592. *Steric and Other Influences on Reactions of* 6- *and* 7-*Methylcholesterol Derivatives.*

By R. K. CALLOW and G. A. THOMPSON.

The possibility of converting 6-methylcholest-5-en-3β-ol (6-methylcholesterol) into 6-methylcholesta-5,7-dien-3β-ol (6-methylprovitamin-D_3) has been investigated. Halogenation at position 7, followed by dehydrohalogenation, did not give the desired 5,7-diene, but only the 4,6-diene. 6-Methylcholest-5-ene-3β,7α-diol 3-benzoate, obtained, together with the 3β,5α-diol, by way of the 7-chloro-compound, could not be converted into the 5,7-diene. Attempts were made to prepare the 7-oxo-compound in the hope of obtaining the 7β-ol, but the ketone could not be prepared either by direct oxidation of 6-methylcholesterol or by oxidation of the 7α-ol, although analogous reactions are known in the unmethylated series.

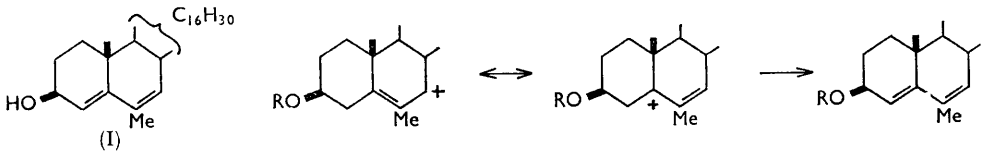
A similar investigation in the 7-methyl series has been made. 7β-Methylcholest-5-en-3β-ol (7β-methylcholesterol) was prepared by reduction of 7-methylenecholest-5-en-3β-ol. Halogenation and dehydrohalogenation yielded only the 7-methylene compound. The configuration of the products formed by interaction of a 7-oxo-group with methylmagnesium iodide is considered. Hydrogenolysis and other evidence supports the constitution 7α-methylcholest-5-ene-3β,7β-diol for the product from 7-oxocholest-5-en-3β-yl acetate, but 7-oxocholestan-3β-yl acetate yields 7β-methylcholestane-3β,7α-diol.

THE 6- and 7-methyl derivatives of calciferol were of interest to us primarily as compounds that might be prepared with a ^{14}C-label for metabolic investigations. Moreover, in the 6-methyl derivatives there might be enhancement of biological activity, as there is in certain steroid hormones. All the analogues of ergocalciferol or cholecalciferol so far described [1] have lower antirachitic activity than the original vitamins. However, the required provitamins, the $\Delta^{5,7}$-compounds, were found not to be accessible by known reactions from either 6- or 7-methyl-substituted compounds. This appears to be a result

[1] Windaus and Gunzel, *Annalen*, 1939, **538**, 120; Grab, *Z. physiol. Chem.*, 1936, **243**, 63; Linsert, *ibid.*, 1936, **241**, 125; Haslewood, *Biochem. J.*, 1939, **33**, 454; Wunderlich, *Z. physiol. Chem.*, 1936, **241**, 116; Windaus and Naggatz, *Annalen*, 1939, **542**, 204; Dimroth and Paland, *Ber.*, 1939, **72**, 187; Bernstein and Sax, *J. Org. Chem.*, 1951, **16**, 685; Strating, *Rec. Trav. chim.*, 1952, **71**, 822; Cooley, Ellis, and Petrow, *J.*, 1955, 2998.

of stereochemical and inductive effects favouring the stability of the *trans*-4,6-diene or the 5,7(exocyclic)-diene rather than the *cis*-5,7-diene.

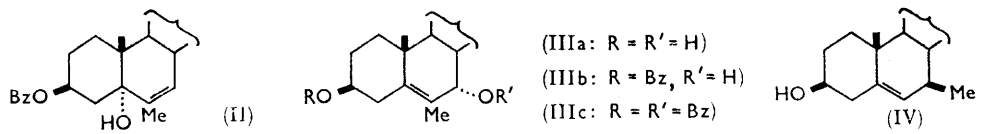
Chlorination of the benzoate of 6-methylcholest-5-en-3β-ol and treatment of the product with a mixture of dimethylaniline and collidine led to the formation of a *trans*-diene alone,



(I)

and, after chromatography, a good yield of the benzoate of 6-methylcholesta-4,6-dien-3β-ol (I) was obtained. The structure of this compound follows from the ultraviolet, infrared, and nuclear magnetic resonance (n.m.r.) spectra of the alcohol. Similar attempts, using bromination with *N*-bromosuccinimide above 40° and dehydrobromination with collidine, yielded the theoretical quantity of collidine hydrobromide, but no crystalline steroid derivative could be isolated. The crude halogenation product may be assumed, by analogy with what is observed with the corresponding methylpregnenolone,[2] to consist almost entirely of the unstable, axial 7α-halogeno-compound. The failure to dehydrohalogenate this to a 5,7-diene by methods that succeed with esters of 7α-bromocholesterol may be attributed to the readier formation of a carbonium ion from the methyl-substituted compound, followed by deprotonation to the relatively stable *trans*-diene, as shown. Such a carbonium ion would be stabilised, relative to that derived from a bromocholesterol, by the inductive or hyperconjugative effect of the methyl group; rearrangement would therefore be more favoured, relative to simple *trans*-elimination to give a 7,8-double bond. The same argument applies to the acid-catalysed dehydration of the 7α-hydroxy-compound, prepared as follows.

3β-Benzoyloxy-6-methylcholest-5-ene was treated with chlorine and the product passed at once down a column of alumina. After gummy material, 3β-benzoyloxy-6-methylcholest-6-en-5α-ol (II) was eluted, followed by 3β-benzoyloxy-6-methylcholest-5-en-7α-ol (IIIb). Both (II) and (IIIb) gave an intense blue colour with a chloroform solution of antimony trichloride. Only the latter could be converted into a dibenzoate (IIIc). The structure of the sterol (IIIa), obtained by hydrolysis, was established by n.m.r. spectroscopy, a signal appearing at 1·81 p.p.m. (CH_3·C:), but none being found that corresponded to an olefinic proton. This spectrum and the molecular rotation (M_D = −260°, 112° more lævorotatory than 6-methylcholesterol) are parallel to those recorded for 3β,7α-dihydroxy-6,16α-dimethylpregn-5-en-20-one (M_D = −170°, 122° more lævorotatory than the parent compound without the 7α-hydroxyl group [2]); the molecular rotations of (II) and its pregnene analogue show similar differences from the molecular rotations of 6-methylcholesterol and its pregnene analogue, respectively. *trans*-Elimination of water from (IIIa) and (IIIb) was attempted, using 0·5—1·0N-ethanolic hydrogen chloride, by analogy with the preparation of cholesta-5,7-dien-3β-ol from cholest-5-ene-



(II) (IIIa: R = R′ = H) (IIIb: R = Bz, R′ = H) (IIIc: R = R′ = Bz) (IV)

3β,7-diol.[3] Reaction occurred at room temperature, but the ultraviolet spectrum of the solution indicated exclusive formation of a *trans*-diene. The only crystalline product

[2] Iriarte, Shoolery, and Djerassi, *J. Org. Chem.*, 1962, **27**, 1139.
[3] Starka, *Pharmazie*, 1962, **17**, 126.

isolated was 6-methylcholesta-4,6-dien-3β-ol (I) or its benzoate. Much gum was eluted; this absorbed strongly in the region 240—250 mμ, suggesting the presence of compounds similar to the B-isomers of ergosterol.[4]

Prolonged treatment of the dibenzoate (IIIc) with boiling dimethylaniline in an inert atmosphere yielded gummy products having no selective absorption at 280 mμ; this is in accordance with the observation of Wintersteiner and Ruigh,[5] and other authors,[6,7] that the preparation of 3β-benzoyloxycholesta-5,7-diene by such means is much less effective with 3β,7α-dibenzoyloxycholest-5-ene than with the corresponding 7β-benzoate. Oxidation of (IIIb) to the corresponding 7-oxo-compound was therefore attempted, with the intention of reducing this to the 7β(equatorial)-alcohol by means of borohydride. Chromic acid oxidation of 3β-acetoxy-7α-hydroxy-6,16α-dimethylpregn-5-en-20-one yields a number of products, none of which is the 7-oxo-compound.[2] Oxidation of (IIIa) and (IIIb) was therefore attempted with manganese dioxide in light petroleum and benzene, and with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone in benzene; infrared and ultraviolet spectra indicated production of but little αβ-unsaturated ketone. This failure to prepare the latter is, in our opinion, a result of the considerable hindrance, as shown by models, of access to the 7-hydrogen atom, although Fieser [8] suggested that steric factors do not control the course of oxidation of allylic alcohols. Attempts to oxidise the benzoate or acetate of 6-methylcholest-5-en-3β-ol directly to the 7-oxo-compound with chromic acid or air yielded only gummy products with no selective absorption in the ultraviolet.

A 7ξ-methylcholestene-3β,7ξ-diol was prepared by Bann, Heilbron, and Spring,[9] and also by Weinhouse and Kharasch,[10] but neither group assigned a configuration to the 7-substituents. Dehydration with ethanolic hydrogen chloride, or with pyridine solutions of thionyl chloride, phosphorus oxychloride, or benzenesulphonyl chloride yielded only the 7-methylene derivative.[9,10] Benzoylation yielded only a monobenzoate under normal conditions or the 7-methylene compound at elevated temperatures. Conversion into 7-methylcholesta-5,7-dien-3β-ol by the method of Haslewood [6] or by the action of dilute acid [3] is, therefore, precluded. Hydrogenation of 7ξ-methylcholestene-3β,7ξ-diol with a platinum catalyst in glacial acetic acid yielded 7β-methylcholestan-3β-ol when the reduction was carried to completion; when interrupted after addition of only 1 mol. of hydrogen, a poor yield of 7β-methylcholest-5-en-3β-ol was obtained, the main product being 7β-methylcholestan-3β-ol. This last compound was also obtained by reduction of the 7-methylene compound under the same conditions. However, in ethyl acetate with a platinum catalyst 7-methylenecholest-5-en-3β-ol gave, in good yield, a product to which we assign the constitution 7β-methylcholest-5-en-3β-ol (IV).

This compound was treated with *N*-bromosuccinimide at temperatures between 40 and 70°, and refluxed with collidine, dimethylaniline, or dimethylacetamide containing finely divided calcium carbonate, conditions which are known to be successful in the preparation of 5,7-dienes from cholesteryl esters. The ultraviolet spectrum of the crude product showed absorption only in the region 230—245 mμ; 3β-benzoyloxy-7-methylenecholest-5-ene was the only product isolated. Whereas bromination at the 7-position should be encouraged by the tertiary nature of this carbon atom, subsequent *trans*-elimination to the 5,7-diene is probably curtailed by formation of a carbonium ion, again stabilised by the inductive effect of the methyl group. Of the possible products from this, the 7-methylene compound is almost certainly thermodynamically more stable, since the double bonds are free to adopt a coplanar position, in contrast to that of the *cis*-diene. Analogous reactions are known involving the A-ring; cholest-4-en-3α-ol is converted by

[4] Windaus, Dithmar, and Suckfüll, *Annalen*, 1931, **488**, 91.
[5] Wintersteiner and Ruigh, *J. Amer. Chem. Soc.*, 1942, **64**, 2453.
[6] Haslewood, *J.*, 1938, 224.
[7] Du Pont de Nemours, U.S.P. 2,209,934/1940.
[8] Fieser and Fieser, "Steroids," Reinhold, New York, 1959, p. 225.
[9] Bann, Heilbron, and Spring, *J.*, 1936, 1274.
[10] Weinhouse and Kharasch, *J. Org. Chem.*, 1936—1937, **1**, 490.

ethanolic hydrogen chloride into cholesta-3,5-diene alone,[11] and the product (reported[12] to be a 1 : 1 mixture of equatorial and axial alcohols) from methylmagnesium iodide and cholest-4-en-3-one yields only 3-methylcholesta-3,5-diene or 3-methylenecholest-4-ene on dehydration.[12] We could not confirm reports[13] of the isolation of 3-methylcholesta-2,4-diene from the product of this Grignard reaction, and the molecular rotation data published for this reputed *cis*-diene[13] are inconsistent with the expected value. We confirmed that the product is a mixture of *trans*-dienes, as suggested by Sondheimer and Mechoulam.[14]

The structure of (IV) was confirmed by n.m.r. spectroscopy; the 6-proton gave a signal at 5·10 p.p.m.. 7α-Methylcholesterol was prepared, for purposes of comparison, from methylmagnesium iodide and 3β-benzoyloxy-7β-bromocholest-5-ene; its spectrum displays a doublet, centred at 5·38 p.p.m. (J ~5 c./sec.). This splitting is evidently caused by coupling between the 7β-proton and the 6-proton.

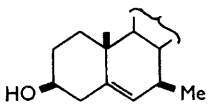
The configuration of the 7ξ-methylcholest-5-ene-3β,7ξ-diol, from the 7-oxo-compound and methylmagnesium iodide, can be assigned with fair certainty in the first instance by analogy with that of 7α-methylpregn-5-ene-3β,7β,20β-triol prepared by a similar method; Robinson *et al.*[15] assigned the 7α(axial)-configuration to the methyl group on account of (a) the likelihood of attack by the Grignard reagent upon the α-face of the steroid molecule, and (b) the conversion of the triol by all methods of dehydration into the 7-methylene compound. Cases are known of apparent attack by Grignard reagents on the β-face of steroid ketones;[16] 3β-benzoyloxy-7β-bromocholest-5-ene appears, however, to be attacked on the α-face. The failure to undergo the elimination to yield a *cis*-diene has little value as structural evidence in view of the discussion above. Additional evidence for the equatorial position of the 7-hydroxy-group in 7-methylcholest-5-ene-3β,7-diol is as follows.

(*a*) Optical rotation data: the M_D value for the compound, −125°, shows a dextrorotatory increment relative to that of cholesterol (−150°), suggesting that the more polarisable group occupies the 7β-position. Comparisons with the corresponding 7-methyl and 7-hydroxy-compounds (as illustrated) are of interest. The M_D value for 7-phenylcholest-5-ene-3β,7-diol, −660°, clearly indicates the 7α-configuration of the phenyl group.[17] Phenylmagnesium bromide is known to react with steroid ketones in much the same way as does methylmagnesium iodide.[16,18]

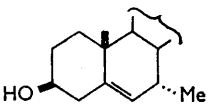
(*b*) Hydrogenolysis experiments; in acetic acid solution, both platinum and palladium–charcoal catalyse the smooth hydrogenolysis of the allylic hydroxyl group of 7-methylcholest-5-ene-3β,7-diol, leaving the methyl group in the 7β-position. Raney nickel, even at 80° and 100 atm. hydrogen pressure, had little action on the compound, almost 90% of which was recovered; the mother-liquor yielded about 6% of 7α-methylcholesterol on chromatography. These results suggest that platinum and palladium attack the α-face of the molecule, hydrogenolysis of the C–O bond occurring with inversion by the S_N2 mechanism; the hydrogenolysis, which, as for cholest-5-ene-3β,7β-diol,[5,19] evidently proceeds faster than saturation of the double bond, presumably removes the steric hindrance which the axial methyl group would present to the catalyst. Nickel, which normally effects hydrogenolysis without inversion,[18,20,21] is unable to do this if the α-face of the molecule is

[11] McKennis and Gaffney, *J. Biol. Chem.*, 1949, **175**, 217; Schoenheimer and Evans, *ibid.*, 1936, **114**, 567.
[12] Musgrave, *J.*, 1951, 3121.
[13] Kucherova and Ushakov, *Zhur. obshchei Khim.*, 1953, **23**, 315.
[14] Sondheimer and Mechoulam, *J. Amer. Chem. Soc.*, 1957, **79**, 5029.
[15] Robinson, Gnoj, Charney, Gilmore, and Oliveto, *J. Amer. Chem. Soc.*, 1959, **81**, 408.
[16] Just and Nagajaran, *Experientia*, 1962, **18**, 402.
[17] Sneen, *J. Amer. Chem. Soc.*, 1958, **80**, 3971; Brewster, *ibid.*, 1959, **81**, 5475.
[18] Zderic, Ribera, and Limon, *J. Amer. Chem. Soc.*, 1960, **82**, 6373.
[19] Henbest and Jones, *J.*, 1948, 1798.
[20] Bonner, Zderic, and Casaletto, *J. Amer. Chem. Soc.*, 1952, **74**, 5086; Bonner and Zderic, *ibid.*, 1956, **78**, 3218.
[21] Mitsui, Senda, and Konno, *Chem. and Ind.*, 1963, 1354.

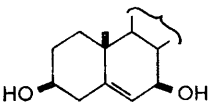
presented to the catalyst; the 7α-methyl group also hinders saturation of the double bond. The formation of a small amount of 7α-methylcholesterol at high temperature and pressure is attributed to attack upon the β-face of the molecule. A number of benzyl-type alcohols and ethers have been submitted both to hydrogenolytic inversion over palladium and to hydrogenolysis with retention of configuration over Raney nickel,[21] the optical purity of the product being 70—90% in each case.



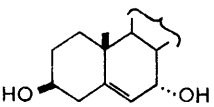
M_D +6°



M_D −329°



M_D +28°



M_D −362°

The isolation of the 7β(equatorial)-alcohol from methylmagnesium iodide and 3β-acetoxycholest-5-en-7-one contrasts with the isolation, from the Grignard reagent and 3β-acetoxycholestan-7-one, of 7β-methylcholestane-3β,7α-diol alone (as 3-benzoate); the structure of this compound follows from the good yield of 3β-benzoyloxy-7-methylcholest-7-ene obtained on treating it with pyridine and phosphorus oxychloride. These reactions are analogous to reduction by metal hydrides. Thus, 60% of the equatorial alcohol and 5% of the axial alcohol can be isolated [22] from 3β-acetoxycholest-5-en-7-one and lithium aluminium hydride, the corresponding yields [23] for reduction by sodium borohydride being 54 and 15%; whilst optical rotation measurements on total product indicate that 3β-acetoxycholestan-7-one is reduced by lithium aluminium hydride to 45% equatorial alcohol and 55% axial alcohol, and by sodium borohydride to 27% equatorial alcohol and 73% axial alcohol.[24] Cholestan-4- and -6-one are reduced by lithium aluminium hydride mainly to axial alcohols, but cholest-5-en-4-one and 3,5-cyclocholestan-6-one yield mainly the equatorial alcohols.[16] It has been suggested [25] that axial groups or atoms β to the carbonyl group exert the most important screening effect in such reactions; it is probable that the attack of 3β-acetoxycholestan-7-one from the β-side is at least partly due to hindrance by the 5α-hydrogen atom.

Experimental

Melting points were determined on a Kofler hot-stage apparatus, and are corrected. Solvents for chromatography were purified and dried; unless stated otherwise, aluminium oxide (Spence type H, activity I—II) was used for column chromatography, and Merck silica gel G (system A) or Merck aluminium oxide G (system B) for thin-layer chromatography, spots being detected with iodine vapour. The phrase " usual isolation " denotes extraction with ether, washing with 2N-hydrochloric acid, saturated sodium hydrogen carbonate solution, and water, and brief drying (Na_2SO_4). Ultraviolet spectra were determined for ethanol solutions in a Unicam S.P. 500 spectrophotometer, and infrared spectra were measured for potassium chloride discs or paraffin oil mulls in a Perkin-Elmer model 21 double-beam instrument with a sodium chloride prism. N.m.r. spectra were kindly determined by Dr. J. E. Page of Glaxo Research Ltd., with a Varian spectrometer (60 Mc.), using solutions in chloroform with tetramethylsilane as internal reference. Optical rotations refer to chloroform solutions.

6-*Methylcholesta*-4,6-*dien*-3β-*ol* (I).—(*a*) 3β-Benzoyloxy-6-methylcholest-5-ene (1·05 g.) in dry carbon tetrachloride (10 ml.) was treated at 0° with a solution of chlorine in carbon tetrachloride (5 ml.; 1N). The flask was immediately connected to a water-pump and shaken gently for 2—3 min.; collidine (3 ml.) was added, and the remaining solvent removed below 20° at the pump. Dimethylaniline (6 ml.) was added, and the solution heated under nitrogen for

[22] Fieser, Fieser, and Chakravarti, *J. Amer. Chem. Soc.*, 1949, **71**, 2226.
[23] Bergmann and Meyers, *Annalen*, 1959, **620**, 46.
[24] Dauben, Blanz, Jiu, and Micheli, *J. Amer. Chem. Soc.*, 1956, **78**, 3752.
[25] Kamernitzky and Akhrem, *Tetrahedron*, 1962, **18**, 705.

30 min. at 130—140°, cooled, and filtered. The usual isolation yielded a pale yellow oil (1·08 g.) with a strong absorption below 250 mμ but none near 280 mμ. This was chromatographed on a column of alumina (27 g.) prepared in light petroleum (b. p. 40—60°): elution with ether–benzene (1 : 99; 4 × 20 ml.) gave 3β-*benzoyloxy*-6-*methylcholesta*-4,6-*diene* (580 mg.), m. p. 120—121°, $[\alpha]_D$ −59° (*c* 2·1), $\lambda_{max.}$ 238 mμ (log ε 4·49) (Found: C, 84·0; H, 9·8. $C_{35}H_{50}O_2$ requires C, 83·6; H, 10·0%). Hydrolysis of this benzoate in cold ethanolic sodium hydroxide for 24 hr., followed by the usual isolation, yielded 6-*methylcholesta*-4,6-*dien*-3β-*ol* (I), m. p. 152—153° (from acetone–methanol), $[\alpha]_D$ −17° (*c* 2·7), $\lambda_{max.}$ 242 mμ (log ε 4·35), $\nu_{max.}$ 3200s, 1620w, 1285s, 1050s, and 855ms cm.$^{-1}$, n.m.r. absorption at 0·7—1·0 (CH_3·C), 1·8 (CH_3·C:), 4·2 (H·C·O·), and 5·5 (·CH:) p.p.m. (Found: C, 84·2; H, 11·0. $C_{28}H_{46}O_2$ requires C, 84·4; H, 11·6%). After 4 days in air at room temperature the same sample gave C, 81·9; H, 11·6%, being then slightly yellow and melting over the range 142—147°. This type of behaviour is reported for cholesta-4,6-dien-3β-ol.[26]

(*b*) 3β-Benzoyloxy-6-methylcholest-5-ene (800 mg.), and in another experiment the corresponding acetate (710 mg.), was treated in light petroleum (10 ml.) with *N*-bromosuccinimide (315 mg.), the flask being directly above a photoflood bulb (Philips Photolita No. 1, 275w), which maintained steady boiling. After 6 min. collidine (0·40 ml.) was added, and the mixture was rapidly cooled and filtered. After evaporation of the filtrate at 0—5° *in vacuo*, the residual yellow gum was treated with more collidine (0·3 ml.) and xylene (6·0 ml.), refluxed under nitrogen for 15 min., cooled, diluted with ether, and filtered to give collidine hydrobromide (305 mg., Calc. 321 mg.). The usual isolation yielded a pale yellow gum from the filtrate, absorbing strongly below 250 mμ, and not responding to attempts at crystallisation or chromatographic purification.

3β-*Benzoyloxy*-6-*methylcholest*-6-*en*-5α- (II) *and* -7α-*ol* (IIIb).—3β-Benzoyloxy-6-methylcholest-5-ene (2·10 g.) in dry carbon tetrachloride (20 ml.) was treated at 0° with a solution of chlorine in the same solvent (10 ml.; 1N). The solution was immediately evaporated down to 5 ml., below 20°, and chromatographed on alumina (60 g.), prepared in benzene. Gummy material (810 mg.) was eluted with ether–benzene (1 : 49; 15 × 50 ml.). Ether–benzene (1 : 9; 3 × 50 ml.) then eluted the 5α-*ol* (II) (170 mg.), double m. p. 146° and 169° (from ethanol), $[\alpha]_D$ +32° (*c* 2·2), $\lambda_{max.}$ 231 mμ (log ε 4·21) (Found: C, 80·9; H, 10·2. $C_{35}H_{52}O_3$ requires C, 80·7; H, 10·0%), and ether–benzene (1 : 4; 6 × 50 ml.) eluted the 7α-*ol* (IIIb) (520 mg.), m. p. 171—172° (from ethanol), $[\alpha]_D$ −34° (*c* 3·0), $\lambda_{max.}$ 231 mμ (log ε 4·22) (Found: C, 80·5; H, 10·0. $C_{35}H_{52}O_3$ requires C, 80·7; H, 10·0%). The ester (IIIb) (100 mg.) was left overnight in dry pyridine (1·2 ml.) and benzoyl chloride (0·7 ml.); the usual isolation yielded 3β,7α-*dibenzoyloxy*-6-*methylcholest*-5-*ene* (IIIc) (67 mg.), m. p. 141° (from acetone), $[\alpha]_D$ −100° (*c* 1·2), $\lambda_{max.}$ 231 mμ (log ε 4·49) (Found: C, 80·3; H, 9·1. $C_{42}H_{56}O_4$ requires C, 80·7; H, 9·0%). Benzoylation under similar conditions was without effect on (II).

6-*Methylcholest*-5-*ene*-3β,7α-*diol* (IIIa).—Hydrolysis of the ester (IIIb) in cold ethanolic sodium hydroxide for 24 hr. and the usual isolation yielded the *diol*, m. p. 159° (from methanol), $[\alpha]_D$ −62° (*c* 1·9), $\nu_{max.}$ 3460s, 1650w, 1060ms, 1010ms cm.$^{-1}$, strong line at 1·81 p.p.m. (CH_3·C:) but none corresponding to an olefinic proton (Found: C, 80·8; H, 11·5. $C_{28}H_{48}O_2$ requires C, 80·7; H, 11·6%).

Treatment of (IIIa) *and* (IIIb) *with Ethanolic Hydrogen Chloride*.—The above diol (600 mg.) in methanol (400 ml.) was treated with methanolic hydrogen chloride (100 ml.; 2·5N) at room temperature. The absorption of the solution at 243 mμ increased rapidly, attaining a maximum after about 1 hr.; it decreased thereafter as the absorption near 305 mμ increased. The usual method of extraction, 1 hr. after mixing, yielded a colourless gum (520 mg.), which was chromatographed on alumina (20 g.). After elution with benzene of gum (330 mg.), 6-methylcholesta-4,6-dien-3β-ol (95 mg.), identical with the sample obtained previously, was eluted in ether–benzene (1 : 19, 2 × 20 ml.). This result was not substantially altered by using N-hydrogen chloride; when (IIIa) was replaced by its benzoate, (IIIb), no absorption near 305 mμ was evident after 2 hr., and a somewhat better yield of the 4,6-diene was obtained.

7β-*Methylcholestan*-3β-*ol*.—(*a*) 7α-Methylcholest-5-ene-3β,7β-diol (415 mg.) was shaken with hydrated platinum oxide (20 mg.) in glacial acetic acid (25 ml.) under hydrogen at room temperature and pressure; after 2 hr. the uptake (47 ml.; 2·1 moles) was complete. The usual isolation yielded the 3β-*ol* (355 mg.), double m. p. 59° and 89° (from methanol), $[\alpha]_D$ +49° (*c* 2·3) (Found: C, 83·5; H, 12·6. $C_{28}H_{50}O_2$ requires C, 83·5; H, 12·6%).

[26] Spring and Swain, *J.*, 1941, 320.

(*b*) Replacement of the platinum oxide by 10% palladium–charcoal (200 mg.) made no substantial change.

(*c*) 7-Methylenecholest-5-en-3β-ol (220 mg.) was shaken with hydrated platinum oxide (15 mg.) in glacial acetic acid (15 ml.) under hydrogen at room temperature and pressure; after 75 min. the uptake (25 ml.; 2·0 moles) was complete. The usual isolation yielded 7β-methylcholestan-3β-ol (168 mg.).

7β-Methylcholest-5-en-3β-ol (IV).—(*a*) 7α-Methylcholest-5-ene-3β,7β-diol (520 mg.) was shaken with hydrated platinum oxide (20 mg.) in glacial acetic acid (30 ml.) under hydrogen at room temperature and pressure; after 25 min. the uptake was 28 ml. (1·0 mole), whereupon the mixture was rapidly filtered and the product isolated as a sticky solid (510 mg.). Thin-layer chromatography (system A, 1 : 5 ethyl acetate–chloroform) showed three compounds to be present, R_F 0·35 (corresponding to starting material), 0·67 (unknown), and 0·71 (corresponding to 7β-methylcholestan-3β-ol). The yield of the unknown compound, later identified as (IV), was about 10%; the other two spots were of similar size.

(*b*) 3β-Benzoyloxy-7-methylenecholest-5-ene (320 mg.), or in another experiment the corresponding weight of the sterol, was shaken with hydrated platinum oxide (15 mg.) in ethyl acetate (10 ml.) under hydrogen at room temperature and pressure; after 2 hr., uptake was complete (16 ml.; 1·1 moles). The usual isolation yielded *3β-benzoyloxy-7β-methylcholest-5-ene* (195 mg.), m. p. 136—137° (from ethanol), $[\alpha]_D$ +11° (*c* 2·0), $\lambda_{max.}$ 231 mμ (log ε 4·22) (Found: C, 83·0; H, 10·3. $C_{35}H_{52}O_2$ requires C, 83·3; H, 10·4%). Cold hydrolysis in ethanolic sodium hydroxide, and the usual isolation, gave the *enol* (IV), m. p. 73—75° (from 95% methanol), $[\alpha]_D$ +1·5° (*c* 3·5), $\nu_{max.}$ 3400s, 1650w, and 1050s cm.$^{-1}$, (Found: C, 84·3; H, 11·7. $C_{28}H_{48}O$ requires C, 83·9; H, 12·1%). The n.m.r. spectrum was more complex than that of cholesterol between 0·67 and 1·60 p.p.m., and showed a line at 5·10 (·CH:) p.p.m.

7α-Methylcholest-5-en-3β-ol.—3β-Benzoyloxy-7β-bromocholest-5-ene (2·5 g.) in dry benzene (25 ml.) was added to the Grignard reagent from methyl iodide (2·5 g.) and magnesium (550 mg.) in ether (60 ml.). The mixture was refluxed for 6 hr., cooled, poured on to ice and ammonium chloride, and worked up in the usual way. The colourless gum (2·8 g.) was left overnight with pyridine (10 ml.) and benzoyl chloride (7 ml.), and the steroid benzoate, isolated as a yellow gum (4·5 g.) in the usual way, was chromatographed on alumina (100 g.), prepared in light petroleum. Elution with benzene (3 × 70 ml.) gave *3β-benzoyloxy-7α-methylcholest-5-ene* (950 mg.), m. p. 168—169° (from acetone), $[\alpha]_D$ −50° (*c* 1·9) (Found: C, 83·6; H, 10·3. $C_{35}H_{52}O_2$ requires C, 83·3; H, 10·4%). Elution with ether–benzene (1 : 19, 3 × 70 ml.). gave 3β-benzoyloxycholest-5-ene (310 mg.), identical in all respects with an authentic sample. Hydrolysis of 3β-benzoyloxy-7α-methylcholest-5-ene in cold alcoholic sodium hydroxide yielded the *sterol*, m. p. 128—129° (from light petroleum), $[\alpha]_D$ −82° (*c* 2·2), $\nu_{max.}$ 3310s, 1660w, 1060s, and 840ms cm.$^{-1}$ (Found: C, 83·9; H, 11·8. $C_{28}H_{48}O$ requires C, 83·9; H, 12·1%). The sterol gave a strong yellow colour with tetranitromethane, and developed a deep red colour in the Liebermann–Burchard test; its n.m.r. spectrum showed more complex absorption than cholesterol between 0·67 and 1·60 p.p.m., and contained a doublet centred at 5·38 p.p.m. (J ~5 c./sec.).

Bromination and Dehydrobromination of 3β-Benzoyloxy-7β-methylcholest-5-ene.—The ester (1·35 g.) was treated in light petroleum (25 ml.; b. p. 60—80°) with *N*-bromosuccinimide (550 mg.), the flask being directly over a Photolita No. 1 bulb, which maintained steady boiling. After 10 min. collidine (1·6 ml.) was added, and the mixture cooled, filtered, and evaporated below 10° *in vacuo*. Collidine (1·0 ml.) and xylene (2·0 ml.) were added to the yellow gum and the mixture was refluxed under nitrogen for 15 min., cooled, diluted with ether, filtered, and worked up in the usual way to give a yellow gum (1·55 g.) absorbing only below 250 mμ. Chromatography on alumina (45 g.) yielded, on elution with ether–benzene (1 : 9, 4 × 30 ml.), 3β-benzoyloxy-7-methylenecholest-5-ene (860 mg.), identical with an authentic sample. Use of dimethylaniline, or dimethylacetamide containing finely divided calcium carbonate, did not alter the result significantly; the use of light petroleum (b. p. 40—60°) gave a somewhat lower yield.

Dehydration of 3-Methylcholest-4-en-3-ol.—The procedure of Kucherova and Ushakov was followed:[13] cholest-4-en-3-one (11·4 g.) in ether (75 ml.) was added over 45 min. to the Grignard reagent, stirred at −8°, from methyl iodide (18·2 g.) and magnesium (2·8 g.) in ether (100 ml.). The solution was stirred at 0° for 1 hr., and decomposed by the addition of ammonium chloride (20 g.) in water (180 ml.) without external cooling. The ether layer was dried (Na_2SO_4)

and evaporated *in vacuo*; recrystallisation of the solid yellow residue (13·5 g.) from ether–ethanol (1 : 3) yielded a product (8·1 g.), m. p. 61—67°, $[\alpha]_D$ −15° (*c* 1·9), $\lambda_{max.}$ 239 mμ (log ε 4·34) [lit.,[13] (8·7 g.), m. p. 68—69°, $[\alpha]_D$ −12·5° (*c* 1·4), $\lambda_{max.}$ 260—280 mμ]. Thin-layer chromatography (system A, benzene) showed the product to consist of two components in roughly equal proportions, R_F 0·51 and 0·45 (corresponding to authentic samples of 3-methylcholesta-3,5-diene and 3-methylenecholest-4-ene).

Hydrogenolysis of 7-Methylcholest-5-ene-3β,7-diol by Raney Nickel.—The diol (950 mg.) and freshly prepared " W2 " Raney nickel [27] (300 mg.) were stirred for 24 hr. in ethanol (40 ml.) at 80° and 100 atm. hydrogen pressure. After filtration, partial evaporation, and fractional crystallisation of the solution, starting material (790 mg.) was isolated. The mother-liquors were evaporated to dryness and left overnight with pyridine (1 ml.) and benzoyl chloride (0·5 ml.). After the usual isolation, the gummy product (300 mg.) was chromatographed on alumina (10 g.). Elution with benzene yielded 3β-benzoyloxy-7α-methylcholest-5-ene (55 mg.), identical in all respects with a sample prepared as described above. Experiments performed in an identical manner, but using " W6 " Raney nickel [27] at 20° and 1 atm. hydrogen pressure, or B.D.H. stabilised Raney nickel under the conditions described above, led to complete recovery of unchanged starting material.

3β-Benzoyloxy-7β-methylcholestan-7α-ol.—3β-Acetoxycholestan-7-one (12 g.) in dry benzene (50 ml.) was added over 10 min. to the Grignard solution from methyl iodide (38 g.) and magnesium (8 g.) in ether (200 ml.). After being refluxed for 3 hr., the solution was treated with ice and ammonium chloride, and worked up in the usual way; the resultant gum (12·5 g.) was left overnight with pyridine (30 ml.) and benzoyl chloride (17·5 ml.). The yellow gum (26 g.) obtained by the usual isolation crystallised readily on contact with methanol; the crude solid (10·7 g.) was chromatographed on alumina (300 g.). After elution of gummy material, ether–light petroleum (2 : 1; 6 × 200 ml.) eluted *3β-benzoyloxy-7β-methylcholestan-7α-ol* (7·4 g.), m. p. 149—150° (from ethanol), $[\alpha]_D$ +18° (*c* 3·3), $\lambda_{max.}$ 231 mμ (log ε 4·21) (Found: C, 80·3; H, 10·4. $C_{35}H_{54}O_3$ requires C, 80·4; H, 10·4%). Thin-layer chromatography gave a single spot, R_F 0·69 (system A, 1 : 5 ether–chloroform) and 0·53 (system B, 1 : 3 chloroform–light petroleum).

3β-Benzoyloxy-7-methylcholest-7-ene.—3β-Benzoyloxy-7β-methylcholestan-7α-ol (7·3 g.), pyridine (73 ml.), and phosphorus oxychloride (32 ml.) were refluxed for 90 min., cooled, treated with ether and ice, and worked up in the usual way; the resultant gum crystallised on contact with acetone to give the *ester* (4·3 g.), m. p. 127—128° (from methanol–acetone), $[\alpha]_D$ −18° (*c* 2·1), $\lambda_{max.}$ 231 mμ (log ε, 4·21), (Found: C, 83·5; H, 10·2. $C_{35}H_{52}O_2$ requires C, 83·3; H, 10·4%). Thin-layer chromatography gave a single spot, R_F 0·79 (system A, 1 : 5 ether–chloroform) and 0·73 (system B, 1 : 5 chloroform–light petroleum).

7-Methylcholest-7-en-3β-ol.—Hydrolysis of the above benzoate in cold ethanolic sodium hydroxide yielded the sterol. This could be recrystallised only from methanol (alone, or containing a little acetone or benzene) as fibrous crystals persistently retaining solvent. After being dried *in vacuo* over P_2O_5 for 48 hr. the *sterol* had m. p. 53—57°, $[\alpha]_D$ −18° (*c* 1·9), $\lambda_{max.}$ 203 mμ (log ε 3·81), $\nu_{max.}$ 3340s, 1640vw, and 1035s cm.$^{-1}$ (Found: C, 83·9; H, 12·0. $C_{28}H_{48}O$ requires C, 83·9; H, 12·1%). Thin-layer chromatography gave a single spot, R_F 0·48 (system A, 1 : 5 ether–chloroform) and 0·43 (system B, 1 : 2 chloroform–light petroleum). The compound rapidly gave an intense coloration in the Liebermann–Burchard, Tortelli–Jaffé, and Fieser tests; on treatment with pyridine and benzoyl chloride it yielded the parent benzoate almost quantitatively.

The authors are indebted to Mr. R. Conant for technical assistance.

National Institute for Medical Research,
The Ridgeway, Mill Hill, London N.W.7. [*Received, November 14th,* 1963.]

[27] *Org. Synth.*, Coll. Vol. III, 1955, p. 176.