ε, 16,000).[5]

4α-*Methylcholest*-5-*en*-3β-*ol*.—(*a*) 4α-methylcholest-5-en-3-yl benzoate (3·37 g.) was heated under reflux with ethanolic potassium hydroxide (7%, 200 ml.) for 3 hr. After distillation of most of the ethanol the product was isolated with ether. Crystallisation from acetone gave small needles (2·27 g.), m. p. 166—167°, $[\alpha]_D$ −23°. Julia and Lavaux [4] give m. p. 162—163°, $[\alpha]_D$ −16°. A further quantity of the alcohol (240 mg.), m. p. 162—164°, was obtained from the mother-liquor. The acetate, prepared with pyridine–acetic anhydride, had m. p. 114—116°.

(*b*) To a solution of lithium aluminium hydride (20 mg.) in ether (10 ml.) was added 4α-methylcholest-5-en-3-one (18 mg.) in ether (10 ml.). It was heated under reflux for 30 min. The excess of reagent was then destroyed with aqueous hydrochloric acid. Isolation with ether gave 4α-methylcholesterol, characterised as its acetate (m. p. 114—116° after crystallisation from methanol; m. p. undepressed when mixed with an authentic sample).

4α-*Methylcholest*-5-*en*-3β-*yl Methanesulphonate*.—To a solution of 4α-methylcholest-5-en-3β-ol (1·0 g.) in pyridine (2·0 ml.) was added methanesulphonyl chloride (2·0 ml.). After 16 hr. at 0° a few drops of water were added followed, after a further 15 min., by more water. The product was isolated with ether; crystallisation from light petroleum–ether gave the *methanesulphonate* (0·76 g.), m. p. 126—128° (decomp.) (Found: C, 73·05; H, 10·5. $C_{29}H_{50}O_3S$ requires C, 72·8; H, 10·5%).

Solvolysis of 4α-*Methylcholest*-5-*en*-3β-*yl Methanesulphonate*.—The methanesulphonate (0·814 g.) in acetone–water (4 : 1, 20 ml.) containing potassium acetate (1 g.) was heated under reflux for 16 hr. Most of the acetone was distilled off, the product was isolated with ether as an oil (0·685 g.) which was chromatographed on alumina (activity I; 50 g.) giving the following materials: (i) eluted with light petroleum–benzene (7 : 3) and (6 : 4), a mixture of acetates (64 mg., 8·5%) of 4α-methylcholesterol (59%), and 3α,5-cyclo-4α-methyl-5α-cholestan-6β-ol (41%) by hydrolysis and measurement of the rotation of the resulting alcohol mixture; (ii) eluted with light petroleum–benzene (1 : 1), 3α,5-cyclo-4α-methyl-5α-cholestan-6β-ol (467

[12] Bowers, Ibanez, Denot, and Becerra, *J. Amer. Chem. Soc.*, 1960, **82**, 4001.

mg., 82%), which crystallised from methanol as needles (200 mg.), m. p. 102—104°, $[\alpha]_D$ +34°, R_F (in benzene–chloroform, 1 : 1) 0·58 (Found: C, 84·3; H, 12·2. $C_{28}H_{48}O$ requires C, 83·9; H, 12·1%); (iii) eluted with benzene–ether (2 : 3), 4α-methylcholesterol (27 mg., 5%) characterised as acetate.

Isomerisation of 4α-*Methyl*-3α,5-*cyclo*-5α-*cholestan*-6β-*ol*.—The cycloalcohol (17·7 mg.) was heated under reflux in aqueous acetone (5%, 4 ml.) containing toluene-*p*-sulphonic aid (*ca.* 1%) for 30 min. After evaporation the product was isolated with ether. Crystallisation from acetone gave needles (7 mg.), m. p. (unchanged on mixing with an authentic sample of 4α-methylcholesterol) 164—166°.

4α-*Methyl*-3α,5-*cyclo*-5α-*cholestan*-6-*one*.—A solution of 4α-methyl-3α,5-cyclocholestan-6β-ol (100 mg.) in dry pyridine (2 ml.) was added to chromium trioxide–pyridine complex, obtained from chromium trioxide (200 mg.) and pyridine (2 ml.). After 18 hr. at 20° water was added and the product was isolated with ether as an oil (68 mg.). Chromatography on alumina (activity I; 6 g.) followed by crystallisation of the fractions eluted with light petroleum–benzene from methanol gave the *ketone* as needles (33 mg.), m. p. 71—72°, $[\alpha]_D$ +20° (Found: C, 84·9; H, 11·8. $C_{28}H_{46}O$ requires, C, 84·3; H, 11·6%).

The ketone was recovered unchanged after treatment with ethanolic potassium hydroxide (1%) at 20° for 16 hr.

4β-*Methylcholesteryl Methanesulphonate*.—4β-Methylcholesterol (2·06 g.) was treated with methanesulphonyl chloride (1·3 ml.) and pyridine (2·5 ml.) in the usual way. Crystallisation from light petroleum gave the *ester* (2·31 g.), m. p. 105—106° (Found: C, 72·2; H, 10·5. $C_{29}H_{50}O_3S$ requires C, 72·8; H, 10·5%).

4β-*Methylcholesteryl Toluene*-p-*sulphonate*.—(*a*) 4β-Methylcholesterol (300 mg.) in pyridine (3 ml.) was treated with toluene-*p*-sulphonyl chloride (310 mg.) at 20° for 15 hr. After addition of ice–water the product was isolated with ether. Crystallisation from light petroleum gave the ester (200 mg.), m. p. 97—98°.

(*b*) 3β-Toluene-*p*-sulphonyloxy-4β-methylcholestan-5α-ol (200 mg.) [4] in pyridine (5 ml.) at 0° was treated with thionyl chloride (1 ml.) during 20 min. The product isolated with ether in the usual way was recrystallised without heating from ether–methanol and had m. p. 95—97° (100 mg.) undepressed on mixing with a sample prepared under (*a*).

Solvolysis of 4β-*Methylcholesteryl Methanesulphonate*.—The ester (10·57 g.) in aqueous acetone (160 ml. of acetone and 40 ml. of water) containing potassium acetate (10·5 g.) was heated under reflux for 16 hr. After distillation of most of the acetone the product was isolated with ether as an oil which was chromatographed on silica gel. Elution with light petroleum gave 4-methylcholesta-3,5-diene (6·76 g., 78%) which was recrystallised from acetone [yield 6·52 g.; m. p. 74—76°, $[\alpha]_D$ −100°, $\lambda_{max.}$ (cyclohexane) 232sh (ε 15,900), 239 (ε 18,200), 247 mμ (ε, 11,200)]. It was homogeneous to gas-liquid chromatography and to thin-layer chromatography on silica gel–silver nitrate (Found: C, 87·8; H, 12·2. Calc. for $C_{28}H_{56}$: C, 87·9; H, 12·1%. Julia and Lavaux [4] give m. p. 71—72°, $[\alpha]_D$ −97°. Further elution of the column with ether gave oxygenated products which were rechromatographed, elution with light petroleum–benzene mixtures giving the following fractions: (i) mixture of acetates (0·015 g.); (ii) 3β-1′-*hydroxyethyl*-A-*norcholest*-5-*ene* (0·606 g., 7%), m. p. 113·5—114° (from methanol), $[\alpha]_D$ −35°, R_F (in benzene) 0·32 (Found: C, 84·2; H, 11·9. $C_{28}H_{48}O$ requires C, 83·9; H, 12·1%); (iii) impure samples of A-nor-alcohol contaminated with 4β-methylcholesterol and other impurities (0·079 g.); (iv) 4β-methylcholesterol (0·236 g., 3%) m. p. 139—142° (from methanol) undepressed on admixture with an authentic specimen, R_F (in benzene) 0·12.

Solvolysis of 4β-*Methylcholesteryl Toluene*-p-*sulphonate*.—The ester (1·43 g.) was solvolysed in buffered aqueous acetone as for the methanesulphonate. Chromatography of the product on alumina gave 4-methylcholesta-3,4-diene (77%) followed by oily fractions shown to contain the A-nor-alcohol (XV) and 4β-methylcholesterol by thin-layer chromatography. Rechromatography of a portion gave crystalline A-nor-alcohol.

Hydrogenation of 4-*Methylcholesta*-3,5-*diene*.—A solution of 4-methylcholesta-3,5-diene (150 mg.) in acetic acid (50 ml.) was hydrogenated over pre-reduced Adams platinum catalyst (2·1 mol. of hydrogen were absorbed). After filtration, the acetic acid was evaporated and the residue crystallised from acetone–methanol giving 4β-*methyl*-5α-*cholestane* (87 mg.) as needles, m. p. 78—79°, $[\alpha]_D$ +28° (Found: C, 86·6; H, 12·8. $C_{28}H_{50}$ requires C, 87·0; H, 13·0%).

Thioketal of 4-*Methylcholest*-4-*en*-3-*one*.—To a solution of 4-methylcholest-4-ene-3-one [13]

[13] Kirk and Petrow, *J.*, 1962, 1091.

(5·2 g.) in acetic acid (40 ml.) was added, at 20°, ethanedithiol (5 ml.), followed by boron trifluoride etherate (10 ml.). After 15 min. the precipitate was filtered off and crystallised from acetone, giving the *thioketal* as long needles (5·1 g.), m. p. 138·5—140°, $[\alpha]_D$ +107° (Found: S, 13·6. $C_{30}H_{50}S_2$ requires S, 13·5%).

4-Methylcholest-4-ene.—Thioketal (5·0 g.) was dissolved in anhydrous ethylamine (250 ml.) and lithium (0·5 g.) was added in small pieces. The mixture was shaken at intervals and when a blue colour persisted (1 hr.) ammonium chloride was added to decompose excess of lithium. After being poured into water the product was isolated with ether as an oil (3·0 g.). Chromatography on alumina (activity I) and elution with light petroleum followed by crystallisation from acetone gave the *olefin* (2·1 g.) as needles, m. p. 56—58°, $[\alpha]_D$ +90° (Found: C, 87·8; H, 12·8. $C_{28}H_{48}$ requires C, 87·4; H, 12·6%).

Hydrogenation of 4-Methylcholest-4-ene.—The olefin (100 mg.) in acetic acid (50 ml.) was hydrogenated over Adams platinum catalyst (1·0 mol. of hydrogen absorbed). After filtration and evaporation, the residue was crystallised from acetone, giving 4β-methyl-5α-cholestane, m. p. 76—78° undepressed on admixture with a sample prepared as above. The infrared spectra of the two samples (in CS_2) were identical.

3-Acetyl-A-norcholest-3-ene.—(*a*) 3β-1′-Hydroxyethyl-A-norcholest-5-ene (55 mg., from solvolysis of 4β-methylcholesteryl methanesulphonate) in pyridine (1 ml.) was oxidised with chromium trioxide (200 mg.) in pyridine (3 ml.) at 20°. After 16 hr. water was added and the product isolated with ether. Chromatography over silica gel and elution with light petroleum–benzene (4 : 6) gave 3β-acetyl-A-norcholest-5-ene (13 mg.), m. p. 73·5—75° (from methanol), $\nu_{max.}$ (in CCl_4) 1715 cm.$^{-1}$, no selective ultraviolet absorption.

The above unconjugated ketone (4 mg.) was warmed with ethanolic potassium hydroxide (1·6%, 1 ml.) for 2 hr. After evaporation, the product was isolated with ether. Chromatography over silica-gel and elution with light petroleum–benzene (1 : 1) gave 3-acetyl-A-norcholest-3-ene (2·3 mg.), m. p. 97—98·5° undepressed on mixture with an authentic sample (see below), $\lambda_{max.}$ (in EtOH) 257·5 mμ (ε, 13,700).

(*b*) Ozonised oxygen was bubbled through a solution of 4-methylcholest-4-ene (1·7 g.) in methylene chloride containing pyridine (2 drops). After 3 hr. the solvent was evaporated and the oily residue was warmed with ethanolic potassium hydroxide (5%, 150 ml.) for 2 hr. Evaporation of most of the ethanol was followed by addition of water and isolation of the product with ether. Chromatography on silica-gel and elution with light petroleum–benzene (1 : 1, 300 ml.) followed by crystallisation from methanol gave *3-acetyl-A-norcholest-3-ene* (600 mg.) as needles, m. p. 97—99°, $[\alpha]_D$ +87°, $\nu_{max.}$ (in CCl_4) 1684, 1658 (C=O), 1616 cm.$^{-1}$ (conj. C=C), [Meyer and Wolfe [14] give $\lambda_{max.}$ 256 mμ (ε, 13,000) and a doublet in the carbonyl region at 1672 and 1653 cm.$^{-1}$ for an analogous bicyclic ketone], $\nu_{max.}$ (KBr disc) 1667, 1613, 1242, and 1183 cm.$^{-1}$ ($CH_3{\cdot}CO{\cdot}\overset{|}{C}{=}\overset{|}{C}-$), R_F (in benzene) 0·47 (Found: C, 84·4; H, 11·8. $C_{28}H_{46}O$ requires C, 84·35; H, 11·65%).

(*c*) 3β-Methanesulphonyloxy-4α-methylcholestane-4β,5α-diol (517 mg.) in t-butyl alcohol (30 ml.) containing sodium (300 mg.) was heated under reflux for 2 hr. Isolation in the usual way was followed by chromatography on alumina. Elution with light petroleum–benzene (8 : 2 to 1 : 1) followed by crystallisation from ether–methanol gave 3-acetyl-A-norcholest-3-ene identical with the material prepared above (mixed m. p., etc.).

3β-Methanesulphonyloxy-4α-methylcholestane-4β,5α-diol.—4α-Methylcholestane-3β,4β,5α-triol [4] (590 mg.) in pyridine (3 ml.) was treated with methanesulphonyl chloride (0·15 ml.) at 0° for 24 hr. The product, isolated with ether, was recrystallised from acetone giving the *methanesulphonate* (532 mg.), m. p. 138—140° (Found: C, 68·1; H, 9·55. $C_{29}H_{52}O_5S$ requires C, 67·95; H, 10·2%).

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[14] Meyer and Wolfe, *J. Org. Chem.*, 1962, **27**, 3263.