1014. *Synthesis of 4α-Ethyl-3β,1′-dimethoxycholest-5-ene.*

By B. R. Brown and D. M. L. Sandbach.

5α-Cholestan-4-ones react with ethynylmagnesium bromide to give 4β-ethynyl-5α-cholestan-4α-ols which can be hydrated to yield 4β-acetyl-5α-cholestan-4α-ols. Pyrolysis of 4α-acetoxy-4β-acetyl-3β-methoxy-5α-cholestane yields a mixture of unsaturated compounds which can be reduced to 4α-acetyl-3β-methoxy-5α-cholestane.

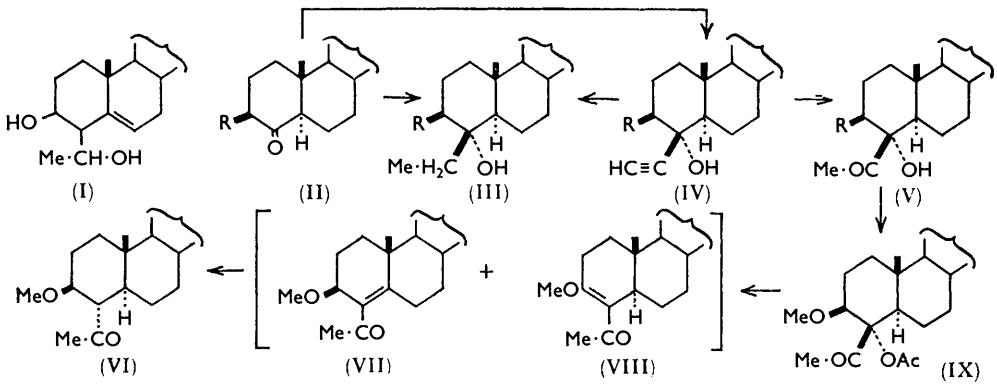
4α-Ethyl-3β,1′-dimethoxycholest-5-ene has been synthesised by the ethynyl method and proved to be identical with the dimethyl ether of one of the diols (B) obtained by the action of lithium aluminium hydride and aluminium chloride on cholestenone enol acetate.

Reaction of cholestenone enol acetate with lithium aluminium hydride and aluminium chloride is known [1] to yield stereoisomeric diols of structure (I). An approach to synthesis of these compounds has been made in which the reaction of organometallic compounds of acetylene with cholestan-4-ones has been investigated as a method for introducing a two-carbon substituent at the 4-position. The method has previously been used with success on cholestan-6-ones.[2]

5α-Cholestan-4-one (II; R = H) with lithium acetylide gave a 4-ethynyl compound (IV; R = H), but yields were variable (40—70%) and starting material was recovered. The Grignard reagent from acetylene proved more satisfactory (yields 80%) and gave the same compound (IV; R = H). Catalytic reduction of this ethynyl alcohol gave a 4-ethyl-5α-cholestan-4-ol (III; R = H), identical with the product from a reaction of 5α-cholestan-4-one with ethylmagnesium bromide. Attempts to cause the ethynyl alcohol (IV; R = H)

[1] Brown, *J.*, 1952, 2756; Brown, Trown, and Woodhouse, *J.*, 1961, 2478.
[2] Ellis, Petrow, and Waterhouse, *J.*, 1960, 2596.

to undergo a Meyer–Schuster rearrangement to an unsaturated ketone resulted either in no reaction or, when vigorous conditions were tried, in intractable non-ketonic products. This contrasts with the ease with which the 6α-ethynyl-6β-hydroxy-system, which contains an axial hydroxyl group, undergoes rearrangement,[2] but parallels the stability shown by the 17α-ethynyl-17β-hydroxy-system,[2,3] which has an equatorial hydroxyl group. We therefore conclude that our ethynyl compound is 4β-ethynyl-5α-cholestan-4α-ol (IV;

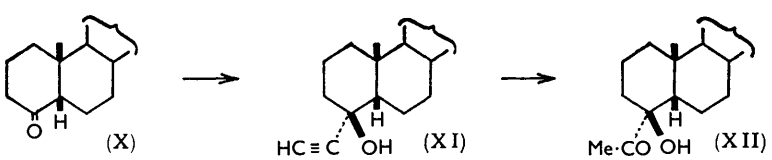


R = H) and that the product from ethylmagnesium bromide and 5α-cholestan-4-one is 4β-ethyl-5α-cholestan-4α-ol (III; R = H), a conclusion supported by the fact that dehydration of the alcohol (III; R = H) gave an inseparable mixture of unsaturated compounds [probably 4-ethylcholest-3- and -4(1')-ene]; the stereoisomer, 4α-ethyl-5α-cholestan-4β-ol, would be expected to undergo easy diaxial dehydration to give only 4-ethylcholest-4-ene.

Our failure to produce a 4-acetyl group by Meyer–Schuster rearrangement led us to investigate hydration of the ethynyl alcohol (IV; R = H). Use of mercuric sulphate and sulphuric acid in methanol [4] gave a compound whose analysis and spectral properties accorded with the structure (V; R = H). Assignment of the stereochemistry shown with 4β-acetyl and 4α-hydroxyl groups follows from the stereochemistry of the ethynyl alcohol and is supported by the fact that the ketone does not undergo ready dehydration.

A parallel series of reactions with 5β-cholestan-4-one (X) and ethynylmagnesium bromide gave 4α-ethynyl-5β-cholestan-4β-ol (XI) which could not be caused to undergo Meyer–Schuster rearrangement but was smoothly hydrated to yield 4α-acetyl-5β-cholestan-4β-ol (XII). Prolonged treatment of this with boiling 98% formic acid in an attempt to cause diequatorial dehydration yielded only starting material.

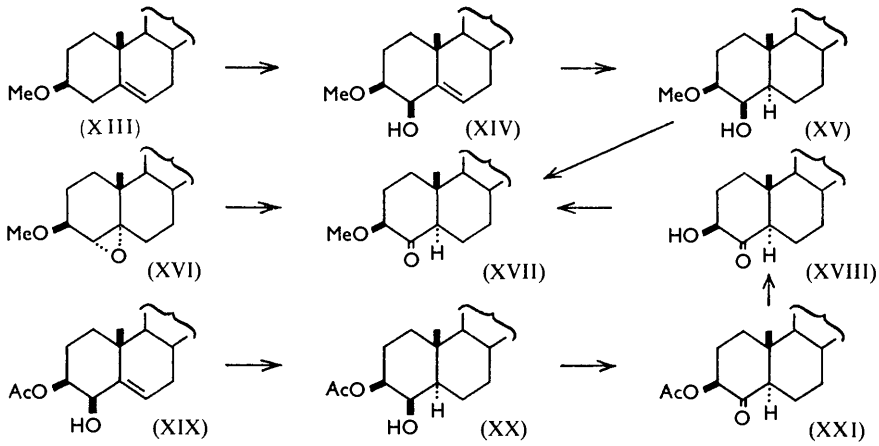
Before similar experiments on 3-substituted compounds could be carried out, it was necessary to resolve an anomaly in the literature. We have prepared 3β-methoxy-



5α-cholestan-4-one (XVII) by three independent routes. 3β-Methoxycholest-5-ene (XIII), when treated with selenium dioxide, yielded 3β-methoxycholest-5-en-4β-ol (XIV), given this structure and stereochemistry by analogy with the reactions of cholesterol and of cholesteryl acetate with selenium dioxide.[5] Catalyic hydrogenation of the product (XIV)

[3] Grenville, Patel, Petrow, Stuart-Webb, and Williamson, *J.*, 1957, 4105.
[4] Halsall and Thomas, *J.*, 1956, 2431.
[5] Rosenheim and Starling, *J.*, 1937, 377.

in acetic acid gave 3β-methoxy-5α-cholestan-4β-ol (XV) (*cis*-addition of hydrogen at the α-face), which on oxidation gave the required methoxy-ketone (XVII). Ruzicka *et al.*[6] investigated the action of potassium carbonate on 2α-acetoxy-5α-cholestan-3-one and



isolated a rearrangement product, m. p. 173—175°, $[\alpha]_D$ +14·5°, which they formulated as 3-hydroxycholestan-4-one or 4-hydroxycholestan-3-one. Its acetate had m. p. 143·5—144·5° and $[\alpha]_D$ −7·5°. Liebermann and Fukushima,[7] however, report that 3β-acetoxy-5α-cholestan-4-one (XXI), prepared by oxidation of 3β-acetoxy-5α-cholestan-4β-ol (XX), has m. p. 117—118° and $[\alpha]_D$ −23°. We prepared the compound (XX) by catalytic reduction of 3β-acetoxycholest-5-en-4β-ol (XIX) and confirmed the result reported by Liebermann and Fukushima [7] and recently confirmed.[8] Hydrolysis of the acetate (XXI) gave 3β-hydroxy-5α-cholestan-4-one (XVIII), m. p. 125—126°, $[\alpha]_D$ +20°, which on methylation, yielded 3β-methoxy-5α-cholestan-4-one (XVII), identical with material prepared as described above. A more convenient preparation of this ketone (XVII) is from 4α,5α-epoxy-3β-methoxycholestane [9] (XVI) by Tiffeneau rearrangement under the influence of the boron trifluoride–ether complex.[10] These three routes to 3β-methoxy-5α-cholestan-4-one leave no doubt about its structure and stereochemistry, nor about the structure and stereochemistry of 3β-hydroxy- and 3β-acetoxy-5α-cholestan-4-one. The structure and stereochemistry of the compound described by Ruzicka *et al.*[6] therefore remains in doubt.

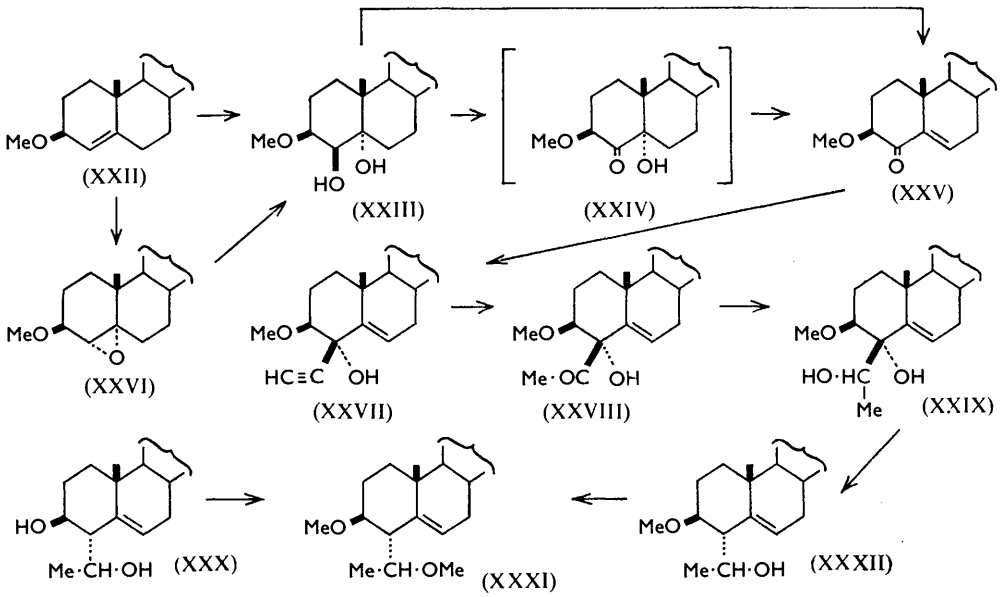
Reaction of 3β-methoxy-5α-cholestan-4-one (II; R = OMe) with ethynylmagnesium bromide followed the path for the unsubstituted compound and yielded 4β-ethynyl-3β-methoxy-5α-cholestan-4α-ol (IV; R = OMe) which on hydration gave 4β-acetyl-3β-methoxy-5α-cholestan-4α-ol (V; R = OMe). Pyrolysis of the acetate (IX) of (V; R = OMe) yielded a product which was probably a mixture of cholestenes (VII) and (VIII) (*cis*- elimination of acetic acid). Reduction of this mixture with lithium in liquid ammonia yielded a pure product (66%) which must be 4α-acetyl-3β-methoxy-5α-cholestane (VI) since this method of reduction is known to result in *trans*-addition of hydrogen atoms to give the thermodynamically more stable product, which in this example has a 4α-acetyl group.

As a result of the stereochemistry of addition of ethynylmagnesium bromide to cholestan-4-ones, which rules out easy dehydration between positions 4 and 5, we have been obliged

[6] Ruzicka, Plattner, and Furrer, *Helv. Chim. Acta*, 1944, **27**, 727.
[7] Liebermann and Fukushima, *J. Amer. Chem. Soc.*, 1950, **72**, 5211.
[8] Kupchan, Slade, Young, and Milne, *Tetrahedron*, 1962, **18**, 499.
[9] Henbest and Wilson, *J.*, 1957, 1958.
[10] Henbest and Wrigley, *J.*, 1957, 4596.

to modify our approach to the synthesis of the diol (I). Since the method is a good one for the introduction of a two-carbon substituent at the 4-position, this feature has been retained, but a 5α-hydroxyl group has been used to introduce a 5,6-double bond by elimination of water early in the synthesis.

Treatment of 3β-methoxycholest-4-ene (XXII) with performic acid yielded 3β-methoxycholestan-4β,5α-diol (XXIII) (30%), obtained in better yield through the known [9] 4α,5α-epoxy-3β-methoxycholestane (XXVI). Oxidation of the diol (XXIII) with *N*-bromosuccinimide gave an unstable compound (XXIV) [$\nu_{max.}$ (in $CHCl_3$) 3360 (OH) and 1705



cm.$^{-1}$ (ketone)], an unpurified sample of which was converted by thionyl chloride and pyridine into 3β-methoxycholest-5-en-4-one (XXV) (10%). A better yield (90%) of this ketone (XXV) was obtained by direct oxidation of the diol (XXIII) with chromic acid. Assignment of stereochemistry to this compound (XXIII) follows from the work of Jones *et al.*[11] on the unsubstituted compounds and leads to formulation of (XXV) as 3β-methoxycholest-5-en-4-one, confirmed by its ultraviolet ($\lambda_{max.}$ 241 mμ; ε 6800) and infrared spectra and by its large negative rotation ($[\alpha]_D$ −85°). Reaction of the unsaturated ketone (XXV) with ethynylmagnesium bromide and hydration of the resulting compound (XXVII) proceeded smoothly and gave 4β-acetyl-3β-methoxycholest-5-en-4α-ol (XXVIII), assigned this stereochemistry on the basis of experiments discussed above.

Reduction of the ketone (XXVIII) with lithium aluminium hydride proceeded stereospecifically to 4β-ethyl-3β-methoxycholest-5-en-4α,1′-diol (XXIX) of unknown absolute configuration at the 1′-position. Reduction of the allylic alcohol (XXIX) with lithium in ethylamine afforded 4α-ethyl-3β-methoxycholest-5-en-1′-ol (XXXII), the thermodynamically more stable isomer with an equatorial 4-hydroxyethyl group being expected.[12]

Methylation of the alcohol (XXXII) gave 4α-ethyl-3β,1′-dimethoxycholest-5-ene (XXXI), identical (m. p. and mixed m. p., infrared in CS_2, and $[\alpha]_D$ value) with the dimethyl ether of one of the diols (B) previously isolated on the reduction of cholestenone enol acetate with lithium aluminium hydride and aluminium chloride,[1]

[11] Jones, Lewis, Shoppee, and Summers, *J.*, 1955, 2876.
[12] Hallsworth, Henbest, and Wrigley, *J.*, 1957, 1969.

Experimental

Rotations were measured on an ETL-NPL Automatic polarimeter of type 143A for chloroform solutions at room temperature. Alumina was Spence's grade H, deactivated, when stated, with acetic acid. Light petroleum refers to the fraction of b. p. 40—60°.

4β-Ethynyl-5α-cholestan-4α-ol (IV; R = H).—(*a*) 5α-Cholestan-4-one (420 mg.) in ether was added during 30 min. with stirring to a solution of lithium acetylide [from lithium (1·1 g.)] in liquid ammonia (500 ml.). After 6 hr. under nitrogen, the mixture was treated with ammonium chloride, and the product isolated in ether in the usual way. Evaporation of ether yielded an oil which was chromatographed in light petroleum on alumina (150 g., 5% deactivated). Elution with light petroleum–benzene (4 : 1 v/v) gave 5α-cholestan-4-one (205 mg.), m. p. and mixed m. p. 100°. Elution with benzene gave the *ethynyl compound* (200 mg.) which separated from methanol as needles, m. p. 124—125°, $[\alpha]_D$ +41° (*c* 1·17) (Found: C, 84·2; H, 11·65. $C_{29}H_{48}O$ requires C, 84·4; H, 11·7%), $\nu_{max.}$ (in CCl_4) 3600 (OH) and 3300 cm.$^{-1}$ (C≡CH).

(*b*) A solution of 5α-cholestan-4-one (1·10 g.) in tetrahydrofuran (25 ml.) was slowly added with stirring to a suspension of ethynylmagnesium bromide [13] [from ethyl bromide (8·0 g.)] in tetrahydrofuran. The mixture was stirred under nitrogen for 5 hr. and kept overnight. A saturated solution of ammonium chloride was added slowly with stirring and the layers were separated. The aqueous layer was extracted with chloroform (2 × 50 ml.). The combined organic phases were washed with saturated ammonium chloride solution, dried, and evaporated. The residue in benzene was filtered through a column of alumina (100 g.) to yield the ethynyl compound (930 mg.), which separated from methanol as needles, m. p. and mixed m. p. 124—125°.

The *4α-acetate*, prepared by the procedure of Plattner *et al.*,[14] separated from methanol as needles, m. p. 137—138°, $[\alpha]_D$ +1° (*c* 1·41) (Found: C, 81·65; H, 11·05. $C_{31}H_{50}O_2$ requires C, 81·85; H, 11·1%).

Attempted Rearrangement of 4β-Ethynyl-5α-cholestan-4α-ol.—The action of concentrated sulphuric acid in acetic acid for 18 hr.[2] yielded 90% of starting material. Use of increased amounts of sulphuric acid caused the production of intractable oils, none of which contained carbonyl groups (infrared). Boiling 98% formic acid [15] or phosphorus pentoxide in boiling benzene [16] likewise produced non-ketonic oils.

4β-Ethyl-5α-cholestan-4α-ol (III; R = H) (with M. Wyatt).—(*a*) 5α-Cholestan-4-one (3·0 g.) in ether (10 ml.) was added slowly to a solution of ethylmagnesium bromide (from 1·0 g. of magnesium) in ether (20 ml.), and the mixture was boiled for 30 min. Decomposition with dilute sulphuric acid and isolation by ether gave a solid which was chromatographed on alumina (100 g.; 10% deactivated). Elution with light petroleum–benzene (9 : 1 v/v; 350 ml.) gave 5α-cholestan-4-one (207 mg.). Further elution with this solvent mixture (1·1 l.) gave *4β-ethyl-5α-cholestan-4α-ol* (2·04 g.) which separated from ethanol as needles, m. p. 97°, $[\alpha]_D$ +20·5° (*c* 1·02) (Found: C, 83·55; H, 12·45. $C_{29}H_{52}O_2$ requires C, 83·6; H, 12·5%), $\nu_{max.}$ (in CCl_4) 3675 cm.$^{-1}$ (OH).

Treatment of the alcohol (500 mg.) with 70% perchloric acid (2 ml.) in acetic acid (40 ml.) at 100° for 1 hr. yielded an oil which gave a positive tetranitromethane test. Attempts to purify the oil by fractional crystallisation or by chromatography on alumina failed and examination on a silica gel chromatoplate in light petroleum–ethyl acetate (sprayed with antimony trichloride in chloroform) gave a dark blue streak, suggesting the presence of more than one unsaturated compound.

(*b*) 4β-Ethynylcholestan-4α-ol (85 mg.) in chloroform (100 ml.) was hydrogenated at 20°/1 atm. over Adams catalyst (50 mg.). Hydrogen uptake was complete in 5 min. Filtration, evaporation, and recrystallisation yielded 4β-ethyl-5α-cholestan-4α-ol (80 mg.), m. p. and mixed m. p. 97°.

4β-Acetyl-5α-cholestan-4α-ol (V; R = H).—4β-Ethynyl-5α-cholestan-4α-ol (135 mg.), mercuric sulphate (115 mg.), concentrated sulphuric acid (2 ml.), water (7 ml.), and methanol (22 ml.) were boiled together for 3 hr. The product, isolated by using ether, was dissolved in benzene

[13] Jones, Skatteböl, and Whiting, *J.*, 1956, 4765.
[14] Plattner, Lang, and Petrzilka, *Helv. Chim. Acta*, 1944, **27**, 513.
[15] Hennion, Davis, and Maloney, *J. Amer. Chem. Soc.*, 1949, **71**, 2813.
[16] "Organic Syntheses." Coll. Vol. III, ed. Horning, John Wiley and Sons, Inc., New York, 1955, p. 22.

and filtered through alumina (25 g.; 5% deactivated), to yield the 4β-*acetyl compound* (92 mg.) which separated from methanol as needles, m. p. 115—117°, $[\alpha]_D$ +30° (*c* 0·97) (Found: C, 80·8; H, 11·7. $C_{29}H_{50}O_2$ requires C, 80·9; H, 11·7%), $\nu_{max.}$ (in CCl_4) 3400 (OH) and 1710 cm.$^{-1}$ (ketone).

After the action of heat (140° for 2 hr.), of hydrogen chloride in boiling toluene (2 hr.), of iodine in boiling toluene (2 hr.), and of boiling 98% formic acid (2 hr.), 4β-acetyl-5α-cholestan-4α-ol was recovered in yields of 80%, 95%, 95%, and 90%, respectively. Thionyl chloride in pyridine (0° for 20 min.) gave intractable oils.

4α-*Ethynyl*-5β-*cholestan*-4β-*ol* (XI).—By the method described above for the 5α-compound, 5β-cholestan-4-one (1·32 g.) gave a product which was chromatographed on alumina (200 g.; 5% deactivated). Elution with light petroleum gave an oil (480 mg.) which was discarded. Elution with 4 : 1 light petroleum–benzene gave the *ethynyl compound* (903 mg.) which separated from acetone as needles, m. p. 219—220°, $[\alpha]_D$ +16° (*c* 1·13) (Found: C, 84·45; H, 11·7. $C_{29}H_{48}O$ requires C, 84·4; H, 11·7%), $\nu_{max.}$ (in CCl_4) 3500 (OH) and 3300 cm.$^{-1}$ (C≡CH). Attempts to cause rearrangement of this compound with sulphuric and acetic acids failed.

4α-*Acetyl*-5β-*cholestan*-4β-*ol* (XII).—By the method described for the 5α-compound, 4α-ethynyl-5β-cholestan-4β-ol (187 mg.) yielded the 4α-*acetyl compound* (146 mg.) which separated from methanol as needles, m. p. 106·5—107°, $[\alpha]_D$ +55° (Found: C, 80·4; 80·6; H, 11·9, 11·5. $C_{29}H_{50}O_2$ requires C, 80·9; H, 11·7%), $\nu_{max.}$ (in CCl_4) 3630 (OH) and 1710 cm.$^{-1}$ (ketone). The *acetate*, prepared as previously,[14] separated from methanol as plates, m. p. 123—124°, $[\alpha]_D$ +33° (*c* 1·17) (Found: C, 78·4; H, 11·15. $C_{31}H_{52}O_3$ requires C, 78·75; H, 11·1%). The hydroxy-ketone was stable to boiling 98% formic acid for 14 hr. (90% recovery).

3β-*Methoxy*-5α-*cholestan*-4-*one* (XVII).—4α,5α-Epoxy-3β-methoxy-5α-cholestane [9] (1·63 g.) and boron trifluoride–ether complex (1·5 ml.) in dry benzene (150 ml.) were kept at room temperature. After 2 min., saturated sodium hydrogen carbonate solution (50 ml.) was added. Evaporation of the benzene gave a residue (1·59 g.) which was dissolved in benzene and adsorbed on alumina (200 g.). After 30 hr., elution with benzene gave colourless 3β-*methoxy*-5α-*cholestan*-4-*one* (720 mg.) which separated from methanol as needles, m. p. 92—93°, $[\alpha]_D$ −24° (*c* 1·13) (Found: C, 80·7; H, 11·75. $C_{28}H_{48}O_2$ requires C, 80·5; H, 11·9%), $\nu_{max.}$ (in CCl_4) 1705 cm.$^{-1}$ (ketone).

3β-*Methoxycholest*-5-*ene* (XIII).—Cholesterol (100 g.), silver oxide (95 g.), and methyl iodide (250 ml.) were boiled for 18 hr. The solution was filtered, the residue was washed with ether, and the solvents were removed, to give an oil which separated from 1 : 1 acetone–methanol as plates (89 g.), m. p. 82—83°, $[\alpha]_D$ −42° (*c* 1·31). Bills and Macdonald [17] give m. p. 83°, $[\alpha]_D$ −42°.

3β-*Methoxycholest*-5-*en*-4β-*ol* (XIV).—Solutions of selenium dioxide (3·6 g.) in water (1·8 ml.) and acetic acid (120 ml.) and of cholesteryl methyl ether (7·2 g.) in benzene (34 ml.) were mixed at 80° and boiled for 1 hr. Sodium acetate (hydrated; 10 g.) was added and the mixture was boiled for 15 min., filtered, and poured into saturated brine. Isolation by ether gave a dark brown residue (7·4 g.) which was dissolved in light petroleum and chromatographed on alumina (200 g.; 10% deactivated). Elution (250 ml. fractions) was as follows: (i) fractions 1—3 (light petroleum) gave crystals (0·73 g.); (ii) fractions 4—7 (light petroleum) gave brown oils (0·51 g.); (iii) fractions 8—10 (19 : 1 light petroleum–benzene) gave brown crystals (1·42 g.); (iv) fractions 11—13 (9 : 1 light petroleum–benzene) gave brown oils (1·22 g.); (v) fractions 14—22 (4 : 1 light petroleum–benzene) gave brown solids (2·53 g.).

Fractions 1—3 separated from acetone–methanol to give cholesteryl methyl ether, m. p. and mixed m. p. 81—82°.

Fractions 8—10 separated from methanol to give 4β-*acetoxy*-3β-*methoxycholest*-5-*ene* as needles, m. p. 123—125°, $[\alpha]_D$ −51° (*c* 1·41) (Found: C, 78·7; H, 11·0. $C_{30}H_{50}O_3$ requires C, 78·6; H, 11·0%), $\nu_{max.}$ (in CCl_4) 1735 cm.$^{-1}$ (OAc). Hydrolysis with methanolic sodium hydroxide gave the parent alcohol (see below).

Fractions 14—22 separated from acetone to give 3β-*methoxycholest*-5-*en*-4β-*ol* as plates, m. p. 164—165°, $[\alpha]_D$ −57° (*c* 1·24) (Found: C, 80·5; H, 11·5. $C_{28}H_{48}O_2$ requires C, 80·5; H, 11·9%), $\nu_{max.}$ (in CCl_4) 3610 cm.$^{-1}$ (OH). The compound gave an intense yellow colour with tetranitromethane in chloroform.

3β-*Methoxy*-5α-*cholestan*-4β-*ol* (XV).—3β-Methoxycholest-5-en-4β-ol (630 mg.) in acetic acid (45 ml.) was hydrogenated at 23°/763 mm. over Adams catalyst (220 mg.). Hydrogen uptake

[17] Bills and Macdonald, *J. Biol. Chem.*, 1927, **72**, 1.

was complete after 2 hr. The product (627 mg.) was chromatographed in light petroleum on alumina (20 g.; 5% deactivated). Elution (25 ml. fractions) was as follows: (i) fractions 1—3 (light petroleum) gave colourless oils (116 mg.); (ii) fractions 4—5 (light petroleum) gave crystals (170 mg.); (iii) fractions 6—11 (4 : 1 light petroleum–benzene) gave a colourless solid (303 mg.).

Fractions 4—5 separated from acetone–methanol to give cholestan-3-yl methyl ether m. p. 82—83°, $[\alpha]_D$ +21° (*c* 0·97) (Found: C, 83·4; H, 12·5. Calc. for $C_{28}H_{50}O$: C, 83·5; H, 12·5%). Beynon, Heilbron, and Spring [18] cite m. p. 83°, $[\alpha]_D$ +19°.

Fractions 6—11 separated from methanol, to give 3β-*methoxy*-5α-*cholestan*-4β-*ol* as needles, m. p. 168—169°, $[\alpha]_D$ +19° (*c* 0·83) (Found: C, 79·9; H, 11·7. $C_{28}H_{50}O_2$ requires C, 80·3; H, 12·0%).

3β-*Methoxy*-5α-*cholestan*-4-*one* (XVII).—3β-Methoxy-5α-cholestan-4β-ol (230 mg.) in benzene (15 ml.) was shaken for 5 hr. with a solution of chromium trioxide (" AnalaR "; 1·2 g.) in water (7 ml.) and acetic acid (21 ml.). Water was added and the mixture was worked up in the usual way, giving an oil (227 mg.) which was dissolved in benzene and filtered through a column of alumina (10 g.); this led to 3β-methoxy-5α-cholestan-4-one (216 mg.) which separated from methanol as needles, m. p. 91—92° undepressed on admixture with material prepared as above, $[\alpha]_D$ −25° (*c* 1·22) (Found: C, 80·8; H, 11·6. Calc. for $C_{28}H_{48}O_2$: C, 80·5; H, 11·9%).

3β-*Acetoxy*-5α-*cholestan*-4β-*ol* (XX).—3β-Acetoxycholest-5-en-4β-ol (1·32 g.) in acetic acid (120 ml.) was hydrogenated at 20°/758 mm. over Adams catalyst (270 mg.). Hydrogen uptake was complete after 3 hr. Filtration and evaporation of the solvent gave a residue which was chromatographed in 9 : 1 light petroleum–benzene on alumina (150 g.; 5% deactivated).

Light petroleum–benzene (9 : 1 v/v) eluted an oil (733 mg.) which was fractionally crystallised from acetone, to give cholestane, m. p. 79—80° and coprostane, m. p. 68—69°.

Light petroleum–benzene (4 : 1 v/v) eluted cholestan-3-yl acetate (329 mg.) which separated from methanol as needles, m. p. 110—111°, $[\alpha]_D$ +23° (*c* 1·07).

Light petroleum–benzene (1 : 1 v/v) eluted a solid (91 mg.) which separated from methanol, to give 3β-acetoxy-5α-cholestan-4β-ol as needles, m. p. 201—202° (decomp.), $[\alpha]_D$ +19° (Found: C, 77·85; H, 11·2. Calc. for $C_{29}H_{50}O_3$: C, 78·0; H, 11·3%). Liebermann and Fukushima [7] report m. p. 200—205°, $[\alpha]_D$ +13°.

3β-*Acetoxy*-5α-*cholestan*-4-*one* (XXI).—3β-Acetoxy-5α-cholestan-4β-ol (650 mg.) in benzene (25 ml.) was shaken for 5 hr. with a solution of chromium trioxide (" AnalaR "; 1·7 g.) in water (15 ml.) and acetic acid (35 ml.). Addition of water and isolation in the usual way gave 3β-acetoxy-5α-cholestan-4-one (635 mg.) which separated from methanol as needles, m. p. 122—123°, $[\alpha]_D$ −20° (*c* 0·94) (Found: C, 78·5; H, 10·45. Calc. for $C_{29}H_{48}O_3$: C, 78·3; H, 10·9%), $\nu_{max.}$ (in CCl_4) 1725 (OAc) and 1710 cm.$^{-1}$ (ketone). Liebermann and Fukushima [7] report m. p. 117—118°, $[\alpha]_D$ −23°.

3β-*Hydroxy*-5α-*cholestan*-4-*one* (XVIII).—3β-Acetoxy-5α-cholestan-4-one (503 mg.) in methanol (150 ml.) was boiled for 3 hr. with sodium hydrogen carbonate (500 ml.) in water (10 ml.). Most of the methanol was removed by distillation, then ether-extraction and evaporation of ether gave 3β-*hydroxy*-5α-*cholestan*-4-*one* (482 mg.) which separated from methanol as needles, m. p. 125—126°, $[\alpha]_D$ +20° (*c* 0·91) (Found: 80·2; H, 11·8. $C_{27}H_{46}O_2$ requires C, 80·5; H, 11·5%), $\nu_{max.}$ (in CCl_4) 3350 (OH) and 1708 cm.$^{-1}$ (ketone).

3β-*Methoxy*-5α-*cholestan*-4-*one* (XVII).—3β-Hydroxy-5α-cholestan-4-one (215 mg.), silver oxide (320 mg.), and methyl iodide (15 ml.) were boiled together for 12 hr. The solution was filtered, the residue was washed with ether, and the solvents were evaporated, to give an oil (203 mg.) which was dissolved in benzene and filtered through alumina (10 g.); the filtrate afforded 3β-methoxy-5α-cholestan-4-one which separated from methanol as needles, m. p. 92—93°, $[\alpha]_D$ −22° (*c* 1·24) (Found: C, 80·6; H, 11·8. Calc. for $C_{28}H_{48}O_2$: C, 80·5; H, 11·9%). The mixed m. p.s with the compound prepared as described above were 91—92° and 92·5—93°, and the infrared spectra of all three specimens were identical.

4β-*Ethynyl*-3β-*methoxy*-5α-*cholestan*-4α-*ol* (IV; R = OMe) (with A. Cox).—3β-Methoxy-5α-cholestan-4-one (1·10 g.) in tetrahydrofuran (50 ml.) was added to a suspension of ethynylmagnesium bromide [from ethyl bromide (25 ml.)] in tetrahydrofuran (260 ml.) and worked up in the usual way, to give the *ethynyl compound* (1·00 g.) which separated from methanol as

[18] Beynon, Heilbron, and Spring, *J.*, 1937, 406.

needles, m. p. 160—161°, $[\alpha]_D$ +11·5° (*c* 1·21) (Found: C, 81·4; H, 11·6. $C_{30}H_{50}O_2$ requires C, 81·6; H, 11·3%). The 4α-*acetate* separated from methanol as plates, m. p. 151—152°, $[\alpha]_D$ +25° (*c* 1·11) (Found: C, 79·2; H, 11·4. $C_{32}H_{52}O_3$ requires C, 79·4; H, 11·2%).

4β-*Acetyl*-3β-*methoxy*-5α-*cholestan*-4α-*ol* (V; R = OMe) (with A. Cox).—4β-Ethynyl-3β-methoxy-5α-cholestan-4α-ol (195 mg.), tetrahydrofuran (200 ml.), mercuric sulphate (150 mg.), water (15 ml.), and concentrated sulphuric acid (4 ml.) were boiled together for 3 hr. The mixture was poured into water (250 ml.). The *product*, isolated by using ether, separated from methanol as plates (100 mg.), m. p. 175—176°, $[\alpha]_D$ +40·5° (*c* 1·13) (Found: C, 78·4; H, 11·5. $C_{30}H_{52}O_3$ requires C, 78·3; H, 11·3%). The 4α-*acetate* separated from methanol as plates, m. p. 170—171°, $[\alpha]_D$ +35° (*c* 1·22) (Found: C, 76·7; H, 10·7. $C_{32}H_{54}O_4$ requires C, 76·5; H, 10·8%).

4α-*Acetyl*-3β-*methoxy*-5α-*cholestane* (VI) (with A. Cox).—4α-Acetoxy-4β-acetyl-3β-methoxy-5α-cholestane (30 mg.) was pyrolysed at 300°/10 mm. pressure for 4 hr. The product in ether (20 ml.) was added with vigorous stirring to lithium (50 mg.) in liquid ammonia (100 ml.). After 3 hr. the excess of lithium was destroyed by addition of ethanol, and treatment of the mixture with aqueous ammonium chloride followed by extraction with ether yielded, on evaporation of ether, the *methoxy-ketone* as crystals which separated from acetone as needles (20 mg.), m. p. 76—77°, $[\alpha]_D$ +33·5° (*c* 0·93) (Found: C, 80·9; H, 11·3. $C_{30}H_{52}O_2$ requires C, 81·2; H, 11·7%).

3β-*Methoxy*-5α-*cholestane*-4β,5α-*diol* (XXIII).—(*a*) Hydrogen peroxide (30%; 11 ml.) was added during 4½ hr. to a stirred solution of 3β-methoxycholest-4-ene (1·93 g.) in benzene (10 ml.) and 98% formic acid (90 ml.). Stirring was continued for 1 hr. after the addition was complete. The mixture was poured into water and extracted with ether. The ethereal extract was washed with ferrous sulphate solution, sodium carbonate solution, and water. Evaporation then gave an oil (2·01 g.) which was boiled in a 5% solution of potassium hydroxide in methanol (100 ml.) for 3 hr. and worked up in the usual way. The resulting solid (1·72 g.) was chromatographed in 9 : 1 light petroleum–benzene on alumina (5% deactivated; 50 g.). Elution with the same solvents gave a colourless oil (103 mg.). Elution with 4 : 1 light petroleum–benzene gave a colourless solid (622 mg., 30%) which afforded 3β-*methoxy*-5α-*cholestane*-4β,5α-*diol* as needles (from acetone), m. p. 172—173°, $[\alpha]_D$ −19° (*c* 1·24) (Found: C, 77·5; H, 11·45. $C_{28}H_{50}O_3$ requires C, 77·35; H, 11·6%).

(*b*) 4α,5α-Epoxy-3β-methoxycholestane [9] (310 mg.) in purified dioxan (10 ml.) was treated with 2N-sulphuric acid (1 ml.) and boiled for 1 hr. Dilution with water and ether-extraction followed by evaporation of the dried extract *in vacuo* gave a colourless solid (295 mg.) which separated from acetone as needles, m. p. and mixed m. p. 172—173°, $[\alpha]_D$ −20° (*c* 1·01).

3β-*Methoxycholest*-5-*en*-4-*one* (XXV).—3β-Methoxy-5α-cholestane-4β,5α-diol (605 mg.) in ether (20 ml.), methanol (3·5 ml.), and water (3 ml.) was shaken with *N*-bromosuccinimide (800 g.). After 50 min. ether was added, and the solution was washed with sodium hydrogen sulphate solution, then with water, and dried. Evaporation of the ether *in vacuo* at room temperature gave a gummy solid (580 mg.) [$\nu_{max.}$ (in $CHCl_3$) 3360 (OH) and 1705 cm.$^{-1}$ (ketone)] which decomposed after 4 hr. to give a brown oil.

A crude, freshly prepared sample of the above solid (452 mg.) in pyridine (3 ml.) was treated at 0° with thionyl chloride (0·3 ml.). After 20 min. at room temperature the mixture was poured into water and worked up in the usual way, to give a brown oil (440 mg.) which was dissolved in benzene and filtered through alumina (Type H; 10 g.); this led to 3β-*methoxycholest*-5-*en*-4-*one* (73 mg.; 16%) which separated from acetone–methanol as needles, m. p. 118—119°, $[\alpha]_D$ −85° (*c* 0·72) (Found: C, 80·7; H, 11·1. $C_{28}H_{46}O_2$ requires C, 81·1; H, 11·2%), $\lambda_{max.}$ (in EtOH) 241 mμ (ε 6080), $\nu_{max.}$ (CCl_4) 1685 cm.$^{-1}$ (conjugated ketone).

(*b*) 3β-Methoxycholestane-4β,5α-diol (90 mg.) in benzene (9 ml.) was shaken for 5 hr. with chromium trioxide (350 mg.) in water (8 ml.) and acetic acid (12 ml.). Water was added and the mixture was worked up in the usual way, to give 3β-methoxycholest-5-en-4-one which separated from acetone–methanol as needles (68 mg.), m. p. and mixed m. p. 118—119°, $[\alpha]_D$ −84° (*c* 0·83).

4β-*Ethynyl*-3β-*methoxycholest*-5-*en*-4α-*ol* (XXVII).—To a solution of ethynylmagnesium bromide [from ethyl bromide (25 ml.)] in dry tetrahydrofuran (220 ml.) was added a solution of 3β-methoxycholest-5-en-4-one (1·1 g.) in tetrahydrofuran (50 ml.), and the mixture was stirred for 18 hr. at room temperature. A saturated solution of ammonium chloride was added, the layers were separated, and the aqueous layer was extracted with ether. The combined extracts were washed with saturated ammonium chloride solution, dried, and evaporated to give

a solid (1·05 g.) which was chromatographed in 4 : 1 light petroleum–benzene on alumina (50 g.; 5% deactivated). Elution with the same solvents gave a yellow oil (720 mg.). Elution with 1 : 1 light petroleum–benzene gave 4β-*ethynyl*-3β-*methoxycholest*-5-*en*-4α-*ol* (700 mg.; 63%) which crystallised from acetone as needles, m. p. 184—185°, $[\alpha]_D$ −15·5° (*c* 0·88) (Found: C, 81·6; H, 11·1. $C_{30}H_{48}O_2$ requires C, 81·75; H, 11·0%), $\nu_{max.}$ (in CCl_4) 3360 (OH) and 3330 cm.$^{-1}$ (C≡CH).

4β-*Acetyl*-3β-*methoxycholest*-5-*en*-4α-*ol* (XXVIII).—Mercuric sulphate (280 mg.) in water (14 ml.) and sulphuric acid (3 ml.) was added to a solution of 4β-ethynyl-3β-methoxycholest-5-en-4α-ol (270 mg.) in purified tetrahydrofuran (100 ml.), and the mixture was boiled for 3 hr. Saturated ammonium chloride solution was added, and the aqueous layer was extracted twice with ether. The combined extracts were washed with sodium hydrogen carbonate solution and with saturated ammonium chloride solution, dried, and evaporated to give a pale yellow solid (264 mg.) which, from acetone–methanol, afforded 4β-acetyl-3β-methoxycholest-5-en-4α-ol (202 mg.) as colourless needles, m. p. 191—192°, $[\alpha]_D$ +187° (*c* 0·78) (Found: C, 78·2; H, 10·95. $C_{30}H_{50}O_3$ requires C, 78·55; H, 11·0%), $\nu_{max.}$ (in CCl_4) 3360 cm.$^{-1}$ (OH), 1708 cm.$^{-1}$ (saturated ketone).

4β-*Ethyl*-3β-*methoxycholest*-5-*ene*-4α,1′-*diol* (XXIX).—4β-Acetyl-3β-methoxycholest-5-en-4α-ol (102 mg.) in dry ether (45 ml.) was treated with lithium aluminium hydride (160 mg.) and boiled for 3 hr. Working up in the usual way gave a colourless solid (100 mg.) which separated from acetone to give 4β-*ethyl*-3β-*methoxycholest*-5-*ene*-4α,1′-*diol* as needles, m. p. 165—166°, $[\alpha]_D$ −44° (*c* 0·88) (Found: C, 77·95, 78·0; H, 11·5, 11·5. $C_{30}H_{52}O_3$ requires C, 78·2; H, 11·1%).

4α-*Ethyl*-3β-*methoxycholest*-5-*en*-1′-*ol* (XXXII).—A solution of 4β-ethyl-3β-methoxycholest-5-ene-4α,1′-diol (220 mg.) in anhydrous ethylamine (60 ml.) was treated at 0° with lithium (0·4 g.) and kept at room temperature with occasional swirling. After 90 min., when a permanent blue colour had developed, methanol was added. Addition of water and ether extraction gave a gummy solid (208 mg.) which was chromatographed in 19 : 1 light petroleum–benzene on alumina (30 g.; 10% deactivated). Light petroleum–benzene mixtures (19 : 1 and 9 : 1 v/v) eluted a colourless oil (90 mg.). Light petroleum–benzene (1 : 1 v/v) eluted a colourless solid (110 mg.), which separated from acetone as needles, m. p. 168—169°, $[\alpha]_D$ +17° (Found: C, 80·8; H, 11·5. $C_{30}H_{52}O_2$ requires C, 81·1; H, 11·7%), $\nu_{max.}$ 3360 cm.$^{-1}$ (OH).

4α-*Ethyl*-3β,1′-*dimethoxycholest*-5-*ene* (XXXI).—4α-Ethyl-3β-methoxycholest-5-en-1′-ol (30 mg.) was boiled for 6 hr. with silver oxide (150 mg.) and methyl iodide (10 ml.). The solution was filtered, the residue was washed with ether, and the solvents were evaporated to yield crystals (28 mg.). Recrystallisation from acetone–methanol gave 4α-*ethyl*-3β,1′-*dimethoxycholest*-5-*ene* (21 mg.), m. p. 94—95°, $[\alpha]_D$ −40° (*c* 0·65) (Found: C, 81·3; H, 11·6. $C_{31}H_{50}O_3$ requires C, 81·15; H, 11·85%).

Dimethyl Ether of Diol B.—Diol B [1] (160 mg.) was methylated as above with silver oxide (400 mg.) and methyl iodide (10 ml.). The product (148 mg.) was chromatographed in light petroleum on alumina (30 g.; 5% deactivated). Elution with 4 : 1 light petroleum–benzene gave a colourless solid, which was twice recrystallised from acetone–methanol to give the dimethyl ether as needles, m. p. 95—96°, $[\alpha]_D$ −40·5° (*c* 0·63). The mixed m. p. with synthetic material was 94·5—96°; the infrared spectra (CS_2) were identical.

Dyson Perrins Laboratory,
The University, Oxford.

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