ON STEROIDS. CXLVI.* B-HOMOSTEROIDS. VII.**

FAVORSKII REARRANGEMENT OF SOME B-HOMOSTEROID BROMO KETONES

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Favorskii rearrangement of the two isomeric 6α- and 7aα-bromo-5α-B-homocholestan-7-ones has been studied and the structures of the products established by chemical and spectral means. On the basis of the products obtained the possible mechanism of the reaction is discussed.

In the course of our stereochemical studies of the B-homosteroid skeleton we became interested in the Favorskii rearrangement of the two bromo ketones *I* and *II*.

The reaction has been carried out either with potassium carbonate in methanol–water or with sodium methoxide in methanol. In all of our experiments similar reaction mixture has been obtained from both bromo ketones. The mixture consisted of three components all of them being 3β-hydroxy-5α-cholestanecarboxylic acid methyl esters as was shown by spectral evidence. The two main components were isolated by chromatography of the reaction mixture. The minor component was by chromatography isolated in a very low yield from the mother liquors after hydrolysis and acetylation.

Further experiments have been carried out in order to prove the structures of these esters. As we intended to use the Baeyer–Villiger oxidation for this purpose they were converted to the acetoxy acids by hydrolysis with lithium iodide in collidine and by acetylation. Though the treatment with thionyl chloride followed by reaction with dimethylcadmium gave easily the corresponding acetyl derivatives, all attempts at oxidation were unsuccessful and only the starting material was recovered in all of the experiments (perbenzoic acid, *m*-chloroperbenzoic acid, pertrifluoroacetic acid in chloroform, dichloromethane, or acetic acid).

Next possibility was the transformation of the carboxy esters to the hydroxymethyl derivatives and their correlation with the hydroxymethyl derivatives synthesised from the corresponding cholestan-6- or 7-ones respectively. This approach

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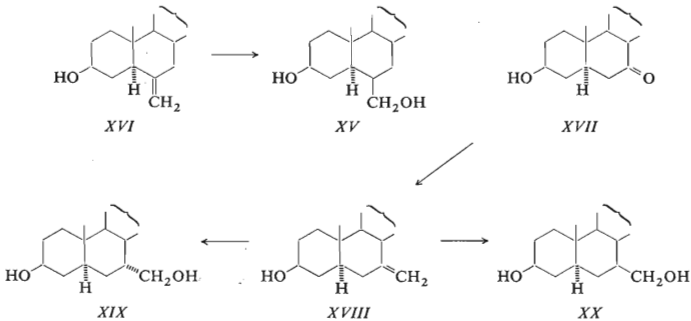
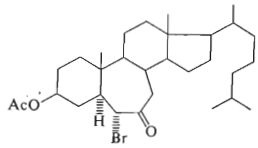
seemed promising because the 6β-hydroxymethyl derivative *XV* has been described in the literature[1]. The epimeric 7-hydroxymethyl derivatives *XIX* and *XX* were prepared on hydroboration of the methylene derivative *XVIII* which in turn was obtained from 3β- hydroxy-5α-cholestan-7-one (*XVII*) by Wittig reaction. Similarly the 6β-hydroxymethyl-5α-cholestan-3β-ol (*XV*) was prepared by hydroboration of the



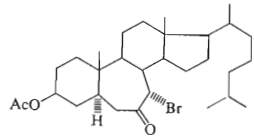
known[2] methylene derivative *XVI* as the sole product. In the next step the carboxylic acid methyl esters were transformed to the corresponding hydroxymethyl derivatives by hydride reduction. The minor product of the Favorskii reaction afforded a hydroxymethyl derivative which was identical with the authentic 6β-compound *XV* and this ester has therefore the structure *XII*. On the other hand the two esters obtained as the main products on the Favorskii reaction gave the hydroxymethyl derivatives identical with the 7-substituted compounds *XIX* and *XX* prepared on hydroboration of the methylene derivative *XVIII*. The two main products are therefore epimers at $C_{(7)}$.

Assignment of the configurations was possible on the basis of their NMR spectra: The half-band width of the 7-proton in the lipophilic component of the Favorskii reaction is 10·5 Hz which corresponds to its equatorial conformation and β-configuration. This compound is therefore methyl 3β-hydroxy-5α-cholestane-7α-carboxylate (*III*). Similar NMR results gave the 7α-substituted derivatives *IV*, *V*, and *VI*. In the 7β-epimeric acids *VIII* and *IX* as well as in the esters *VII* and *X* the signals of the axial 7α-protons have not been detected, evidently because of a very broad signal. In agreement with the assigned structures the signals of the 18- as well as 19-protons are slightly deshielded by the equatorial 7β-carboxy group as shown in Table I. We may now also assign the 7α-configuration to the acetyl derivative *XIII* and hydroxymethyl derivative *XIX* and 7β-configuration to their epimers *XIV* and *XX*.

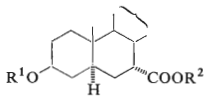
These results allow a discussion of the mechanism of the Favorskii rearrangement. The mechanism proposed by Loftfield[3,4] is generally accepted for bromo ketones of our type. In this mechanism a cyclopropane intermediate is considered and sub-



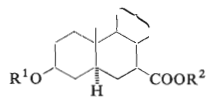
I



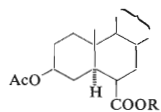
II



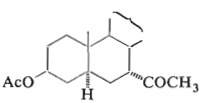
III, $R^1 = H$, $R^2 = CH_3$
IV, $R^1 = R^2 = H$
V, $R^1 = Ac$, $R^2 = H$
VI, $R^1 = Ac$, $R^2 = CH_3$



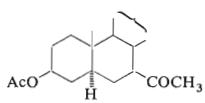
VII, $R^1 = H$, $R^2 = CH_3$
VIII, $R^1 = R^2 = H$
IX, $R^1 = Ac$, $R^2 = H$
X, $R^1 = Ac$, $R^2 = CH_3$



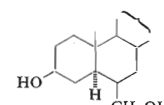
XI, R = H
XII, $R = CH_3$



XIII



XIV



XV

TABLE I

Signals of the 18- and 19-Protons in the 7-Substituted 3β-Acetoxy-5α-cholestanes (p.p.m.)

Compound	*V*	*VI*	*IX*	*X*
18-H	0·65	0·63	0·69	0·69
19-H	0·84	0·83	0·88	0·88

sequent rupture of the cyclopropane ring gives rise to two isomeric acid esters of identical configuration which was pre-determinated by the configuration of the cyclopropanone ring. A nice example represents the rearrangement of the two at $C_{(5)}$ epimeric 3- and 4-bromocholestane-3-ones[5]. Because of the different stereochemistry at $C_{(5)}$ the cyclopropanone intermediate accepts different configuration in each case giving the 2α- and 3α-carboxylic acid esters in 5α-cholestane series and 2β- and 3β-esters in the 5β-epimer. As far as the formation of the cyclopropanone ring intermediate is concerned several possibilities have been discussed, but the zwitterionic intermediate or a closely related one seems to be preferred by most of the workers. Accepting the cyclopropanone and zwitterionic intermediate mechanism of the Favorskii reaction following conclusions may be drawn from our results: In our case two $C_{(7)}$-epimeric esters have been isolated as the main components, evidently products of two epimeric cyclopropanone intermediates the rupture of the ring having taken place with preference between $C_{(6)}$ and $C_{(7)}$. Formation of the two epimeric cyclopropanone intermediates in the B-homosteroid system may well be explained by inspection of the Dreiding models of the two zwitterionic species. In the six-membered ring the model of the zwitterion is rigid – both mesomeric forms have the same conformation and therefore formation of the new σ-bond leads in both cases to the same cyclopropanone intermediate and to esters of the same configuration. On the other hand, in the 7-membered ring models of the ionic species are flexible. In addition, in the twist-chair conformation which was shown[6] to be the prefered one, the stereochemistry of the both mesomeric forms is different (Fig. 1) in that way that each

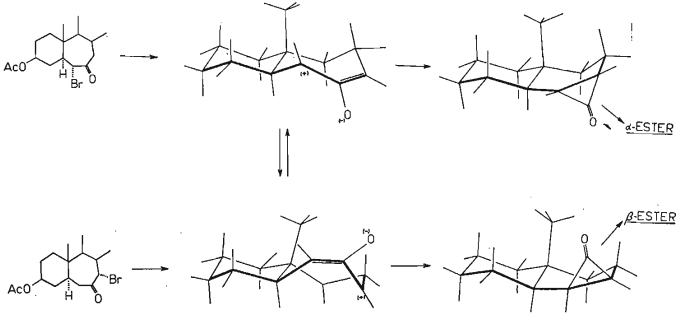


FIG. 1

Stereochemistry of the Intermediates in the Favorskii Reaction

form gives rise to an intermediate with opposite configuration of the cyclopropane ring. The result is a mixture of epimeric esters. Identical reaction mixture obtained from both bromo ketones *I* and *II* is well explained by equilibration of the mesomeric forms of the zwitterion followed by ring closure to an identical mixture of the epimeric cyclopropanone intermediates.

EXPERIMENTAL

Melting points were determined on a Kofler block. Analytical samples were dried at 80°C/0·2 Torr. Optical measurements were carried out in chloroform unless otherwise stated with an error of ±1°. The infrared spectra were recorded on a Zeiss UR 10 spectrometer in tetrachloromethane solution. The mass spectra were recorded on mass spectrometer AEI MS 902. The NMR spectra were recorded on a Varian HA-100 instrument in deuteriochloroform with tetramethylsilane as internal reference. The chemical shifts are given in p.p.m.. The identity of samples prepared by different routes was checked by mixture melting point determination by specific rotation, by thin-layer chromatography and by IR spectra.

Methyl 3β-Hydroxy-5α-cholestane-7α-carboxylate (*III*)

a) *From* 3β-*acetoxy*-6α-*bromo*-B-*homo*-5α-*cholestan*-7-*one* (I) *with potassium carbonate*: The bromo ketone[7] *I* (3 g) in methanol (500 ml) was refluxed with K_2CO_3 (3 g) in water (50 ml) for 2 h. Methanol was removed under reduced pressure the residue diluted with water and the product extracted into ether. The ethereal solution was washed with an ammonium sulphate solution, dried, and evaporated. The residue (2·48 g) was chromatographed over silica gel (200 g) in benzene–ether (9 : 1). The corresponding fractions were combined, evaporated, and the product crystallised from acetone to yield 1·21 g of the methyl ester *III*, m.p. 171—172°C, $[\alpha]_D^{20}$ −2° (*c* 2·44). Mass spectrum M^+ 446; IR: 3620, 1734, 1437, 1166, 1049 cm^{-1}; NMR: 0·61 (s, 18-H), 0·80 (s, 19-H), 0·84 (d, J = 6 Hz, 26-H and 27-H), 0·88 (d, J = 6 Hz, 21-H), 1·46 (s, OH), 2·61 (mt, $W_{1/2}$ = 10·5 Hz, 7β-H), 3·56 (mt, $W_{1/2}$ = 22 Hz, 3α-H), 3·62 (s, methyl ester). For $C_{29}H_{50}O_3$ (446·7) calculated: 77·97% C, 11·28% H; found: 78·16% C, 11·30% H. b) *From* I *with sodium methoxide*: The bromo ketone *I* (2 g) in ether (60 ml) was treated with a solution of sodium (2·4 g) in methanol (80 ml) and allowed to stand at room temperature for 24 h. Solvents were distilled off under reduced pressure, the residue was dissolved in water (40 ml) and methanol (200 ml) and refluxed for 1 h. The reaction mixture was acidified with 1M-H_2SO_4, methanol distilled off under reduced pressure and the residue was extracted with ether. The ethereal solution was washed with water, a $KHCO_3$ solution, dried, and evaporated. The residue (1·76 g) was chromatographed on a silica gel column (170 g) in benzene–ether (9 : 1). Working up of the corresponding fractions and crystallisation from acetone gave 800 mg of the ester *III*, m.p. 171—172°C, $[\alpha]_D^{20}$ −2° (*c* 1·78). c) *From* IV *with diazomethane*: The acid *IV* (200 mg) in ether (10 ml) was treated with an excess of diazomethane in the same solvent at +3°C for 20 h. The excess diazomethane was destroyed with acetic acid, the reaction mixture diluted with ether and the solution was washed with dil. HCl, 5% Na_2CO_3, water, dried, and evaporated. The residue (210 mg) on crystallisation from acetone yielded 165 mg of the methyl ester *III*, m.p. 168—170°C, $[\alpha]_D^{20}$ −2° (*c* 1·32). d) *From* 3β-*acetoxy*-7aα-*bromo*-B-*homo*-5α-*cholestan*-7-*one* (II) *with potassium carbonate*: The bromo ketone[8] *II* (250 mg) in methanol (60 ml) was treated with a solution of K_2CO_3 (250 mg) in water (6 ml) and refluxed for 3 h. Methanol was distilled off, the product taken into ether and the ethereal solution was washed with a saturated ammonium sulphate solution, dried, and evaporated. The residue (180 mg) was chromatographed on silica gel (30 g) in light petroleum (b.p. 40—60°C)–ether (7 : 1). The corresponding fractions gave after working up and crystallisation from acetone 56 mg of the ester *III*, m.p. 167—169°C, $[\alpha]_D^{20}$ −4° (*c* 2·24).

3β-Hydroxy-5α-cholestane-7α-carboxylic Acid (*IV*)

Lithium iodide (800 mg) was added to a solution of the methyl ester *III* (400 mg) in *sym*-collidine (16 ml) and the reaction mixture was heated to 180–190°C for 4 h in a nitrogen atmosphere. The mixture was then poured into water, the product extracted with ether, and the ethereal solution was washed with 5% HCl, a $NaHCO_3$ solution, water, dried, and evaporated. The residue was chromatographed on silica gel (40 g) in benzene–ether (4 : 1). The corresponding fractions were combined, evaporated, and the residue (294 mg) was crystallised from acetone to yield 250 mg of the acid *IV*, m.p. 238–255°C (sublimation), $[\alpha]_D^{20}$ 0° (*c* 1·32; ethanol). IR (nujol): 3260, 2600, 1708, 1036 cm^{-1}. NMR (hexadeuteriodimethyl sulphoxide): 0·58 (s, 18-H), 0·72 (s, 19-H), 0·82 (d, J = 6 Hz, 26-H and 27-H), 0·85 (d, J = 6 Hz, 21-H), 4·37 (mt, 3α-H). For $C_{28}H_{48}O_3$ (443·7) calculated: 77·72% C, 11·18% H; found: 77·93% C, 11·20% H.

3β-Acetoxy-5α-cholestane-7α-carboxylic Acid (*V*)

The hydroxy acid *IV* (585 mg) in pyridine (5 ml) was treated with acetic anhydride (4 ml) and set aside at room temperature for 15 h. Water (7 ml) was then added and the reaction mixture was heated to 100°C for 2 h. The solution was diluted with water and the product extracted into ether. The ethereal solution was washed with 1M-HCl, with a dil. $NaHCO_3$, with a sat. $(NH_4)_2SO_4$, dried, and evaporated. Crystallisation from methanol–water gave 556 mg of the acetate *V*, m.p. 155–157°C, $[\alpha]_D^{20}$ −12° (*c* 1·13). IR: 3500–2500, 1735, 1702, 1246 cm^{-1}. NMR: 0·65 (s, 18-H), 0·84 (s, 19-H), 0·86 (d, J = 6 Hz, 26-H and 27-H), 0·90 (d, J = 6 Hz, 21-H), 2·00 (s, 3β-acetate), 2·68 (mt, $W_{1/2}$ = 8 Hz, 7β-H), 4·72 (broad mt, 3α-H). For $C_{30}H_{50}O_4$ (474·7) calculated: 75·90% C, 10·62% H; found: 75·38% C, 10·87% H.

Methyl 3β-Acetoxy-5α-cholestane-7α-carboxylate (*VI*)

The ester *III* (90 mg) was acetylated with acetic anhydride (5 ml) in pyridine (7 ml) for 20 h at room temperature. The reaction mixture was decomposed with ice and the product isolated with ether. The ethereal layer was washed with dil. HCl, a $NaHCO_3$ solution, water, dried, and evaporated. The residue on crystallisation from methanol yielded 75 mg of the acetate *VI*, m.p. 126–126·5°C, $[\alpha]_D^{20}$ −9·5° (*c* 0·56). IR: 1727, 1440, 1258, 1170, 1030 cm^{-1}. NMR: 0·63 (s, 18-H), 0·83 (s, 19-H), 0·86 (d, J = 6 Hz, 26-H and 27-H), 0·89 (d, J = 6 Hz, 21-H), 2·00 (s, 3β-acetate), 2·53 (mt, $W_{1/2}$ = 12 Hz, 7β-H), 3·64 (s, methyl ester), 4·65 (broad mt, 3α-H). For $C_{31}H_{52}O_4$ (488·7) calculated: 76·18% C, 10·73% H; found: 76·13% C, 10·47% H.

Methyl 3β-Hydroxy-5α-cholestane-7β-carboxylate (*VII*)

a) Further elution of the chromatography after preparation of the ester *III* under *a*) with the same solvent mixture afforded fractions containing the epimeric ester *VII*. Working up and crystallisation from acetone gave 490 mg of the ester *VII*, m.p. 174–176°C, $[\alpha]_D^{20}$ −15° (*c* 1·51). Mass spectrum: M^+ 446. IR: 3610, 1731, 1173 cm^{-1}. NMR: 0·68 (s, 18-H), 0·73 (s, 19-H), 0·83 (d, J = 6 Hz, 26-H and 27-H), 0·87 (d, J = 6 Hz, 21-H), 3·55 (mt, 3α-H), 3·63 (s, methyl ester). For $C_{29}H_{50}O_3$ (446·7) calculated: 77·97% C, 11·28% H; found: 78·01% C, 11·28% H. *b*) Continued elution of the chromatography after preparation of the ester *III* under *b*) with the same solvent mixture gave after working up and crystallisation from acetone 320 mg of the ester *VII*, m.p. 174–176°C, $[\alpha]_D^{20}$ −14° (*c* 1·60). *c*) Elution of the chromatography after preparation of the ester *III* under *d*) with the same solvent mixture afforded after working up and crystallisation from acetone 110 mg of the ester *VII*, m.p. 169–173°C, $[\alpha]_D^{20}$ −12·3°C (*c* 1·17).

3β-Hydroxy-5α-cholestane-7β-carboxylic Acid (*VIII*)

Lithium iodide (370 mg) was added to a solution of the ester *VII* (155 mg) in *sym*-collidine (8 ml) and heated to 170—180°C under nitrogen for 4 h. The reaction mixture was colled off, diluted with water, the product taken into ether, and the ethereal layer washed with 1% HCl, 5% $NaHCO_3$, water, dried, and evaporated. The residue on crystallisation from acetone gave 110 mg of the acid *VIII*, m.p. 252° (sublimation), $[\alpha]_D^{20}$ +31° (*c* 1·67); IR (nujol): 3500—2400, 1697, 1675, 1035 cm^{-1}. For $C_{28}H_{48}O_3$ (432·7) calculated: 77·72% C, 11·18% H; found: 77·81% C, 11·32% H.

3β-Acetoxy-5α-cholestane-7β-carboxylic Acid (*IX*)

The acid *VIII* (680 mg) was acetylated with acetic anhydride (4·5 ml) in pyridine (6 ml) for 16 h at room temperature. The reaction mixture was treated with water (10 ml) and heated to 100°C for 2 h. After cooling off to room temperature the reaction mixture was diluted with water, the product extracted with ether, and the ethereal solution was washed with 5% HCl, 5% $NaHCO_3$, water, dried, and evaporated. The residue (795 mg) was chromatographed on a silica gel column (75 g) in benzene–ether (33 : 1). The corresponding fractions were combined, evaporated, and the residue was crystallised from acetone to yield 555 mg of the acetate *IX*, m.p. 204—206°C, $[\alpha]_D^{20}$ +24·6° (*c* 1·41); IR (chloroform): 3400—2400, 1726, 1706, 1258, 1030 cm^{-1}; NMR: 0·69 (s, 18-H), 0·84 (d, J = 6 Hz, 26-H and 27-H), 0·88 (s, 19-H), 0·89 (d, J = 6 Hz, 21-H), 2·00 (s, 3β-acetate), 4·65 (broad mt, 3α-H). For $C_{30}H_{50}O_4$ (474·7) calculated: 75·90% C, 10·62% H; found: 75·85% C, 11·01% H.

Methyl 3β-Acetoxy-5α-cholestane-7β-carboxylate (*X*)

A solution of the acid *IX* (90 mg) in methanol (40 ml) was treated with diazomethane in ether (excess) for 20 hours. The solvents were removed *in vacuo* and the product crystallised from methanol to yield 65 mg of the ester *X*, m.p. 95—97°C, $[\alpha]_D^{20}$ +29·6° (*c* 1·05); IR: 1736, 1437, 1245, 1155, 1030 cm^{-1}; NMR: 0·69 (s, 18-H), 0·88 (s, 19-H), 0·86 (d, J = 6 Hz, 26-H and 27-H), 0·91 (d, J = 5·8 Hz, 21-H), 2·02 (s, 3β-acetate), 3·64 (s, methyl ester), 4·68 (broad mt, 3α-H). For $C_{31}H_{52}O_4$ (488·7) calculated: 76·18% C, 10·73% H; found: 76·03% C, 10·61% H.

3β-Acetoxy-5α-cholestane-6β-carboxylic Acid (*XI*)

a) The mother liquors after crystallisation of the ester *III* (2·68 g) were dissolved in *sym*-collidine (30 ml) and after addition of lithium iodide (5 g) heated to 170—180°C for 4 h. The reaction mixture was cooled off, diluted with water, and the product isolated with ether. The ethereal solution was washed with 1% HCl, 5% $NaHCO_3$, water, dried, and evaporated. The residue was acetylated with acetic anhydride (10 ml) in pyridine (15 ml) for 18 h at room temperature. The mixture was treated with water (18 ml) and heated to 100°C for 2 h. After cooling off and dilution with water the product was taken into ether, washed with 1% HCl and sat. $(NH_4)_2SO_4$, dried, and evaporated. The residue was chromatographed over silica gel (2·5 kg) in benzene–ether (99 : 1). Next to the acid *V* (1·64 g) 750 mg of the acid *XI* were isolated after crystallisation from methanol, m.p. 192—195°C, $[\alpha]_D^{20}$ −19° (*c* 0·97); IR: 3300—2500, 1732, 1700, 1248, 1030 cm^{-1}; NMR: 0·71 (s, 18-H), 0·86 (d, J = 6 Hz, 26-H and 27-H), 0·87 (s, 19-H), 0·90 (d, J = 6 Hz, 21-H), 2·51 (mt, $W_{1/2}$ = 12 Hz, 6α-H), 2·03 (s, 3β-acetate), 4·68 (broad mt, 3α-H). For $C_{30}H_{50}O_4$ (474·7) calculated: 75·90% C, 10·62% H; found: 75·83% C, 10·82% H. *b*) The mother liquors after crystallisation of the ester *VII* (1·2 g) were treated with lithium iodide (2·5 g) in *sym*-collidine (45 ml) as given under *a*). Similar working up left a residue which was acetylated with acetic anhydride (8 ml) in pyridine (10 ml). The acetylation mixture was worked up similarly to yield

1·3 g of a product which was chromatographed on a silica gel column (125 g) in benzene–ether (99 : 1). Working up and crystallisation from methanol gave 730 mg of the acid *IX* and 350 mg of the acid *XI*, m.p. 190—193°C, $[\alpha]_D^{20}$ —19° (*c* 1·41).

Methyl 3β-Acetoxy-5α-cholestane-6β-carboxylate (*XII*)

The acid *XI* (75 mg) in methanol (30 ml) was treated with excess diazomethane in ether and allowed to stand at room temperature for 18 h. The solvents were removed under reduced pressure and the residue crystallised from methanol to yield 55 mg of the ester *XII*, m.p. 183—184°C, $[\alpha]_D^{20}$ —29·2° (*c* 1·26); IR: 1730, 1240, 1171, 1030 cm^{-1}; NMR: 0·69 (s, 18-H), 0·78 (s, 19-H), 0·86 (d, J = 6 Hz, 26-H and 27-H), 0·90 (d, J = 6 Hz, 21-H), 2·46 (td, $W_{1/2}$ = 12 Hz, 6α-H), 3·67 (s, methyl ester), 4·68 (broad mt, 3α-H). For $C_{31}H_{52}O_4$ (488·7) calculated: 76·18% C, 10·73% H; found: 76·07% C, 10·73% H.

3β-Acetoxy-7α-acetyl-5α-cholestane (*XIII*)

The acid *V* (370 mg) in thionyl chloride (3·7 ml) was allowed to stand at 0°C for 3 days. The excess thionyl chloride was then removed by repeated distillation with benzene under reduced pressure. The residue was dissolved in benzene (10 ml) and added to a solution prepared from methylmagnesium bromide (400 mg) in ether (12 ml) and cadmium chloride (300 mg) by stirring for 1 h. The reaction mixture was stirred for 1 hour at room temperature, decomposed with ice and 1% hydrochloric acid, and the product was taken into ether. The ethereal layer was washed with 5% $NaHCO_3$, with a sat. $(NH_4)_2SO_4$, water, dried, and evaporated. The product (370 mg) was chromatographed on a silica gel column (37 g) in benzene–ether (9 : 1) to yield next to the starting material (204 mg) the ketone *XIII* (107 mg), m.p. 124—126°C (methanol), $[\alpha]_D^{20}$ +34·8° (*c* 1·82); IR: 1736, 1711, 1245, 1030 cm^{-1}; NMR: 0·62 (s, 18-H), 0·81 (s, 19-H), 0·85 (d, J = = 6·4 Hz, 26-H and 27-H), 0·88 (d, J = 5·6 Hz, 21-H), 1·98 and 2·10 (2s, 3β-acetate and 7α-acetyl), 2·76 (mt, $W_{1/2}$ = 13 Hz, 7β-H), 4·65 (broad mt, 3α-H). For $C_{31}H_{52}O_3$ (472·7) calculated: 78·76% C, 11·09% H; found: 78·72% C, 11·15% H.

3β-Acetoxy-7β-acetyl-5α-cholestane (*XIV*)

A solution of the acid *IX* (255 mg) in thionyl chloride (5 ml) was allowed to stand at 0°C for 24 h. After evaporation, the chloride was dissolved in benzene (10 ml) and added to a solution of dimethylcadmium prepared from methylmagnesium bromide (600 mg) and cadmium chloride (800 mg) in ether (18 ml). The reaction mixture was stirred at room temperature for 1 h, decomposed with ice and 1% HCl and the product isolated with ether. The residue after evaporation of the solvent (210 mg) was chromatographed over silica gel (22 g) in benzene–ether (25 : 1). Working up of the corresponding fractions and crystallisation from acetone afforded 120 mg of the ketone *XIV*, m.p. 135—138°C, $[\alpha]_D^{20}$ +28° (*c* 0·43); IR: 1735, 1715, 1243, 1030 cm^{-1}. For $C_{31}H_{52}O_3$ (442·7) calculated: 78·76% C, 11·09% H; found: 78·80% C, 11·12% H.

6β-Hydroxymethyl-5α-cholestan-3β-ol (*XV*)

a) *From methyl* 3β-*acetoxy*-5α-*cholestane*-6β-*carboxylate* (XII): The ester *XII* (40 mg) in tetrahydrofuran (15 ml) was added in a solution of lithiumaluminium hydride (200 mg) in tetrahydrofuran (35 ml) and refluxed for 5 h. The excess hydride was decomposed with ethyl acetate and water, and the product was isolated with ether. The ethereal layer was washed with 5% HCl, 5% $NaHCO_3$, a sat. $(NH_4)_2SO_4$, dried, and evaporated. The residue was chromatographed

on a silica gel plate (20 × 20 cm) in ether–acetone (9 : 1). The corresponding zone was worked up and the product crystallised from acetone to yield 20 mg of the diol *XV*, m.p. 224—226°C, $[\alpha]_D^{20}$ —8° (*c* 0·69) (literature[1] records m.p. 222—223°C, $[\alpha]_D^{20}$ —13°); IR: 3315, 1048, 1038 cm^{-1}; NMR (hexadeuteriodimethyl sulphoxide): 0·66 (s, 18-H), 0·75 (s, 19-H), 0·85 (d, *J* = 6 Hz, 26-H and 27-H), 0·89 (d, *J* = 6 Hz, 21-H), 2·8 and 3·3—3·8 (2 broad mt, 3α-H and 6β-methylene). For $C_{28}H_{50}O_2$ (418·6) calculated: 80·32% C, 12·04% H; found: 80·23% C, 12·19% H. b) *From 6-methylene-5α-cholestan-3β-ol* (XVI): A solution of the methylene derivative[2] *XVI* (570 mg) in ether (12 ml) containing boron trifluoride etherate (0·9 ml) was treated at 0°C with lithium aluminium hydride (190 mg) in ether (25 ml) and the reaction mixture was stirred for 2 h at the same temperature. The excess hydride was then decomposed with acetone (8·5 ml) and a sat. Na_2SO_4 and diluted with ether (10 ml). The organic layer was separated, dried, and ether distilled off. The residue was dissolved in tetrahydrofuran (22 ml), cooled to 0°C and treated with an alkaline hydrogen peroxide solution (30 ml) prepared from KOH (3 g), water (27 ml) and 30% H_2O_2 (18 ml). The reaction mixture was allowed to stand at 0°C for 1 h, diluted with water, the product extracted with chloroform, washed with 5% HCl, 5% $NaHCO_3$, water, dried, and chloroform distilled off. The residue (600 mg) was chromatographed on a silica gel column (60 g) in benzene–ether (3 : 2) to yield 300 mg of the starting material. Elution with ether–acetone (9 : 1) gave 150 mg of the diol *XV*, m.p. 224—225·5°C (acetone), $[\alpha]_D^{20}$ —7·6° (*c* 1·31).

7-Methylene-5α-cholestan-3β-ol (*XVIII*)

Lithium (1·8 g) was dissolved in bromobenzene (16 ml) and ether (500 ml) by stirring and refluxing for 6 h. The solution was then treated with triphenylmethylphosphonium iodide (46 g) and stirred at room temperature for 3 h. A solution of the ketone *XVII* (3·3 g) in dioxane (100 ml) and ether (100 ml) was then added drop by drop during 30 min and the reaction mixture was stirred at room temperature for 8 h. Dioxane was added (350 ml), the volatile components were distilled off at 80°C and the residue heated to 80°C for 8 h. The reaction mixture was diluted with water, the product extracted into chloroform, the extract was washed with 5% hydrochloric acid, 5% $NaHCO_3$, a sat. $(NH_4)_2SO_4$, water, dried, and evaporated. The residue was chromatographed over silica gel (200 g) in light petroleum (b.p. 40—60°C)–ether (4 : 1). Working up of the corresponding fractions and crystallisation from acetone gave 2·37 g of the alcohol *XVIII*, m.p. 118·5—119·5°C, $[\alpha]_D^{20}$ —42·8° (*c* 2·21); literature[9] records m.p. 115°C, $[\alpha]_D^{20}$ —31°; IR: 3610, 1643, 1085, 1030, 890 cm^{-1}; NMR: 0·68 (s, 18-H), 0·94 (s, 19-H), 0·87 (d, *J* = 6·2 Hz, 26-H and 27-H), 0·93 (d, *J* = 6 Hz, 21-H), 1·47 (s, 3β-OH), 3·58 (broad mt, 3α-H), 4·59 and 4·67 (two narrow mt, 7-methylene). For $C_{28}H_{48}O$ (400·7) calculated: 83·93% C, 12·08% H; found: 84·12% C, 12·31% H.

7α-Hydroxymethyl-5α-cholestan-3β-ol (*XIX*)

a) Elution of the chromatography after isolation of the 7β-epimer *XX* under *a*) with the same solvent mixture yielded fraction containing the 7α-epimer *XIX*. Working up and crystallisation from methanol afforded 560 mg of the alcohol *XIX*, m.p. 214—215°C, $[\alpha]_D^{20}$ —6·6° (*c* 0·85; methanol–chloroform 1 : 1); IR (nujol): 3250, 1058, 1033 cm^{-1}; NMR (hexadeuteriodimethyl sulphoxide): 0·62 (s, 18-H), 0·79 (s, 19-H), 0·84 (d, *J* = 6 Hz, 26-H and 27-H), 0·88 (d, *J* = 6 Hz, 21-H), 3·46 (broad mt, 3α-H), 3·58 (d, *J* = 6 Hz, 7α-CH_2—). For $C_{28}H_{50}O_2$ (418·6) calculated: 80·32% C, 12·04% H; found: 80·84% C, 11·98% H. *b*) A solution of the methyl ester *III* (150 mg) in tetrahydrofuran (15 ml) was added to a solution of lithiumaluminium hydride (450 mg) in tetrahydrofuran (20 ml) and refluxed for 90 min. The excess hydride was then decomposed with ethyl acetate, the reaction mixture was diluted with water, the ethereal layer was washed

with 5% HCl, 5% $NaHCO_3$, a sat. $(NH_4)_2SO_4$, dried, and evaporated. The residue on crystallisation from methanol gave 90 mg of the diol *XIX*, m.p. 214—215°C, $[\alpha]_D^{20}$ −4·3° (*c* 0·87; chloroform–methanol, 1 : 1).

7β-Hydroxymethyl-5α-cholestan-3β-ol (*XX*)

a) A solution of the alcohol *XVIII* (1 g) in ether (20 ml) containing boron trifluoride etherate (1·8 ml) was treated at −5°C with a solution of lithiumaluminium hydride (400 mg) in ether (35 ml). After stirring for 2 hours at 0°C the excess hydride was removed with acetone (14 ml), the reaction mixture was diluted with ether and treated with a sat. Na_2SO_4. The organic layer was separated, dried, and evaporated. The residue was dissolved in tetrahydrofuran (35 ml), and treated at 0°C with a solution of KOH (4·7 g) in water (48 ml) and 30% H_2O_2 (27 ml). After stirring at 0°C for 1 h the mixture was diluted with water, the product taken into ether and the ethereal solution was worked up and evaporated. The residue (1 g) was chromatographed on a silica gel column (100 g) in benzene–ether (1 : 1). The corresponding fractions were combined, evaporated, and the residue crystallised from methanol to give 240 mg of the diol *XX*, m.p. 183—183·5°C, $[\alpha]_D^{20}$ +56·3° (*c* 1·37; chloroform–methanol, 1 : 1); IR: 3370, 1048, 1030 cm^{-1}; NMR (hexadeuteriodimethyl sulphoxide): 0·66 (s, 18-H), 0·75 (s, 19-H), 0·85 (d, $J = 6·5$ Hz, 26-H and 27-H), 0·89 (d, $J = 6$ Hz, 21-H), 2·98 (t, CH_2—O<u>H</u>), 3·3—3·8 (group of mt, 3α-H and 7β-CH_2-). For $C_{28}H_{50}O_2$ (418·6) calculated: 80·32% C, 12·04% H; found: 80·61% C, 12·36% H. *b*) A solution of the ester *X* (135 mg) in tetrahydrofuran (10 ml) was added to a solution of lithiumaluminium hydride (400 mg) in tetrahydrofuran (10 ml) and refluxed for 3 h. The excess hydride was decomposed with wet ether and a sat. Na_2SO_4. Solid sodium sulphate was then added, ethereal layer separated and evaporated to dryness. The residue was chromatographed on a silica gel column (20 g) in benzene–methanol (25 : 1). Working up and crystallisation from acetone gave 80 mg of the diol *XX*, m.p. 182—183°C, $[\alpha]_D^{20}$ +58·4° (*c* 1·43; chloroform–methanol 1 : 1).

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