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ACID-CATALYSED DEHYDRATION OF 3-HYDROXYSTEROIDS—III

THE PREPARATION OF 3α- AND 3β-METHYLCHOLESTEROL AND SOME REACTIONS OF THESE COMPOUNDS

M. S. PATEL and W. J. PEAL*
Department of Chemistry, Makerere University College, Kampala, Uganda

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Abstract—The variation in yield of elimination and substitution products obtained when 3α-methylcholesterol (I) was treated for 2 hr. at 80° in various solvents showed a similar solvent dependency to that found for cholesterol; at 26° substitution products were formed dominantly in all solvents. However, 3β-methylcholesterol (II) reacting with 2M HCl in either di-isopropyl ether or ethanol at 26° gives almost entirely 3-methylcholesta-3,5-diene (VI). The reactions at 26° are considered to occur through unimolecular processes in which it is suggested that the differing products from the two epimers arise from the tendency of the 3α-methylcholesterol carbonium ion to react with a nucleophile and of the 3β-methylcholesteryl ion to react by proton expulsion. Possible reaction mechanisms for the dominant acid-catalysed dehydration of 3α-methylcholesterol (I) in some solvents (e.g. ethanol) at higher temperatures are discussed.

THE preceding paper[1] described a study of the reactions of cholesterol with hydrogen chloride in various solvents. It was tentatively concluded that the elimination reaction which proceeds dominantly in these steroidal alcohols occurs through a solvent stabilized protonated steroid, by either a unimolecular or a bimolecular process. It was shown that the products of unimolecular substitution also occur and that these in some solvents are predominant. The tertiary alcohols, 3α- and 3β-methylcholesterol (I and II), offered the possibility of studying similar reactions in which unimolecular processes would be expected to be of greater significance.

The epimeric 3-methylcholesterols were prepared by Grignard reaction between methylmagnesium iodide and cholest-5-en-3-one.[2] Chromatography of the product yielded 3α-methylcholesterol (I) and 3β-methylcholesterol (II). The configurations of these two compounds were established by (a) hydrogenation to the known 3α-methylcholestanol (III) and 3β-methylcholestanol (IV), (b) order of elution during alumina chromatography and (c) the greater readiness to undergo dehydration shown by 3β-methylcholesterol (II) (to be discussed later).

When cholestanone is treated with Grignard reagents the two epimerides are produced in nearly equal amounts. However, the Grignard reaction of cholest-5-en-3-one with methylmagnesium iodide gives epimers in an approximately 5:1 ratio

* To whom correspondence should be addressed.

[1] Part II, M. S. Patel and W. J. Peal, preceding paper.
[2] J. Strating, *Rec. Trav. Chim.* **71**, 822 (1952).

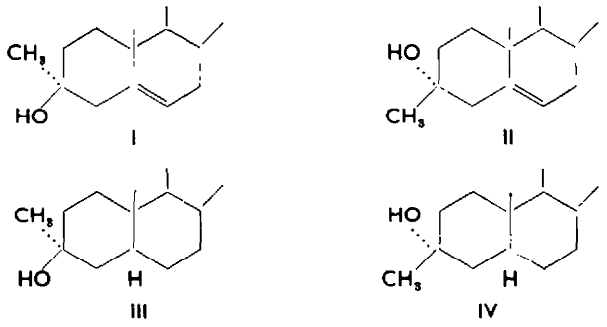


TABLE 1. PHYSICAL CONSTANTS OF 3-METHYLCHOLESTEROLS AND 3-METHYLCHOLESTANOLS

Steroid		m.p.	$[\alpha]_D$	Literature m.p.	Literature $[\alpha]_D$	Reference
3α-Methylcholesterol	(I)	167–168	−30	167·5–168	−28	2
3β-Methylcholesterol	(II)	120–121	−29	—	—	
3α-Methylcholestanol	(III)	150–152	+25	147–149	+34	3
				151–152	+30	4
3β-Methylcholestanol	(IV)	127–129	−26	127	+27	4

(Table 2). It thus appears that the C_5—C_6 double bond exerts a controlling influence on the stereochemical course of this reaction.

Reaction of 3α-methylcholesterol (I) with phosphorus pentachloride gives a mixture of 3β-chloro-3α-methylcholest-5-ene (V) and 3-methylcholesta-3,5-diene (VI). However reaction with thionyl chloride readily yields the chloride (V). Attempts to

TABLE 2. YIELDS OF EPIMERIC 3α[a]- AND 3β[a]-TERTIARY STEROIDAL ALCOHOLS FROM REACTION OF CHOLEST-5-EN-3-ONE AND CHOLESTANONE WITH MeMgI AND PhMgBr

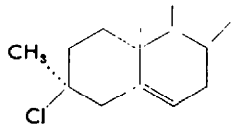
Steroidal Alcohol	3α[a] (%)	3β[a] (%)	Reference
3-Phenylcholestanol	43	40	5
3-Methylcholestanol	53	40	3
3-Methylcholesterol (3-Methylcholest-5-en-3-ol)	62	11	This work

[a] α and β refer to configuration of substituent methyl and phenyl groups.

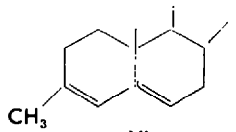
obtain 3β-chloro-3α-methylcholestane[3] by hydrogenation of the 3-chloride (V) were unsuccessful; the major product obtained under various hydrogenation conditions being a hydrocarbon. The chloride (V) is assumed to possess the 3β-chloro configuration since (1) the C_5—C_6 double bond in cholesterol is known[6] to exert a configuration retaining influence at C_3, (2) Barton[3] has shown that, in the chlorination of both 3α- and 3β-methylcholestanols (III and IV), only 3β-chloro-3α-methylcholestane is formed, thus demonstrating the presence of stereochemical control in favour of the

[3] D. H. R. Barton, A. da S. Campos-Neves and R. C. Cookson, *J. Chem. Soc.* 3500 (1956).
[4] C. S. Barnes and A. Palmer, *Austral. J. Chem.* **9**, 105 (1956).
[5] J. A. Zderic, M. E. C. Rivera and D. C. Limon, *J. Amer. Chem. Soc.* **82**, 6373 (1960).
[6] C. W. Shoppee, *J. Chem. Soc.* 1147 (1946).

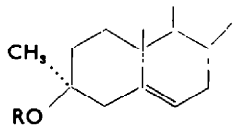
formation of the 3β-chloro compound, and (3) 3β-methoxy-3α-methylcholest-5-ene (VII, R = CH_3) is formed in the reaction between 2M methanolic hydrogen chloride and 3α-methylcholesterol (I), the formation of which, by analogy with cholesterol,[1] proceeds by an S_N1 process. Thus direct substitution by the methoxyl group gives the substituent in the 3β-configuration. The configuration of 3β-methoxy-3α-methylcholest-5-ene (VII, R = CH_3) was established by preparation of an identical specimen from the potassium derivative of 3α-methylcholesterol (I) and methyl iodide.



V

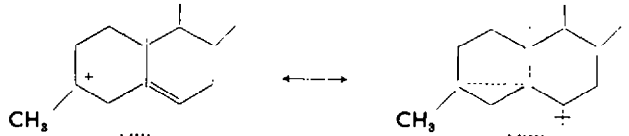


VI



VII

Attempts to isolate the *p*-toluenesulphonate or the methanesulphonate of 3α-methylcholesterol (I) were unsuccessful. However when 3α-methylcholesterol (I) is left for 2 hours at 0° in pyridine containing methanesulphonyl chloride, methanol added, the product evaporated to dryness under reduced pressure and chromatographed, a small yield of 3β-methoxy-3α-methylcholest-5-ene (VII, R = CH_3) is obtained together with much 3-methylcholesta-3,5-diene (VI). No 3,5-cyclosteroid is formed under these conditions which on the other hand give 6β-methoxy-3α, 5-cyclo-5α-cholestane with cholesterol.[7] This is presumably because of the expected negligible contribution of the canonical form VIIIb in the mesomeric ion (VIIIa ↔ VIIIb).



VIIIa ⟷ VIIIb

When the pyridine solution of 3α-methylcholesterol (I) and methanesulphonyl chloride is left for longer than 4 hours and then treated with methyl alcohol no substitution products are obtained showing the instability of 3α-methylcholesteryl methanesulphonate in pyridine,

Both 3α- and 3β-methylcholesterol (I and II) yield 3-methylcholesta-3,5-diene (VI) on refluxing with ethanolic or methanolic hydrochloric acid. The purest specimens of the 3,5-diene (VI) are derived from 3β-methylcholesterol (II). The 3,5-diene is also readily obtained pure by the action of ethanolic hydrochloric acid on 3ξ-methylcholest-4-en-3ξ-ol[8,9] at room temperature.

In the preceding paper[1] it was shown that the products formed during reaction between hydrogen chloride and cholesterol vary depending on the nature of the solvent used. Three classes of solvent were distinguished dependent on the yields and products of the reaction:

(A) Those in which reaction occurs slowly giving dominantly substitution products.
(B) Those in which reaction occurs more rapidly giving dominantly elimination products.

[7] M. S. Patel and W. J. Peal, *J. Chem. Soc.* 1544 (1963).
[8] O. C. Musgrave, *J. Chem. Soc.* 3121 (1951).
[9] N. F. Kucherova and M. I. Ushakov, *Zh. Obsch. Khim.* **23**,3 15 (1953); *Chem. Abstr.* **48**, 2744 (1954).

(C) Those in which reaction occurs rapidly with the dominant production, under conditions of low acid concentration, of substitution products.

When 3α-methylcholesterol (I) is treated with hydrogen chloride at elevated temperature mixtures of products analogous to the mixtures obtained with cholesterol, are obtained and these show a similar solvent dependence (Table 3). The reactions are more rapid than in the cholesterol case, indeed 2 hours at 80° with 2M hydrogen chloride causes complete reaction in methanol. Once again it was found that hydrogen chloride in 2-chloroethanol is very reactive towards a 3β-hydroxy-Δ^5-steroid. A 20% yield of the ether, 3β-(2-chloroethoxy)-3α-methylcholest-5-ene (VII, R = $ClCH_2$ CH_2) is obtained when 3α-methylcholesterol (I) is left overnight in 2-chloroethanol containing 0·013 M hydrogen chloride.

Treatment of 3α-methylcholesterol (I) with hydrogen chloride in various solvents at room temperature yields dominantly substitution products; however solvents in group B also give significant quantities of 3-methylcholesta-3,5-diene (VI). The reaction in solvents of group A demonstrates the ready formation of substitution products from the ion VIIIa. The low yield of 3-methylcholesta-3,5-diene (VI) in these cases is good evidence that very little, if any, elimination occurs through a straightforward unimolecular process. On the other hand when 3β-methylcholesterol (II) is treated at 26° or 80° with 2M hydrogen chloride in di-isopropyl ether (group A solvent) almost pure 3-methylcholesta-3,5-diene (VI) is obtained. Clearly carbonium ion VIIIa is not formed during this elimination. Since 3β-methylcholesterol (II) possesses the anti-periplanar configuration at C_3—C_4 it is evident that either a bimolecular elimination process occurs with no concomitant unimolecular substitution or that the configuration of the carbonium ion from 3β-methylcholesterol (II) is such that elimination is the only route for its reaction. Since, in general, bimolecular reactions only occur at tertiary centres when there are strong nucleophiles[10] present we consider the unimolecular process more probable. It has been found that yields from 3β-methylcholesterol (II) are greater than those from 3α-methylcholesterol (I) under identical acid-catalysed conditions implying that the 3β-methylcholesteryl cation is formed more readily than the 3α-methylcholesteryl ion. The more rapid reaction of the compound with the 3α-hydroxy configuration is in agreement with the findings of the previous paper[1] where it is noted, however, that cholesteryl (3β-) derivatives undergo unimolecular solvolytic reactions more rapidly than epicholesteryl (3α-) derivatives.[11] It seems probable, therefore, that the more rapid acid-catalysed reaction of 3β-methylcholesterol (II) compared with 3α-methylcholesterol (I) arises from greater solvent stabilization of protonated 3α-methylcholesterol rather than from constitutional factors.

The nature of the elimination reaction between 3α-methylcholesterol (I) and hydrogen chloride in various solvents (Table 3) is uncertain. Because the elimination is from a tertiary compound it is most probably unimolecular but, as in the case of cholesterol,[1] the free carbonium ion VIIIa is clearly not involved. Three mechanisms, similar to those postulated for cholesterol,[1] appear to be possible namely: (a) rearrangement of the C_5—C_6 double bond to C_4—C_5 followed by allylic elimination, (b) a modified unimolecular process and (c) flip of ring A of the sterol giving a molecule with the more readily dehydrated 3α-hydroxy configuration.

[10] P. B. de La Mare and C. A. Vernon, *J. Chem. Soc.* 41 (1956).

[11] C. W. Shoppee and D. F. Williams, *J. Chem. Soc.* 686 (1955).

TABLE 3. YIELDS OF PRODUCTS FORMED IN THE REACTION BETWEEN HYDROGEN CHLORIDE AND 3α-METHYLCHOLESTEROL IN VARIOUS SOLVENTS

		48 hr at 26°						2 hr at 80°					
			Elimination product	Substitution products		Uncharacterized product[b]			Elimination product	Substitution products		Uncharacterized product[b]	
Solvent	Acid concentration	Total[a] reaction %	3-Methylcholesta-3,5-diene (VI) %	Chloride (V) %	Ether (VII) %	A %	B %	Total[a] reaction %	3-Methylcholesta-3,5-diene (VI) %	Chloride (V) %	Ether (VII) %	A %	B %
1. Di-isopropyl ether	2 M	12·8	0·7	8·5	—	3·6	—	54·1	9·7	44·4	—	—	—
2. Dioxan	2 M	58·5	3·5	37·8	—	4·7	12·5	79·2	5·2	74·0	—	—	—
3. Methanol	2 M	55·1	9·4	16·3	24·7	3·8	0·9	100	91·0	—	—	4·0	5·0
4. Ethanol	2 M	25·9	4·2	8·9	11·3	1·5	0	96·7	60·9	23·4	3·1	7·1	2·2

[a] Total reaction—Overall recoveries were between 90–100% in all experiments. "Total reaction" denotes the % yield of recovered products in the total recovered material. Uncharacterized products were assumed to have the same empirical formulae as 3α-methylcholesterol.

[b] Uncharacterized product A represents substances in the 3-methylcholesta-3,5-diene – 3β-chloro-3α-methylcholest-5-ene fraction whilst product B was a yellow gum and was normally eluted with benzene.

The much more rapid elimination of water from 3α-methylcholesterol (I) than from cholesterol would not be found if rearrangement (mechanism a) is the rate controlling process since these two compounds would be expected to undergo rearrangement of the C_5—C_6 double bond to C_4—C_5 at very similar rates. However 3α-methylcholesterol (I) dehydration would be expected to be more rapid than that of cholesterol if rupture of the C_3—OH bond is involved in the rate controlling stage. Thus the rearrangement mechanism (a) is unlikely as a significant contributor to the acid-catalysed dehydration of 3α-methylcholesterol (I) or cholesterol.[1]

Evidence that the 3α-methylcholesteryl carbonium ion (VIIIa) undergoes reaction with a nucleophile and not proton explusion has been found in the dominant substitution reactions between 3α-methylcholesterol and hydrogen chloride in various solvents at 26°. A unimolecular process to account for the extensive elimination which occurs at higher temperatures, must therefore involve an intermediate differing from the cation VIIIa. Such a modified unimolecular process (mechanism b), considered also for cholesterol[1] is that of Manassen and Klein[12] in which the carbonium ion is shielded by solvent molecules. The β-proton is then expelled from the shielded ion together with a solvent molecule.

Mechanism c for the acid-catalysed dehydration of 3α-methylcholesterol (I) takes account of the facile dehydration of 3β-methylcholesterol (II). It is suggested that elimination from 3α-methylcholesterol (I) occurs after flip of ring A of the sterol or protonated sterol. Ring A then has a conformation at C_3—C_4 similar to 3β-methylcholesterol (II) from which elimination of water can readily take place.

Mechanism (b) and (c), which seem to us the more probable, require solvent stabilization of the protonated sterol. The variation in yield of substitution and elimination products during reaction between 3α-methylcholesterol (I) and hydrogen chloride in various solvents thus appears to depend on the extent to which the various solvents stabilize the protonated sterol preventing formation of ion VIIIa and causing elimination by one of the alternative pathways discussed.

EXPERIMENTAL

General experimental details are given in the previous paper.

3α- and 3β-Methylcholesterol (I and II)

A solution of cholest-5-en-3-one (6·3 g) in dry ether (120 ml) was added dropwise to a cold (0°) well stirred solution of methylmagnesium iodide prepared from methyl iodide (7·5 g) and Mg turnings (1·3 g) in dry ether (60 ml) under an atmosphere of N_2. After warming to room temp overnight the solution was poured into an NH_4Cl–ice mixture and the ether layer separated. The aqueous layer was extracted twice with ether, the ether solutions were combined and dried ($MgSO_4$) after washing with water. The gummy residue (6·37 g) obtained on concentrating the ether solution was chromatographed from a light petroleum–benzene (3:1) solution on alumina (190 g). Initially solid product (1·42 g) was eluted with this solvent followed, on elution with benzene, by 3α-methylcholesterol (I) (4·04 g, 62%) m.p. 167–168°; $[\alpha]_D$ −30° (*c*, 1·25). Strating[2] quotes m.p. 167·5–168°; $[\alpha]_D$ −28° for this compound. Only gums (0·53 g) were obtained on further elution of the column with benzene–chloroform. The initial fraction was re-chromatographed from light petroleum on alumina (120 g) and yielded gummy product (0·37 g) followed by 3β-methylcholesterol (II) (0·73 g, 11%) which after recrystallization from ethyl acetate–methanol had m.p. 119–120°; $[\alpha]_D$ −29° (*c*, 0·94). (Found: C, 83·7; H, 12·0. $C_{28}H_{48}O$ requires: C, 83·9; H, 12·0%). Further elution of this column gave cholest-4-en-3-one (0·19 g) from its IR spectrum and m.p., mixed m.p. with authentic material 76–80°; further uncharacterized gums (0·33 g) were eluted with benzene and benzene–chloroform mixtures.

[12] J. Manassen and F. S. Klein, *J. Chem. Soc.* 4203 (1960).

3α-Methylcholesteryl acetate

3α-Methylcholesterol was left with excess acetyl chloride in dry pyridine overnight. Isolation, chromatography and recrystallization from methanol–ethyl acetate gave 3α-methylcholesteryl acetate, m.p. 134–135°; $[\alpha]_D$ −23° (*c*, 0·9). Strating[2] quotes m.p. 133·5–134°; $[\alpha]_D$ −18° for this compound.

The acetate (16 mg), m.p. and mixed m.p. 133–135° was also prepared by treating the sterol (52 mg) with excess acetic anhydride in pyridine for 2 weeks. Strating[2] did not obtain any acetate by this method.

3β-Methylcholesteryl acetate

3β-Methylcholesterol on refluxing with excess acetic anhydride and fused sodium acetate gave, after isolation and alumina chromatography, 3β-methylcholesteryl acetate, m.p. 86·5–87°; $[\alpha]_D$ +3° (*c*, 0·88). (Found: C, 81·1; H, 11·2. $C_{30}H_{50}O_2$ requires: C, 81·4; H, 11·4%).

3α-Methylcholestanol (III)

3α-Methylcholesterol was hydrogenated in ethyl acetate in the presence of 10% Pd-C for 6 hr. The product obtained after filtration and concentration of the solvent and 2 recrystallizations from methanol, had m.p. 148–150°; $[\alpha]_D$ +25° (*c*, 1·14). Barnes[4] quotes m.p. 151–153°; $[\alpha]_D$ +30° and Barton[5] *et al.* found m.p. 147–149°; $[\alpha]_D$ +34° for this compound.

3β-Methylcholestanol (IV)

3β-Methylcholesterol was hydrogenated in ethyl acetate in the presence of 10% Pd-C. The product, obtained as in the previous experiment, had m.p. 126–127°; $[\alpha]_D$ +26° (*c*, 1·14). For this substance Barnes[4] found m.p. 127°; $[\alpha]_D$ +27° and Barton[5] *et al.* 126–127°; $[\alpha]_D$ +28°.

3β-Chloro-3α-methylcholest-5-ene (V)

(a) *With thionyl chloride.* 3α-Methylcholesterol (180 mg) was dissolved in purified thionyl chloride (2 ml) and left for 30 min. The reactants were poured into water, extracted with ether and washed successively with $NaHCO_3$ and water. The ether solution was concentrated after drying ($MgSO_4$) and the yellow gummy residue recrystallized several times from methanol–ethyl acetate to give the chloride m.p. 122–123°; $[\alpha]_D$ −29° (*c*, 1·3). (Found: C, 80·2; H, 11·3; Cl, 8·7. $C_{28}H_{47}Cl$ requires: C, 80·2; H, 11·3; Cl, 8·5%).

(b) *With phosphorus pentachloride.* The chloride (700 mg) was added to 3α-methylcholesterol (420 mg) dissolved in chloroform (20 ml). The product was isolated in the usual way and after 2 recrystallizations from methanol–ethyl acetate had m.p. 106–108°; ϵ_{228}, 2,000 (EtOH). (Found: C, 80·9; H, 11·4; Cl, 8·0. $C_{28}H_{47}Cl$ requires: C, 80·2; H, 11·3; Cl, 8·5%). The analysis and UV spectrum indicated approximately 8% of 3-methylcholesta-3,5-diene in the product.

(c) *Hydrogen chloride in dioxan.* 3α-Methylcholesterol (100 mg) was left in 2M HCl–dioxan for 8 days. The product was worked up in the usual way and on chromatography on alumina gave an initial fraction (85 mg), m.p. and mixed m.p. with 3β-chloro-3α-methylcholest-5-ene 122–123°, (no peak at 240 mμ) after crystallization from methanol–ethyl acetate. Elution of the column with benzene yielded uncharacterized gum (10 mg).

Attempted preparations of 3β-chloro-3α-methylcholestane

(1) 3β-Chloro-3α-methylcholest-5-ene (35 mg) was hydrogenated in ethyl acetate (50 ml) containing 10% Pd-C (70 mg) for 2 hr. After filtration the solvent was evaporated off and the residue chromatographed on alumina. Light petroleum eluted a fraction (11·5 mg), m.p. 94–96°; $[\alpha]_D$ −35° (*c*, 0·5), with a negative Beilstein test. Further elution with this solvent gave a gummy fraction (4·5 mg) followed by a chlorine containing product (6 mg) which from its IR spectrum and m.p. 124–132° (after 2 recrystallizations from methanol–ethyl acetate) appears to be a mixture of 3β-chloro-3α-methylcholestane and 3β-chloro-3α-methylcholest-5-ene.

(2) 3β-Chloro-3α-methylcholest-5-ene (41 mg) was hydrogenated for 30 min over PtO_2 (70 mg) in ethyl acetate (50 ml) containing perchloric acid (4 drops). Isolation, chromatography and recrystallization as in (1) gave a hydrocarbon (9 mg), m.p. 95–110° and unchanged 3β-chloro-3α-methylcholest-5-ene (27 mg), m.p. 122–127° after recrystallization, presumably contaminated with 3β-chloro-3α-methylcholestane. Barton *et al.*[3] record m.p. 154–156°; $[\alpha]_D$ +33° for 3β-chloro-3α-methylcholestane.

3β-Methoxy-3α-methylcholest-5-ene (VII, R = CH_3)

(a) 3α-Methylcholesterol (200 mg) in dry benzene (10 ml) was added to K (100 mg) emulsified under benzene. Methyl iodide (1 ml) was added and, after the reactants had been heated under reflux for 1·5 hr, methanol (1 ml) was added. The products were isolated in the usual way, chromatographed on alumina, to yield from benzene–light petroleum (1:5) 3β-methoxy-3α-methylcholest-5-ene (100 mg) double m.p. 98–99°, 107–108°; $[\alpha]_D$ −32° (*c*, 0·5). (Found: C, 83·9; H, 12·2; OCH_3, 6·9. $C_{29}H_{50}O$ requires: C, 84·0; H, 12·2; OCH_3, 7·5%).

(b) 3β-Chloro-3α-methylcholest-5-ene (48 mg) was heated under reflux in methanol (40 ml) containing Na (0·1 g). The product was isolated in the usual way and chromatographed on alumina. Light petroleum eluted gummy product (17 mg) with a positive Beilstein test and further elution gave 3β-methoxy-3α-methylcholest-5-ene (22 mg), double m.p. and mixed m.p. 97–99°, 104–106°; $[\alpha]_D$ −30° (*c*, 1·18).

Attempt to obtain 6β-methoxy-3α,5-cyclo-3β-methyl-5α-cholestane

3α-Methylcholesterol (2 g) was dissolved in dry pyridine (26 ml) and methanesulphonyl chloride (0·6 ml) was added and allowed to stand 1 hr. Methanol (120 ml) was added and after the solution had refluxed 1 hr $NaHCO_3$ was added. The gummy residue obtained on evaporation under red. press. was dissolved in ether, washed successively with dil. HCl aq, $NaHCO_3$ aq and water, dried ($MgSO_4$) and the ether distilled off. Chromatography on alumina of a light petroleum–benzene (3:1) solution gave on elution with this solvent gummy product (0·382 g). 3α-Methylcholesterol (1·42 g) was eluted with benzene–chloroform (4:1).

The experiment was repeated thrice with similar quantities, the gummy products (1·08 g) combined and chromatographed on a silica-gel column from a light petroleum solution. Elution with this solvent gave initially a gum (0·32 g), ϵ_{239}, 11,800; Cl, 1·68% followed by 3β-methoxy-3α-methylcholest-5-ene (0·370 g), double m.p. 95–97°, 106–108°; $[\alpha]_D$ −31° (*c*, 0·88). There was no depression of the double m.ps on admixture with an authentic specimen. The IR spectra of fractions from this chromatogram were inspected but there was no evidence in any of a peak at ca. 1020 cm^{-1}.

In one such experiment an ether was obtained m.p. 123–125°; $[\alpha]_D$ −14°. (Found: C, 84·1; H, 12·2; OCH_3, 9·4. $C_{29}H_{50}O$ requires C, 84·0; H, 12·2; OCH_3, 7·5%). The IR spectrum of this compound and of 3β-methoxy-3α-methylcholest-5-ene were identical and no depression of the m.p. of the authentic ether was obtained on admixture with what is presumed to be a second form of the ether.

3β-Ethoxy-3α-methylcholest-5-ene (VII, R = C_2H_5)

This ethyl ether was prepared by method (a) used for the methyl ether. After recrystallization from methanol–ethyl acetate it had m.p. 124–125°; $[\alpha]_D$ −22° (*c*, 0·73). (Found: C, 84·1; H, 12·1. $C_{30}H_{52}O$ requires: C, 84·1; H, 12·2%).

3-Methylcholesta-3,5-diene (VI)

(a) 3β-Methylcholesterol (200 mg) was heated under reflux for 1 hr in ethanol (20 ml) containing conc. HCl aq (2 ml). On standing crystals (100 mg) m.p. 77–80° separated which after two further recrystallizations had m.p. 80–81°; $[\alpha]_D$ −129° (*c*, 1·15), ϵ_{240}, 24,500. Musgrave[8] quotes m.p. 79–79·5°; $[\alpha]_D$ −129° and ϵ_{239}, 22,700.

(b) When 3α-methylcholesterol was treated in a similar manner the product had m.p. 75–78°, no depression when mixed with the product from (a), and ϵ_{239}, 21,400 (EtOH).

(c) When 3ξ-methylcholest-4-en-3ξ-ol prepared according to Musgrave[8], m.p. 114–116°, was treated with 2M ethanolic HCl for 1 min and the products worked up immediately in the usual way 3-methylcholesta-3,5-diene m.p. 80–81°; $[\alpha]_D$ −124° (*c*, 0·8), ϵ_{240}, 23,800 was obtained. Two other similar experiments gave the 3,5-diene with ϵ_{240}, 24,600 and ϵ_{240}, 23,800.

3-Methylcholesta-3,5-diene is subject to the same type of instability as cholesta-3,5-diene. Thus a specimen with ϵ_{240}, 23,600 and $[\alpha]_D$ 124° had after preservation for 6 days ϵ_{240}, 14,000 and $[\alpha]_D$ −102°. The extinction coefficient at 240 mμ of 3-methylcholesta-3,5-diene is taken as 24,000 (cyclohexane) in this work.

Reaction of 3α-methylcholesterol (I) *with* 2M HCl *in various solvents reacting at* 80° *for* 2 *hr*

The preparation of solutions of HCl in the purified solvents is described in Paper II[1] and the experiments were set up in a manner similar to that previously used.

1. *Di-isopropyl ether.* 3α-Methylcholesterol (100 mg) on heating in 2M HCl–di-isopropyl ether (20 ml) for 2 hr gave, after the usual isolation and chromatography, product (53 mg) and unchanged starting material (44 mg). Elution of the alumina chromatogram gave a fraction (53 mg), ϵ_{240}, 4,500; Cl, 7·4%, indicating 3-methylcholesta-3,5-diene (9 mg, 9·7%), and 3β-chloro-3α-methylcholest-5-ene (46 mg, 44·4%). This fraction on recrystallization from methanol–ethyl acetate had m.p. 115–118°. Further elution of the column with chloroform gave only 3α-methylcholesterol (44 mg).

2. *Dioxan.* Heating 3α-methylcholesterol (100 mg) in 2M HCl–dioxan (20 ml) for 2 hr followed by the usual isolation procedure gave product (80 mg) and unchanged starting material (20 mg). Chromatographic analysis of the product gave an initial crystalline fraction (39 mg), ϵ_{240}, 3,200, m.p. 118–120° after recrystallization, followed by a second crystalline fraction (41 mg), m.p. 122–124° after recrystallization. No depression of m.p. was observed on admixture of either of these fractions with 3β-chloro-3α-methylcholest-5-ene. 3-Methylcholesta-3,5-diene (5 mg, 5·2%) and 3β-chloro-3α-methylcholest-5-ene (75 mg, 74%) were indicated. Elution of the column with chloroform gave 3α-methylcholesterol (20 mg).

3. *Methanol.* When 3α-methylcholesterol (100 mg) was heated for 2 hr at 80° in 2M HCl–methanol (20 ml) and the product (95 mg) isolated and chromatographed in the usual way no unchanged 3α-methylcholesterol was detected. Chromatography yielded slightly impure 3-methylcholesta-3,5-diene (90 mg), ϵ_{240}, 22,900, m.p. 79–81° after recrystallization from methanol–ethyl acetate indicating 3,5-diene (86 mg, 91%). Elution of the column with chloroform gave uncharacterized solid (5 mg, 5%) shown from its IR spectrum to be different from 3α-methylcholesterol.

4. *Ethanol.* 3α-Methylcholesterol (200 mg) on heating for 2 hr at 80° in 2M ethanolic HCl (20 ml) gave product (175 mg) and unchanged starting material (6 mg). Chromatographic analysis of the product yielded, on elution with light petroleum, a fraction (165 mg), ϵ_{240}, 15,500; Cl, 2·33%, showing 3-methylcholesta-3,5-diene (106 mg, 60·9%) and 3β-chloro-3α-methylcholest-5-ene (45 mg, 23·4%), m.p. 87–103° after one recrystallization from methanol–ethyl acetate. Elution of the column with benzene gave 3β-ethoxy-3α-methylcholest-5-ene (6 mg, 3·1%) identified from its IR spectrum, m.p. and mixed m.p. 123–125°, followed by uncharacterized gum (4 mg, 2·2%). Elution with chloroform gave unchanged 3α-methylcholesterol (6 mg).

Reactions of 3α-*methylcholesterol* (I) *with* 2M HCl *in various solvents at* 26°

Hydrogen chloride solutions in the various purified solvents were prepared as before.

(1) *Di-isopropyl ether.* 3α-Methylcholesterol (103 mg) was left in 2M HCl–di-isopropyl ether (40 ml) for 48 hr. After the usual isolation procedure, followed by chromatography on alumina, product (12 mg), ϵ_{240}, 1,100; Cl, 5·74% and unchanged starting material (79 mg) were obtained. After recrystallization the product had m.p. and mixed m.p. with 3β-chloro-3α-methylcholest-5-ene, 119–120°, indicating chloride (8 mg, 8·5%) and 3-methylcholesta-3,5-diene (0·6 mg, 0·7%).

(2) *Dioxan.* 3α-Methylcholesterol (100 mg) was kept at 26° in 2M HCl–dioxan (20 ml) for 48 hr. The crude product obtained after the usual isolation procedure was chromatographed from a light petroleum solution on alumina to give product (58 mg) and unchanged 3α-methylcholesterol (40 mg). Light petroleum eluted a fraction (46 mg), ϵ_{240}, 1,700; Cl, 7·05%, showing 3β-chloro-3α-methylcholest-5-ene (38 mg, 37·8%), 3-methylcholesta-3,5-diene (3·3 mg, 3·5%). After one recrystallization from methanol–ethyl acetate this product had m.p. and mixed m.p. with 3β-chloro-3α-methylcholest-5-ene, 122–124°. Elution with benzene gave an uncharacterized yellow gum (12 mg, 12·5%) followed by unchanged 3α-methylcholesterol.

(3) *Methanol.* 3α-Methylcholesterol (100 mg) was kept in 2M methanolic HCl (50 ml) for 48 hr. The usual isolation procedure followed by alumina chromatography yielded product (53 mg) and unchanged 3α-methylcholesterol (42 mg). Development of the alumina chromatogram with light petroleum gave an initial fraction (28 mg), ϵ_{240}, 7,200; Cl, 4·85%, showing 3-methylcholesta-3,5-diene (8·5 mg, 9·4%) and 3β-chloro-3α-methylcholest-5-ene (16 mg, 16·3%). After recrystallization of this fraction from methanol–ethyl acetate it had m.p. 110–115° and showed no depression of m.p. with the authentic chloride. Elution of the column with light petroleum–benzene (3:1) gave 3β-methoxy-3α-methylcholest-5-ene (24 mg, 24·7%), double m.p. and mixed double m.p. 98–99°, 107–109°; $[\alpha]_D$ −28° (*c*, 0·5). Further elution gave, with benzene, uncharacterized yellow gum (1 mg) and with benzene–chloroform 3α-methylcholesterol (42 mg).

(4) *Ethanol.* When 3α-methylcholesterol (150 mg) was left in 2M ethanolic HCl (50 ml) for 48 hr product (40 mg) and unchanged 3α-methylcholesterol (110 mg) were isolated by the usual

procedure. Elution of the alumina chromatogram with light petroleum gave an initial fraction (22 mg), ϵ_{240}, 6,500; Cl, 5·33%, showing 3-methylcholesta-3,5-diene (6 mg, 4·2%) and 3β-chloro-3α-methylcholest-5-ene (14 mg, 8·9%). After recrystallization from ethyl acetate–methanol this fraction had m.p. and mixed m.p. with authentic 3β-chloro-3α-methylcholest-5-ene, 115–120°. Elution of the column with light petroleum–benzene (3:1) gave 3β-ethoxy-3α-methylcholest-5-ene (18 mg, 11·3%), m.p. and mixed m.p. with the authentic ether 123–125°. Finally elution with chloroform yielded unchanged 3α-methylcholesterol.

Reaction of 3α-*methylcholesterol* (I) *with* 0·013M HCl *in* 2-*chloroethanol at* 26°

Preparation of 3β-(2-*chloroethoxy*)-3α-*methylcholest-5-ene* (VII, R = $ClCH_2CH_2$). 3α-Methylcholesterol (257 mg) was left in 0·013M HCl–2-chloroethanol (25 ml) for 24 hr at 26°. The products were isolated in the usual manner. Elution of the alumina chromatogram with light petroleum gave 3β-(2-chloroethoxy)-3α-methylcholest-5-ene (69 mg) which after recrystallization (methanol–ethyl acetate) had m.p. 102–103°; $[\alpha]_D$ −12° (*c*, 0·5). (Found: C, 77·9; H, 10·9. $C_{30}H_{51}OCl$ requires: C, 77·8; H, 11·1%). Traces of 3-methylcholesta-3,5-diene (ϵ_{240}, 700) were found in this fraction prior to recrystallization. Unchanged 3α-methylcholesterol (180 mg) was obtained on elution with chloroform.

Reaction of 3β-*methylcholesterol* (II) *with ethanolic* 2M HCl *at* 26°

3β-Methylcholesterol (100 mg) was left for 6 hr at 26° in 2M ethanolic HCl (20 ml). The product (80 mg) obtained as usual gave, after chromatography, 3-methylcholesta-3,5-diene (21 mg, 26%), ϵ_{240}, 20,000; negative Beilstein test, and unchanged 3β-methylcholesterol (59 mg).

Reaction of 3β-*methylcholesterol* (II) *with* 2M HCl *in di-isopropyl ether at* 26°

3β-Methylcholesterol (235 mg), dissolved in 2M HCl–di-isopropyl ether (20 ml) was kept at 26° for 6 hr. The product, 3-methylcholesta-3,5-diene (15 mg, 7·9%), ϵ_{240}, 21,300; negative Beilstein test; m.p. 75–78° (recrystallized from ethyl acetate–methanol) was isolated and separated from unchanged 3β-methylcholesterol (175 mg) by chromatography.

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