ACETOLYSIS OF 4β-METHANESULPHONYLOXY-6β,7aβ-CYCLO--B-HOMO-5α-CHOLESTANE*

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Synthesis of 4β-methanesulphonyloxy-6β,7aβ-cyclo-B-homo-5α-cholestane is described. During its acetolysis a kind of conjugative stabilization of the carbocation formed was observed. The mechanism of the reaction is discussed.

In some of our previous papers[1–4] we studied acetolyses of steroids carrying cyclopropane ring attached to the steroid skeleton. Our interest concentrated on such reactions in which the cyclopropane ring took part, especially reactions in which a carbocation is involved and undergoes stabilisation under participation with the cyclopropane ring. In some of those reactions the carbocation underwent conjugative stabilisation prior to the participation with the cyclopropane ring like for example in the 3-substituted 5,7-cyclocholestanes[3] whereas in the 3-substituted 5,7-cyclo--B-homocholestane series such stabilisation was not observed[1]. A closer study of reactions of this type was therefore of interest and we selected the mesylate *XXII* for our experiments. In this paper we describe the synthesis of this mesylate and its acetolysis.

To synthesise the olefin *XIX*, required for the subsequent Simmons–Smith methylenation, we started from the known[5] 4β-acetoxy-5-cholestene (*I*). Oxidation at $C_{(7)}$ to the ketone *II* was carried out by two methods: Either by oxidation with tert-butyl chromate directly to the desired ketone or by oxidation with N-bromosuccinimide in dioxane to a mixture of the ketone *II* and alcohol *V* which was converted to the ketone *II* by Jones' oxidation. Both routes afforded the ketone *II* in about 50% yield. Hydride reduction of the ketone *II* yielded an alcohol not identical with the product of the N-bromosuccinimide oxidation of the olefin *I*. Both alcohols afforded on oxidation the ketone *II*. Spectral evidence proves 7α-configuration of the hydroxyl in the product obtained on N-bromosuccinimide oxidation and 7β-configuration of the hydroxyl in the product obtained on reduction. Catalytic hydrogenation (ethyl acetate–ethanol, $Pd/CaCO_3$) of the double bond in the ketone *II* was accompanied

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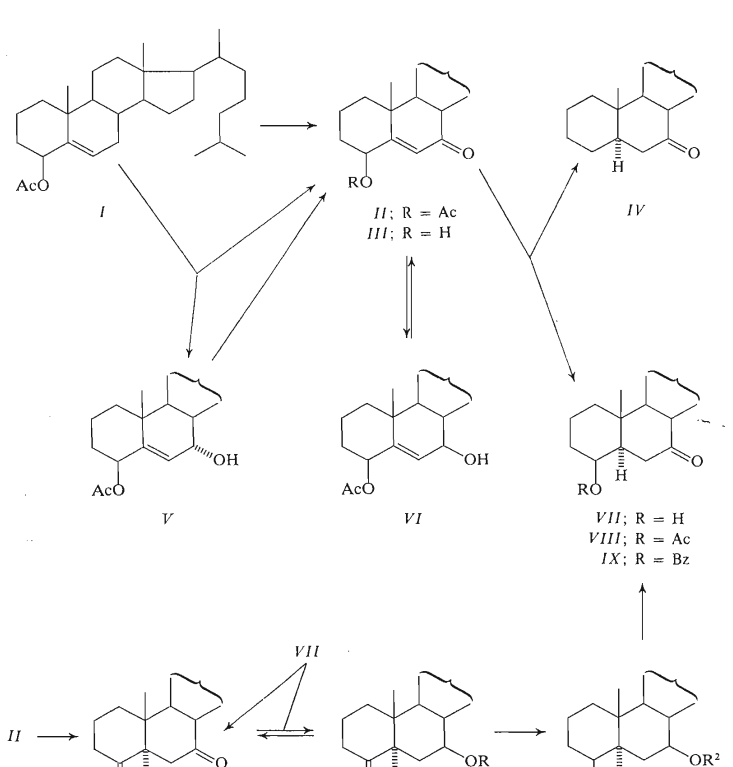
by hydrogenolysis of the 4β-acetoxy group and gave only about 20% of the desired saturated ketone *VIII*. The main product of the reaction was the ketone *IV* (50%) and the reaction mixture still contained the starting ketone *II*. Somewhat better yields were obtained on hydrogenation of the alcohol *III*. We therefore worked out an alternative route: The acetate *II* was transformed by treatment with alkali to the dione *X* which on metal hydride reduction afforded two hydroxy ketones: The already obtained derivative *VII* and the known[6] isomeric hydroxy ketone *XI*. This proves also 5α-configuration of our saturated compounds. The ketone *XI* could easily be transformed to the required 4β-hydroxy-7-oxo derivative *VII* by reduction of the acetate *XII* to the diol monoacetate *XIII* followed by benzoylation and partial hydrolysis of the diester *XIV* to the alcohol *XV* and oxidation to the ketone *IX*. Next step, bromination of the ketone *VIII*, was carried out with bromine in tetrachloromethane to yield the bromo ketone *XVI* as the sole product. Its structure follows from spectral evidence: Carbonyl maximum in IR is shifted by $+21\ cm^{-1}$ when compared with the parent ketone *VIII* which points to the equatorial 6α-configuration of the bromine atom. Metal hydride reduction led to a mixture of two bromohydrins. On the basis of the ^{1}H-NMR evidence the lipophilic main product is the *cis* bromohydrin *XVII* and the minor polar product is the *trans* derivative *XVIII*. Both bromohydrins afforded on oxidation the parent bromo ketone *XVI* and on reaction with zinc in ethanol the desired olefin *XIX*. This olefin was submitted to the Simmons–Smith methylenation to yield one single adduct- the 4β-acetoxy-6β,7aβ-cyclo-B-homo-5α-cholestane (*XX*) in about 12% yield. Configuration of the cyclopropane ring follows from the ^{1}H-NMR spectrum: Like in the 4β-acetoxy isomers[7], where the steric situation is analogous, we may expect a strong shielding effect on the $C_{(19)}$ protons in the 6α,7aα-cyclo derivative and a slight effect in the 6β,7aβ-isomer. Table I shows the chemical shifts of these protons in our cyclo derivatives and the corresponding parent compounds. As in our case the chemical shifts of the $C_{(19)}$ protons are not affected by addition of the cyclopropane ring we may

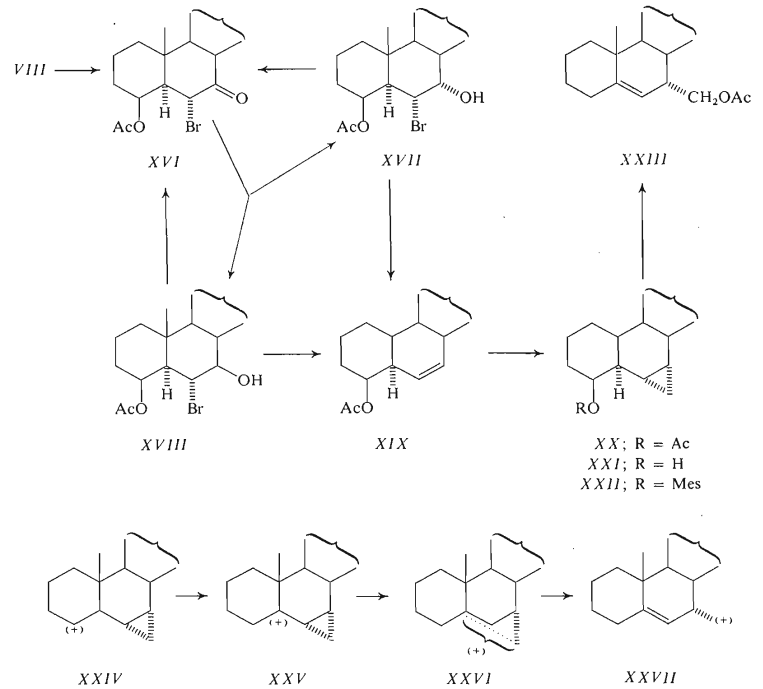
TABLE I
Chemical Shift Values for 19-Proton Signals

Compound	19-H
5α-Cholestan-3β-ol 3-acetate[10]	0·84
6β,7aβ-Cyclo-B-homo-5α-cholestan-3β-ol 3-acetate[7]	0·84
5α-Cholestan-4β-ol[11]	1·02
6β,7aβ-Cyclo-B-homo-5α-cholestan-4β-ol (*XXI*)	1·02

conclude that the adduct is the 6β,7aβ-isomer *XX*. Hydrolysis of the 4β-acetoxy group afforded the alcohol *XXI* which was transformed to the desired mesylate *XXII* on reaction with methanesulphonyl chloride in pyridine.

The acetolysis was carried out in acetic acid–acetic anhydride under the presence of sodium acetate and yielded smoothly (reflux 30 min) the acetoxymethyl derivative





XXIII as the only product. No elimination or simple S_N2 substitution were observed. In this case, therefore, again the conjugative stabilization of the carbocation originally formed at $C_{(4)}$ took place and we may explain formation of the product *XXXIII* by the pathway given by forms *XXIV*–*XXVII*.

EXPERIMENTAL

Melting points were determined on a Kofler block. Optical measurements were carried out in chloroform with an error of ±3°. CD spectra were recorded on Dichrograph II (Jouan Roussel) in chloroform. The infrared spectra were recorded on the Zeiss UR 20 spectrometer in tetrachlormethane. The ^{1}H-NMR spectra were recorded on the Tesla 60 MHz instrument in deuterio-

chloroform and corrected to tetramethylsilane (7·25 ppm) unless otherwise stated. The chemical shift is given in ppm. The mass spectra were recorded on the mass spectrometer AEI MS 902. The identity of samples prepared by different routes was checked by mixture melting point determination, by thin layer chromatography (TLC), and by infrared and ^{1}H-NMR spectra. Plates with 200 × 200 × 0·7 mm silica gel were used for preparative TLC. Usual working up of a solution implies washing the solution with 5% aqueous hydrochloric acid, water, 5% aqueous potassium hydrogen carbonate solution, water, drying with sodium sulphate or filtration through Whatman IPS paper and evaporation of the solvent *in vacuo*. Light petroleum refers to the fraction of b.p. 40—62°C.

4β-Hydroxy-5-cholesten-7-one 4-Acetate (*II*)

a) *From* 4β-*hydroxy*-5-*cholestene* 4-*acetate* (I) *with tert-butyl chromate*: A solution of the olefin[5] *I* (260 mg in tetrachloromethane (5 ml) was heated to 70°C and treated under stirring in a nitrogen atmosphere simultaneously with a solution of tert-butyl chromate and with a mixture of acetic acid (0·6 ml) and acetic anhydride (0·25 ml). The reaction mixture was kept under the same conditions for additional 4 h. After cooling off to room temperature a solution of oxalic acid (440 mg) in water (0·9 ml) and then solid oxalic acid (300 mg) were added and the mixture stirred at room temperature for 2 h. Water was then added and the product extracted into tetrachloromethane. The organic layer was washed with a potassium hydrogen carbonate solution, water, dried, and the solvent removed. The residue (250 mg) was purified by preparative TLC in ligroin–ether (9 : 1) to yield 141 mg of a product which was crystallised from methanol to yield 103 mg of the ketone *II*, m.p. 145—146°C, $[\alpha]_D^{20}$ —45 (*c* 1·24). IR spectrum: 1745, 1235, 1017 (acetate), 1682, 1637 cm^{-1} (C=C—C=O). Mass spectrum: M^+ 442. ^{1}H-NMR spectrum: 0·69 (s, 18-H), 0·87 (d, J = 6 Hz, 26-H and 27-H), 0·93 (d, J = 6 Hz, 21-H), 1·31 (s, 19, H), 2·02 (s, 4β-acetate), 5·41 (mt, $W_{1/2}$ = 6 Hz, 4α-H), 5·87(s, 6-H). For $C_{29}H_{46}O_3$(442·7) calculated: 78·68% C, 10·48% H; found: 78·61%C, 10·24% H.

b) *From* 4β-*hydroxy*-5-*cholestene* 4-*acetate* (I) *with* N-*bromosuccinimide*: A solution of the olefin *I* (1 g) in dioxan (100 ml) was treated with water (10 ml), N-bromosuccinimide (1 g), and calcium carbonate (1·2 g) and stirred in a nitrogen atmosphere at 20°C under illumination with a Nitraphot lamp (500 W) for 1 h. The solids were filtered off, the solution was treated with water and the product was extracted with ether. The ethereal solution was washed with water, dried, and ether removed. The residue was chromatographed on a silica gel column in ligroin–ether (33 : 1) to yield fractions with the lipophilic component. Working up gave 465 mg of a product which on crystallisation from methanol afforded 390 mg of the ketone *II*, m.p. 143—145°C, $[\alpha]_D^{20}$ —43° (*c* 1·14).

c) *From* 5-*cholesten*-4β,7α-*diol* 4-*monoacetate* (V): A solution of the alcohol *V* (30 mg) in acetone (5 ml) treated with excess Jones' reagent and allowed to stand at room temperature for 10 min. The excess reagent was removed with methanol, the mixture was diluted with water, and the product taken into ether. The ethereal solution was washed with a sodium hydrogen carbonate solution, water, dried, and ether was distilled off. The residue (30 mg) was crystallised from methanol to yield 12 mg of the ketone *II*, m.p. 142—145°C, $[\alpha]_D^{20}$ —41° (*c* 1·14).

d) *From* 5-*cholesten*-4β,7β-*diol* 4-*monoacetate* (VI): The alcohol *VI* (125 mg) in acetone (10 ml) oxidised with Jones' reagent as described in the foregoing experiment. Similar working up and crystallisation from methanol gave 81 mg of the ketone *II*, m.p. 144—146°C, $[\alpha]_D^{20}$ —44° (*c* 1·12).

4β-Hydroxy-5-cholesten-7-one (*III*)

The acetate *II* (100 mg) in methanol (8 ml) was treated with a solution of potassium carbonate (100 g) in water (1·5 ml) and allowed to stand at room temperature for 18 h. Methanol was distilled off under reduced pressure, the residue was diluted with water, and the product extracted with ethyl acetate. The extract was washed with water, dried, and solvent removed. The residue was purified by preparative TLC in ligroin–ether (3 : 1) to yield 70 mg of a product which after crystallisation from methanol afforded 43 mg of the ketone *III*, m.p. 166—170°C, $[\alpha]_D^{20}$ —45° (*c* 1·47). IR spectrum: 3620, 1005, 970 (hydroxyl), 1677, 1669, 1630 cm^{-1} (C=C—C=O). ^{1}H-NMR spectrum (100 MHz Varian instrument): 0·69 (s, 18-H), 0·86 (d, J = 6·5 Hz, 26-H and 27-H), 0·92 (d, J = 6 Hz, 21-H), 1·39 (s, 19-H), 4·31 (mt, $W_{1/2}$ = 7 Hz, 4α-H), 5·74 (s, 6-H). For $C_{27}H_{44}O_2$ (400·6) calculated: 80·94% C, 11·07% H; found: 80·22% C, 10·63% H.

5α-Cholestan-7-one (*IV*)

a) *From* 4β-*hydroxy-5-cholesten-7-one* 4-*acetate* (II) *on hydrogenation over* $Pd/CaCO_3$ *catalyst*: The olefin *II* (120 mg) in ethyl acetate (3 ml) and ethanol (3 ml) was hydrogenated over 5% $Pd/CaCO_3$ catalyst (50 mg) for 5 h. The catalyst was filtered off, washed with ether and the filtrate was evaporated. The residue contained next to the starting material two new products. The mixture was separated by preparative TLC in ligroin–ether (9 : 1) to yield 60 mg of the lipophilic product. Crystallisation from methanol afforded 45 mg of the ketone *IV*, m.p. 114—116°C, $[\alpha]_D^{20}$ —36° in accordance with the literature[8].

b) *From* 4β-*hydroxy-5-cholesten-7-one* 4-*acetate* (II) *on hydrogenation over Adams' catalyst*: The olefin *II* (35 mg) in ethanol (5 ml) was hydrogenated over Adams' catalyst (50 mg) for 30 min. Catalyst was filtered off, washed with ether, solvents were removed and the residue was separated by TLC as described above. Crystallisation of the lipophilic product from methanol gave 3 mg of the ketone *IV*, m.p. 112—115°C, $[\alpha]_D^{20}$ —38° (*c* 1·16).

c) *From* 4β-*hydroxy-5-cholesten-7-one* (III): The olefin *III* (30 mg) in ethanol (5 ml) was hydrogenated over 5% $Pd/CaCO_3$ catalyst for 40 min. The catalyst was filtered off, washed with ether, and the filtrate evaporated. The residue was purified by preparative TLC in ligroin–ether (4 : 1) to yield after working up 14 mg of a product which on crystallisation from methanol gave 6·5 mg of the ketone *IV*, m.p. 113—115°C, $[\alpha]_D^{20}$ —40° (*c* 1·12).

4-Cholesten-4β,7α-diol 4-Monoacetate (*V*)

Elution of the chromatography after isolation of the ketone *II* under *b*) with ligroin–ether (9 : 1) afforded fractions with the polar component. Working up and crystallisation from methanol yielded 85 mg of the alcohol *V*, m.p. 60—64°C, $[\alpha]_D^{20}$ —80° (*c* 1·68). IR spectrum: 3620 (hydroxyl), 1738, 1243, 1018 (acetate), 1685, 1665 cm^{-1} (double bond). ^{1}H-NMR spectrum (100 MHz Varian instrument): 0·68 (s, 18-H), 0·86 (d, J = 6 Hz, 26-H and 27-H), 0·93 (d, J = 6 Hz, 21-H), 1·11 (s, 19-H), 2·00 (s, acetate), 3·92 (mt, $W_{1/2}$ = 11 Hz, 7β-H), 5·36 (mt, $W_{1/2}$ = 7 Hz, 4α-H), 5·90 (d, J = 5 Hz, 6-H). For $C_{29}H_{48}O_3$ (444·7) calculated: 78·33% C, 10·88% H; found: 78·37% C, 10·74% H.

5-Cholesten-4β,7β-diol 4-Monoacetate (*VI*)

A solution of the ketone *II* (150 mg) in tetrahydrofuran (20 ml) was treated with lithium tri-tert-butoxyaluminium hydride (600 mg) and allowed to stand at room temperature for 2 h. The excess hydride was decomposed with 1% acetic acid, the mixture was diluted with water, and the product

taken into ether. The ethereal solution was washed with potassium hydrogen carbonate solution water, dried, and solvent removed. The residue was chromatographed over silica gel (10 g) in ligroin–ether (4 : 1). The corresponding fractions were combined, solvent removed, and the residue (111 mg) was crystallised from methanol to yield 65 mg of the monoacetate *VI*, m.p. 117—123°C, $[\alpha]_D^{20}$ —35° (*c* 1·79). IR spectrum: 3610 (hydroxyl), 1741, 1242, 1020 cm^{-1} (acetate). ^{1}H-NMR spectrum (100 MHz Varian instrument): 0·69 (s, 18-H), 0·86 (d, J = 6 Hz, 28-H and 27-H), 0·92 (d, J = 6 Hz, 21-H), 1·16 (s, 19-H), 2·00 (s, acetate), 3·34 (dd, J = 8 Hz, J = 2·5 Hz, 7α-H), 5·31 (mt, $W_{1/2}$ = 6·5 Hz, 4α-H), 5·63 (d, J = 2·5 Hz, 6-H). For $C_{29}H_{48}O_3$ (444·7) calculated: 78·33% C, 10·88% H; found: 77·65% C, 10·67% H.

4β-Hydroxy-5α-cholestan-7-one (*VII*)

a) *From* 4β-*hydroxy-5-cholesten-7-one* 4-*acetate* (II) *on hydrogenation over palladium catalyst*: Elution of the chromatography after isolation of the ketone *IV* under *a*) with the same solvent mixture afforded fractions with the polar compound. Working up and crystallisation from methanol yielded 6·6 mg of the alcohol *VII*, m.p. 148—149°C, $[\alpha]_D^{20}$ —23° (*c* 1·48). IR spectrum: 3635, 1001 (hydroxyl), 1710 cm^{-1} (carbonyl). ^{1}H-NMR spectrum (100 MHz Varian instrument): 0·66 (s, 18-H), 0·87 (d, J = 6 Hz, 26-H and 27-H), 0·91 (d, J = 6·5 Hz, 21-H), 1·30 (s, 19-H), 3·80 (mt, $W_{1/2}$ = 6 Hz, 4α-H). For $C_{27}H_{46}O_2$ (402·6) calculated: 80·54% C, 11·52% H; found: 80·31% C, 11·53% H.

b) *From* 4β-*hydroxy-5-cholesten-7-one* 4-*acetate* (II) *on hydrogenation over Adams' catalyst*: Elution of the chromatography after isolation of the ketone *IV* under *b*) with the same solvent mixture afforded fractions with the polar compound. Working up and evaporation of the solvents gave 3·4 mg of the alcohol *VII*, m.p. 146—147°C, $[\alpha]_D^{20}$ —20° (*c* 0·65).

c) *From* 5α-*cholestan*-4,7-*dione* (X): The ketone *X* (2 g) in tetrahydrofuran (50 ml) was treated at 0°C with lithium tri-tert-butoxyaluminiumhydride (2 g) and allowed to stand at the same temperature for 10 min. The mixture was diluted with water, acidified with acetic acid, and the product was isolated with ether. The ethereal solution was washed with sodium hydrogen carbonate, water, dried, and solvent removed. The residue was chromatographed on a silica gel column (120 g) in ligroin–ether (19 : 1). Fractions with the lipophilic component were combined, solvent removed, and the residue (679 mg) was crystallised from methanol afforded 450 mg of the ketone *VII*, m.p. 147—149°C, $[\alpha]_D^{20}$ —25° (*c* 1·19). Further elution afforded after working up of the fractions 140 mg of the starting dione *X*.

d) *From* 4β-*hydroxy*-5α-*cholestan*-7-*one* 4-*benzoate* (IX): The benzoate *IX* (50 mg) in methanol (10 ml) was refluxed with a solution of potassium hydroxide (200 mg) in methanol (4 ml) for 2 h. After cooling off the excess alkali was removed with acetic acid, and methanol distilled off under reduced pressure. The residue was diluted with water, the product taken into ether, and the ethereal extract was washed with a potassium hydrogen carbonate solution, water, dried, and ether removed. Crystallisation from methanol afforded 32 mg of the alcohol *VII*, m.p. 145—148°C, $[\alpha]_D^{20}$ —20° (*c* 1·15).

4β-Hydroxy-5α-cholestan-7-one 4-Acetate (*VIII*)

a) *From* 4β-*hydroxy-5-cholesten-7-one* 4-*acetate* (II): Elution of the chromatography after isolation of the ketone *IV* under *a*) with the same solvent mixture afforded fractions with the polar component. Working up and crystallisation from methanol gave 25 mg of the acetate *VIII*, m.p. 142—144°C, $[\alpha]_D^{20}$ —19° (*c* 0·88). IR spectrum: 1745, 1239, 1020 (acetate), 1711 cm^{-1} (carbonyl). ^{1}H-NMR spectrum (100 MHz Varian instrument): 0·65 (s, 18-H), 0·86 (d, J = 6·5 Hz,

26-H and 27-H), 0·905 (d, $J = 6$ Hz, 21-H), 1·26 (s, 19-H), 2·06 (s, acetate), 4·88 (mt, $W_{1/2} = 7$ Hz, 4α-H). For $C_{29}H_{48}O_3$ (444·7) calculated: 78·33% C, 10·88% H; found: 78·93% C, 10·64% H.

b) *From* 4β-*hydroxy*-5α-*cholestan*-7-*one* (VII): The alcohol *VII* (115 mg) in pyridine (5 ml) was acetylated with acetic anhydride (3 ml) at room temperature for 18 h. The mixture was decomposed with ice, the product extracted with ether, and the ethereal solution was worked up. The residue after evaporation of the solvent was crystallised from methanol to yield 80 mg of the acetate *VIII*, m.p. 144—145°C, $[\alpha]_D^{20}$ —23° (*c* 2·28).

4β-Hydroxy-5α-cholestan-7-one 4-Benzoate (*IX*)

The monobenzoate *XV* (50 mg) in acetone (20 ml) was treated at room temperature with excess Jones' reagent and allowed to stand for 5 min. The excess reagent was removed with methanol, the mixture was diluted with water, and the product taken into ethyl acetate. The extract was washed with a potassium hydrogen carbonate solution, water, dried, and solvent removed to yield 50 mg of a product which on crystallisation from methanol afforded 38 mg of the ketone *IX*, m.p. 134—136°C, $[\alpha]_D^{20}$ +30 (*c* 1·25). IR spectrum: 1 725, 1 270 (benzoate), 1 715 cm^{-1} (carbonyl). ^{1}H-NMR spectrum: 0·65 (s, 18-H), 0·85 (d, $J = 5·5$ Hz, 26-H and 27-H), 0·90 (d, $J = 5$ Hz, 21-H), 1·43 (s, 19-H), 5·15 (mt, $W_{1/2} = 5·5$ Hz, 4α-H), 7·38—8·17 (mt, benzoate). For $C_{34}H_{50}O_3$ (506·8) calculated: 80·58% C, 9·95% H; found: 80·60% C, 9·92% H.

5α-Cholestan-4,7-dione (*X*)

a) *From* 4β-*hydroxy*-5-*cholesten*-7-*one* 4-*acetate* (II): The acetate *II* (20 g) in methanol (1 000 ml) was refluxed with a solution of potassium hydroxide (20 g) in methanol (100 ml) for 10 min. Methanol was distilled off under reduced pressure, the residue was diluted with water, and the product extracted into ethyl acetate. The extract was washed with water, dried, and solvent removed to yield 18·5 g of a product which on crystallisation from methanol afforded 10·5 g of the dione *X*. Working up of the mother liquors afforded additional 6·9 g of the dione *X*, m.p. 147—149°C, $[\alpha]_D^{20}$ —23·5° (*c* 1·16). CD spectrum: $\Delta\varepsilon = -2·42$ (290 nm) in accordance with the literature[9]. IR spectrum: 1 720, 1 715 cm^{-1}. ^{1}H-NMR spectrum (100 MHz Varian instrument): 0·66 (s, 18-H), 0·87 (d, $J = 6·5$ Hz, 27-H and 27-H), 0·91 (d, $J = 6$ Hz, 21-H), 1·01 (s, 19-H). For $C_{27}H_{44}O_2$ (400·6) calculated: 80·94% C, 11·07% H; found: 80·97% C, 11·09% H.

b) *From* 4β-*hydroxy*-5α-*cholestan*-7-*one* (VII): The alcohol *VII* (420 mg) in acetone (50 ml) was oxidised with excess Jones' reagent for 10 min at room temperature. Methanol was added to remove the excess agent, the mixture was treated with water, and the product taken into ethyl acetate. Working up and crystallisation from methanol yielded 260 mg of the dione *X*, m.p. 146—148°C, $[\alpha]_D^{20}$ —20° (*c* 1·15).

c) *From* 7β-*hydroxy*-5α-*cholestan*-4-*one* (XI): The alcohol *XI* (100 mg) was oxidised with Jones' reagent in acetone (5 ml) as described in the previous experiment. Similar working up and crystallisation from methanol afforded 70 mg of the dione *X*, m.p. 142—144°C, $[\alpha]_D^{20}$ —21° (*c* 1·19).

7β-Hydroxy-5α-cholestan-4-one (*XI*)

Elution of the chromatography after isolation of the ketone *VII* under *c*) with the same solvent mixture afforded fractions with the polar compound. Combination and evaporation left 1 060 mg of a residue which on crystallisation from methanol gave 770 mg of the hydroxy ketone *XI*,

m.p. 151—153°C (recrystallisation at 136—147°C), $[\alpha]_D^{20}$ +57° (*c* 2·03) in accordance with the literature[6]. IR spectrum: 3655, 3625, 1080, 1075 (hydroxyl), 1713, 1698 cm^{-1} (carbonyl). ^{1}H-NMR spectrum: 0·68 (s, 18-H), 0·87 (d, J = 6 Hz, 26-H and 27-H), 0·77 (s, 19-H), 0·92 (d, J = 4·5 Hz, 21-H), 2·10 (s, hydroxyl), 3·32 (mt, $W_{1/2}$ = 26 Hz, 7α-H). For $C_{27}H_{46}O_2$ (402·6) calculated: 80·54% C, 11·52% H; found: 80·63% C, 11·11% H.

7β-Hydroxy-5α-cholestan-4-one 7-Acetone (*XII*)

The alcohol *XI* (200 mg) in pyridine (1 ml) was acetylated with acetic anhydride (0·5 ml) for 18 h at room temperature. The mixture was decomposed with water and ice, the product taken into ethyl acetate, and the extract was worked up. The crude product obtained after evaporation of the solvent (220 mg) was chromatographed on a silica gel column (20 g) in ligroin–ether (9 : 1). The corresponding fractions were combined, solvents distilled off, and the residue (165 mg) was crystallised from methanol to yield 116 mg of the acetate *XII*, m.p. 101—102°C, $[\alpha]_D^{20}$ +66° (*c* 1·44) in accordance with the literature[6]. IR spectrum: 1732, 1244, 1033, 1028 (acetate), 1720 cm^{-1} (carbonyl). ^{1}H-NMR spectrum: 0·68 (s, 18-H), 0·77 (s, 19-H), 0·85 (d, J = 5·5 Hz, 26-H and 27-H), 0·90 (d, J = 5 Hz, 21-H), 1·98 (s, acetate), 4·45 (mt, $W_{1/2}$ = 22 Hz, 7α-H). For $C_{29}H_{48}O_3$ (444·7) calculated: 78·33% C, 10·88% H; found: 78·64% C, 10·76% H.

5α-Cholestan-4β,7β-diol 7-Monoacetate (*XIII*)

The ketone *XII* (400 mg) in tetrahydrofuran (8 ml) was treated at room temperature with solid lithium tri-tert-butoxyaluminiumhydride (800 mg) and allowed to stand 15 min. The mixture was then poured into 1% acetic acid, the product taken into ethyl acetate, and the organic layer was worked up. The residue after evaporation of the solvents (400 mg) was crystallised from methanol to yield 278 mg of the alcohol *XIII*, m.p. 97—100°C, $[\alpha]_D^{20}$ —54° (*c* 1·77). IR spectrum: 3630 (hydroxyl), 1723, 1248, 1026 cm^{-1} (acetate). ^{1}H-NMR spectrum: 0·67 (s, 18-H), 0·85 (d, J = 5·7 Hz, 26-H and 27-H), 0·89 (d, J = 5 Hz, 21-H), 1·06 (s, 19-H), 2·00 (s, acetate), 3·47 (s, hydroxyl), 3·78 (mt, $W_{1/2}$ = 8 Hz, 4α-H), 4·58 (mt, $W_{1/2}$ = 20 Hz, 7α-H). For $C_{29}H_{50}O_3$ (446·7) calculated: 77·98% C, 11·28% H; found: 77·72% C, 11·35% H.

5α-Cholestan-4β,7β-diol 4-Benzoate 7-Acetate (*XIV*)

The alcohol *XIII* (310 mg) in pyridine (4 ml) was treated with benzoyl chloride (1·2 ml) and allowed to stand at room temperature for 18 h. The mixture was decomposed with ice and water, the product taken into ethyl acetate, and the excess was worked up as usual. The oily residue (380 mg) was crystallised from methanol to yield 290 mg of the benzoate *XIV*, m.p. 186—187°C, $[\alpha]_D^{20}$ +115° (*c* 2·32). IR spectrum: 1732, 1256, 1028 (acetate), 1723, 1270 cm^{-1} (benzoate). ^{1}H-NMR spectrum: 0·68 (s, 18-H), 0·85 (d, J = 5·5 Hz, 26-H and 27-H), 0·90 (d, J = 5 Hz, 21-H), 1·22 (s, 19-H), 1·94 (s, acetate), 4·62 (mt, $W_{1/2}$ = 27 Hz, 7α-H), 5·15 (mt, $W_{1/2}$ = 6 Hz, 4α-H), 7·36—7·60 and 7·92—8·13 (two mt, benzoate). For $C_{26}H_{54}O_4$ (550·8) calculated: 78·50% C, 9·88% H; found: 78·49% C, 7·78% H.

5α-Cholestan-4β,7β-diol 4-Monobenzoate (*XV*)

A solution of the diester *XIV* (200 mg) in chloroform (1·5 ml) was treated with a solution of conc. hydrochloric acid (0·3 ml) in methanol (15 ml) and allowed to stand at 36°C for 9 days. Solvents were removed under reduced pressure, the residue was diluted with water, and the product taken into ethyl acetate. The organic solution was washed with saturated sodium hydrogen

carbonate solution, water, dried, and solvent distilled off. The residue was purified by preparative TLC in ligroin–ether (3 : 1) to yield 72 mg of the starting diester and after crystallisation from methanol 110 mg of the benzoate *XV*, m.p. 205—207°C, $[\alpha]_D^{20}$ +83° (*c* 0·67). IR spectrum: 3 545 (hydroxyl), 1 720, 1 709, 1 271 cm^{-1} (benzoate). ^{1}H-NMR spectrum: 0·68 (s, 18-H), 0·86 (d, J = 5·5 Hz, 26-H and 27-H), 0·91 (d, J = 5 Hz, 21-H), 1·20 (s, 19-H), 3·36 (mt, $W_{1/2}$ = 20 Hz, 7α-H), 5·16 (mt, $W_{1/2}$ = 7 Hz, 4α-H), 7·27—8·17 (mt, benzoate). For $C_{34}H_{52}O_3$ (508·8) calculated: 80·26% C, 10·30% H; found: 80·16% C, 10·33% H.

4β-Hydroxy-6α-bromo-5α-cholestan-7-one 4-Acetate (*XVI*)

a) *From* 4β-*hydroxy*-5α-*cholestan*-7-*one* 4-*acetate* (VIII): The ketone *VIII* (4·4 g) in tetrachloromethane (30 ml) was treated with a solution of bromine (2·7 g) in the same solvent (15 ml) and allowed to stand at room temperature for 30 min. The mixture was diluted with water, the organic layer was separated and washed successively with water, a sodium thiosulphate solution, a potassium hydrogen carbonate solution, water, and dried over sodium sulphate. The solvent was removed and the residue (4·8 g) was chromatographed on a silica gel column (500 g) in ligroin–ether (19 : 1). Working up of the corresponding fractions afforded a product (4·12 g) which was crystallised from methanol to yield 2·95 g of the bromo ketone *XVI*, m.p. 173—176°C, $[\alpha]_D^{20}$ +12° (*c* 0·84). IR spectrum: 1·748, 1 241, 1 235 (acetate), 1 732 cm^{-1} (carbonyl). ^{1}H-NMR spectrum (100 MHz Varian instrument): 0·67 (s, 18-H), 0·87 (d, J = 6 Hz, 26-H and 27-H), 0·915 (d, J = 6-Hz, 21-H), 1·34 (s, 19-H), 2·07 (s, acetate), 4·84 (d, J = 13 Hz, 6β-H), 5·35 (mt, $W_{1/2}$ = 7 Hz, 4α-H). For $C_{29}H_{47}BrO_3$ (523·6) calculated: 66·52% C, 9·04% H, 15·26% Br; found: 66·28% C, 9·18% H, 15·12% Br.

b) *From* 6α-*bromo*-5α-*cholestan*-4β,7α-*diol* 4-*acetate* (XVII): The bromohydrin *XVII* (150 mg) in acetone (10 ml) was treated with excess Jones' reagent and allowed to stand at room temperature for 5 min. Methanol was added to destroy the oxidising agent, the mixture was diluted with water and the product taken into ethyl acetate. The organic layer was washed with a potassium hydrogen carbonate solution, water, dried, and the solvent was distilled off. The residue was crystallised from methanol to yield 104 mg of the bromo ketone *XVI*, m.p. 173—175°C, $[\alpha]_D^{20}$ +14° (*c* 1·12).

c) *From* 6α-*bromo*-5α-*cholestan*-4β,7β-*diol* 4-*acetate* (XVIII): The bromohydrin *XVIII* (25 mg) in acetone (5 ml) was oxidised with Jones' reagent as described in the foregoing experiment. Similar working up gave 22 mg of a product which was purified by preparative TLC in ligroin–ether (3 : 1). Working up of the corresponding zones afforded 18·5 mg of a residue which on crystallisation from methanol yielded 6·5 mg of the bromo ketone *XVI*, m.p. 172—175°C, $[\alpha]_D^{20}$ +11° (*c* 1·16).

6α-Bromo-5α-cholestan-4β,6α-diol 4-Acetate (*XVII*)

The bromo ketone *XVI* (120 mg) in ethanol (20 ml) was treated at room temperature with sodium borohydride (240 mg) and allowed to stand for 1 h. The mixture was poured in water, acidified with 1% hydrochloric acid, and the product taken into ethyl acetate. Working up of the organic layer gave 110 mg of a product containing according to the TLC two products. Separation by preparative TLC in ligroin–ether (2 : 1) afforded the lipophilic component which on crystallisation from methanol gave 65 mg of the bromohydrin *XVII*, m.p. 164—166°C, $[\alpha]_D^{20}$ +49° (*c* 1·36). IR spectrum: 3 580 (hydroxyl), 1 744, 1 249, 1 233, 1 021 cm^{-1} (acetate). ^{1}H-NMR spectrum (100 MHz Varian instrument): 0·65 (s, 18-H), 0·87 (d, J = 6·5 Hz, 26-H and 27-H), 0·90 (d, J = 6 Hz, 21-H), 1·07 (s, 19-H), 2·05 (s, acetate), 3·95 (mt, $W_{1/2}$ = 5 Hz, 7β-H), 4·54 (dd,

J = 2 Hz, J' = 12 Hz, 6β-H), 5·24 (mt, $W_{1/2}$ = 7 Hz, 4α-H). For $C_{29}H_{49}BrO_3$ (525·6) calculated: 66·27% C, 9·40% H, 15·09% Br; found: 66·25% C, 8·99% H, 15·40% Br.

6α-Bromo-5α-cholestan-4β,7β-diol 4-Acetate (*XVIII*)

Working up of the corresponding zones from the preparative TLC of the foregoing experiment afforded the polar product which after crystallisation from methanol gave 15 mg of the bromohydrin *XVIII*, m.p. 143—146°C, $[\alpha]_D^{20}$ +49° (*c* 1·88). IR spectrum: 3585 (hydroxyl), 1744, 1257, 1228, 1021 cm^{-1} (acetate). ^{1}H-NMR spectrum (100 MHz Varian instrument): 0·69 (s, 18-H), 0·86 (d, J = 6 Hz, 27-H and 27-H), 0·90 (d, J = 6 Hz, 21-H), 1·04 (s, 19-H), 2·03 (s, acetate), 3·46 (dd, J = 9 Hz, J' = 9 Hz, 7α-H), 4·24 (dd, J = 9 Hz, J' = 12 Hz, 6β-H), 5·39 (mt, $W_{1/2}$ = = 8 Hz, 4α-H). For $C_{29}H_{49}BrO_3$ (525·6) calculated: 66·27% C, 9·40% H, 15·09% Br; found: 66·15% C, 9·46% H, 15·33% Br.

4β-Hydroxy-5α-cholest-6-ene 4-Acetate (*XIX*)

a) *From* 6α-*bromo*-5α-*cholestan*-4β,7α-*diol* 4-*acetate* (XVII): A solution of the bromohydrin *XVII* (150 mg) in acetic acid (10 ml) was refluxed with zinc dust (300 mg) for 3 h. The metal was filtered off, the filtrate was diluted with water, and the product extracted into ethyl acetate. The organic layer was worked up as usual and solvent removed. The residue (135 mg) was crystallised from methanol to yield 75 mg of the olefin *XIX*, m.p. 95—100°C. $[\alpha]_D^{20}$ —101° (*c* 0·79). IR spectrum: 3020, 1645 (double bond), 1740, 1245, 1235 cm^{-1} (acetate). ^{1}H-NMR spectrum: 0·68 (s, 18-H), 0·85 (d, J = 5·5 Hz, 26-H and 27-H), 0·90 (d, J = 5 Hz, 21-H), 0·94 (s, 19-H), 5·12 (mt, $W_{1/2}$ = 5 Hz, 4α-H), 5·46 (mt, $W_{1/2}$ = 4·5 Hz, 6-H and 7-H). For $C_{29}H_{48}O_2$ (428·7) calculated: 81·25% C, 11·29% H; found: 81·32% C, 11·23% H.

b) *From* 6α-*bromo*-5α-*cholestan*-4β,7β-*diol* 4-*acetate* (XVIII): The bromohydrin *XVIII* (116 mg) in acetic acid (10 ml) was treated with zinc dust (232 mg) as described in the previous experiment. Similar working up afforded 90 mg of the crude product which on crystallisation from methanol gave 48 mg of the olefin *XIX*, m.p. 95—100°C, $[\alpha]_D^{20}$ —96° (*c* 1·16).

6β,7aβ-Cyclo-B-homo-5α-cholestan-4β-ol 4-Acetate (*XX*)

The Zn–Cu couple (0·7%) was prepared by adding zinc dust (5·2 g) into a solution of cupric acetate monohydrate (120 mg) in acetic acid (10 ml) at 50—60°C and shaking until the solution decolorised. The metal was decanted with eight portions of ether (10 ml each.) The couple was transferred to an autoclave, a solution of the olefin *XX* (1·5 g) in ether (25 ml) and diiodomethane (4·6 ml) were added and heated to 100°C for 7 h. After cooling off to room temperature the liquid portion was separated, the solids were decanted with ether, the washings combined with the liquid portion and poured into 5% potassium hydrogen carbonate solution. The ethereal layer was washed with water, 5% hydrochloric acid, 5% potassium hydrogen carbonate, water, 10% sodium thiosulphate solution, water, dried, and solvent removed. The residue was chromatographed over silica gel (20 g) in ligroin–ether (19 : 1). Fractions containing the starting olefin and the desired product (identical polarity on TLC) were combined and solvents removed to yield 850 mg of an oil. It was dissolved in ether (50 ml) and treated with a solution of perphthalic acid (850 mg) in ether (6 ml). After 18 h at room temperature the excess peracid was removed by extraction with potassium carbonate solution. The ethereal solution was washed with water, dried, and solvent distilled off. The residue was chromatographed on a silica gel column (50 g) in ligroin–ether (9 : 1). Fractions containing the lipophilic component were combined, solvents removed and the residue (240 mg) was crystallised from methanol to yield 105 mg of the cyclo

derivative *XX*. The mother liquors afforded additional 87 mg of the adduct, m.p. 108—109°C, $[\alpha]_D^{20}$ —71° (*c* 0·93). IR spectrum: 3065 (cyclopropane), 1738, 1250, 1237 cm^{-1} (acetate), ^{1}H-NMR spectrum: —0·22 to +0·11 (mt, cyclopropane protons), 0·725 (s, 18-H), 0·885 (d, J = 5·5 Hz, 26-H and 27-H), 0·985 (s, 19-H), 2·08 (s, acetate), 5·19 (mt, $W_{1/2}$ = 6·5 Hz, 4α-H). For $C_{30}H_{50}O_2$ (442·7) calculated: 81·39% C, 11·38% H; found: 81·89% C, 11·47% H.

6β,7aβ-Cyclo-B-homo-5α-cholestan-4β-ol (*XXI*)

The acetate *XX* (250 mg) in methanol (100 ml) was refluxed with a solution of potassium hydroxide (250 mg) in methanol (5 ml) for 2 h. Methanol was distilled off under reduced pressure, the residue was treated with water, and the product taken into ethyl acetate. The organic extract was washed with water, dried, and solvent removed. The residue was chromatographed over silica gel (50 mg) in ligroin–ether (19 : 1). Working up of the corresponding fractions gave 195 mg of a crude product which on crystallisation from methanol afforded 155 mg of the alcohol *XXI*, m.p. 70—72°C, $[\alpha]_D^{20}$ —33° (*c* 1·72). IR spectrum: 3630, 1000, 970 (hydroxyl), 3060 cm^{-1} (cyclopropane). ^{1}H-NMR spectrum: —0·22 to +0·10 (mt, cyclopropane protons), 0·72 (s, 18-H), 0·88 (d, J = 6 Hz, 26-H and 27-H), 0·91 (d, J = 4·5 Hz, 21-H), 1·02 (s, 19-H), 21·8 (s, hydroxyl), 4·09 (mt, $W_{1/2}$ = 8 Hz, 4α-H). For $C_{27}H_{48}O$ (386·6) calculated: 83·87% C, 11·99% H; found: 83·76% C, 11·84% H.

6β,7aβ-Cyclo-B-homo-5α-cholestan-4β-ol 4-Methanesulphonate (*XXII*)

The alcohol *XXI* (170 mg) in pyridine (3·4 ml) was treated at 0°C with methanesulphonyl chloride (0·34 ml) and allowed to stand at the same temperature for 14 h. The mixture was decomposed with ice, diluted with water, and the product taken into ethyl acetate. Usual working up afforded 150 mg of the oily mesylate *XXII* pure on TLC. $[\alpha]_D^{20}$ —10·8° (*c* 1·94). IR spectrum: 3070 (cyclopropane), 1343, 1179 cm^{-1} (mesylate). ^{1}H-NMR spectrum: 0·70 (s, 18-H), 0·86 (d, J = 6 Hz, 26-H and 27-H), 0·92 (d, J = 5 Hz, 21-H), 0·93 (s, 19-H), 3·00 (s, mesylate), 5·05 (mt, $W_{1/2}$ = = 5·5 Hz, 4-proton).

7α-Acetoxymethyl-5-cholestene (*XXIII*)

The mesylate *XXII* (150 mg) in acetic acid (3·75 ml) and acetic anhydride (0·38 ml) was refluxed with anhydrous sodium acetate (150 mg) for 30 min. The mixture was poured in water and the product extracted into ether. The ethereal solution was washed with water, a sodium hydrogen carbonate solution, water, dried, and solvent distilled off. The residue was purified by preparative TLC in ligroin–ether (2 : 1) to yield after working up of the corresponding zones 61 mg of the olefin *XXIII* which resisted all attempts at crystallisation. $[\alpha]_D^{20}$ —105° (*c* 1·49). IR spectrum: 1742, 1245, 1232 (acetate), 1669 cm^{-1} (double bond). ^{1}H-NMR spectrum: 0·64 (s, 18-H), 0·84 (d, J = 5·5 Hz, 26-H and 27-H), 0·89 (d, J = 5 Hz, 21-H), 0·98 (s, 19-H), 2·02 (s, acetate), 3·82 (dd, J = 8 Hz, J' = 10·5 Hz) and 4·26 (dd, J = 5 Hz, J' = 10·5 Hz) (AB system, $—CH_2—O$), 5·33 (d, J = 4·5 Hz, 6-H), decoupling experiment (irrad. at 2·28 ppm): 3·82 and 4·22 (two d, J = 11 Hz, $—CH_2—O$), 5·33 (s, 6-H). For $C_{30}H_{50}O_2$ (442·7) calculated: 81·32% C, 11·38% H; found: 81·42% C, 11·61% H.

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REFERENCES

1. Kohout L., Fajkoš J.: This Journal *38*, 913 (1973).
2. Kohout L., Fajkoš J.: This Journal *39*, 1601 (1974).
3. Fajkoš J., Joska J., Šorm F.: This Journal *33*, 3324 (1968).
4. Fajkoš J., Joska J.: This Journal *37*, 3483 (1972).
5. Jones D. N., Lewis J. R., Shoppee C. W., Summers G. H. R.: J. Chem. Soc. *1955*, 2876.
6. Davies A. R., Summers G. H. R.: J. Chem. Soc. C *1967*, 1227.
7. Kohout L., Fajkoš J.: This Journal *40*, 3924 (1975).
8. Barton D. H. R., Robinson C. H.: J. Chem. Soc. *1954*, 3045.
9. Snatzke G., Kinsky K.: Tetrahedron *28*, 295 (1972).
10. Malinowski E. R., Manhas M. S., Müller G. H., Bose A. K.: Tetrahedron Lett. *1963*, 1161.
11. Shoppee C. W., Lack R. E., Sharma S. C.: J. Chem. Soc. C, *1968*, 2083.

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