ACETOLYSES OF THE EPIMERIC 4-METHANESULPHONYLOXY-5,7β-CYCLO-B-HOMO-5β-CHOLESTANES*

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Acetolyses of $C_{(4)}$ epimeric methanesulphonates of the 5,7β-cyclo-B-homocholestane series have been studied and the structure of the products established by chemical and spectral means.

In our previous papers[1-3] we studied the solvolyses of methanesulphonyloxy derivatives of cyclosteroids derived from normal as well as from B-homosteroid skeleton and proposed mechanism involved in these reactions. For further informations the solvolytic studies of the 4-methanesulphonyloxy derivatives of the B-homoseries were desirable. In this paper we describe the synthesis of the $C_{(4)}$ epimeric methanesulphonates of the 5,7β-cyclo-B-homo-5β-cholestane series and their behaviour under acetolytic conditions.

We set out from 5,7β-cyclo-B-homo-5β-cholestan-4-one[4] (*I*) which on reduction with lithium tri-tert-butoxyaluminium hydride in tetrahydrofuran afforded two epimeric alcohols. The more lipophilic main product was identical with the 4α-epimer *V* the synthesis of which we have recently[4] described; the minor product must therefore be the 4β-hydroxy derivative *II*. Its oxidation yielded the starting ketone *I*. Both alcohols were transformed to the corresponding acetates *III* and *VI* with acetic anhydride in pyridine and to the methyl ethers *IV* and *VII* with diazomethane under catalysis of aluminium chloride. The desired methanesulphonates were obtained by standard procedure with methanesulphonyl chloride in pyridine. Whereas the 4α-alcohol *V* gave a stable and well characterised methanesulphonate *VIII*, the epimeric methanesulphonate derived from the 4β-alcohol *II* proved unstable under purification experiments. Therefore the solvolysis was carried out with the crude unpurified product of esterification as the thin layer chromatography showed reasonably high content of the methanesulphonate.

When the two epimeric methanesulphonates were submited to the acetolytic conditions (glycial acetic acid, acetic anhydride, and sodium acetate) the same

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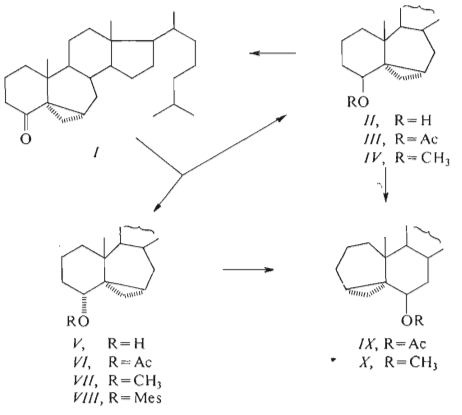
compound was obtained from both reactions in high yield. It contained acetoxy group and the cyclopropane ring but was not identical with any of the acetates *III* or *VI*. Spectral evidence pointed to the structure *IX* for this compound and we therefore synthesised authentic 6β-acetoxy-4β,5-cyclo-A-homo-5β-cholestane (*IX*) for comparison.



The olefin *XIX* desired for the final step – Simmons-Smith methylenation – was prepared from cholesterol (*XI*) in eight steps without isolation of the intermediates. Peracid oxidation gave a mixture of epoxides *XII* which was transformed to the mixture of toluenesulphonates *XIII*. Cleavage of the epoxide ring with perchloric acid in acetone yielded the diol *XIV* which on reaction with *sym*-collidine followed by catalytic hydrogenation afforded the saturated diol *XVI*. It was oxidised with N-bromosuccinimide to the hydroxy ketone *XVII*, the hydroxyl group was eliminated with thionyl chloride in pyridine and the resulting unsaturated ketone *XVIII* was reduced with lithiumaluminium hydride in ether to yield 4-cholesten-6β-ol (*XIX*) in an overall yield of 32%. Simmons–Smith methylenation led to a mixture of two adducts contaminated with the starting olefin *XIX*. It was oxidised with peracid to make the separation of the starting material easier then separated by column chromatography to yield 24% of the 4β,5-cyclo derivative *XXI* and 28% of the 4α-epimer *XXIV*. The configurations were assigned on the basis of the NMR spectra and by analogy with the 3-hydroxylated series[5] (Table I).

The alcohol *XXI* was oxidised by Jones' reagent to the ketone *XXVII* which on metal hydride reduction gave both at $C_{(6)}$ epimeric alcohols *XX* and *XXI* the 6α-

-epimer *XXI* being the main product. The alcohol *XXIV* when treated similarly afforded the ketone *XXVIII* and its reduction led exclusively to the starting 6α-hydroxy derivative *XXIV*; the 6β-epimer was not detected. The alcohols *XX*, *XXI*, and *XXIV* were transformed to their acetates *IX*, *XXII*, and *XXV* and the acetate *IX* prepared

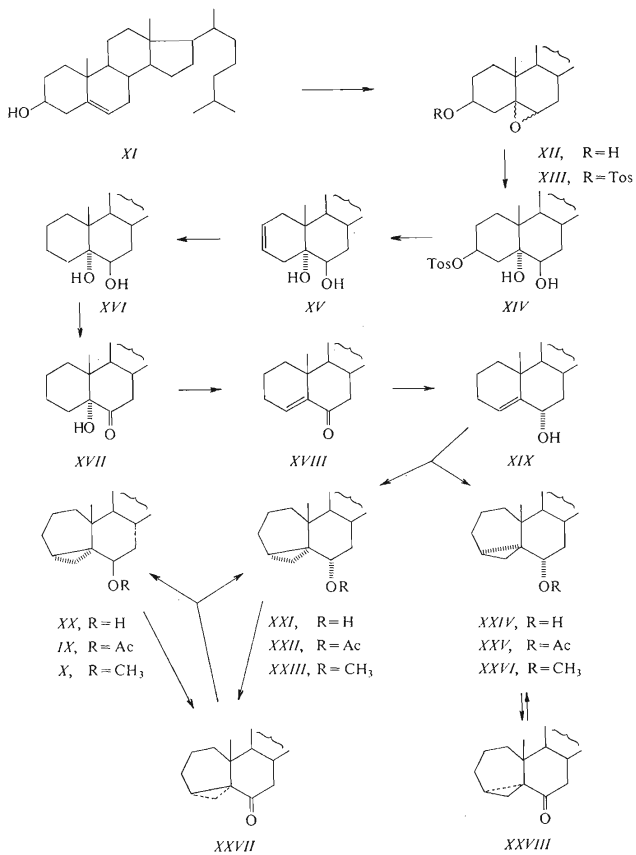


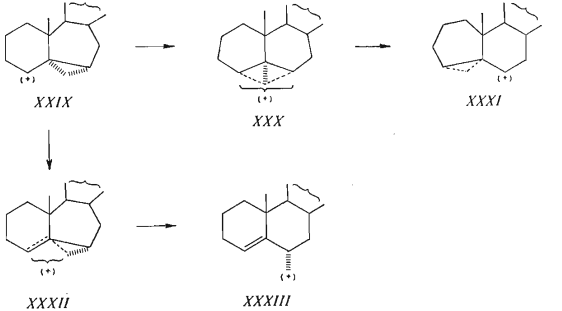
TABLE I

19-Proton Signals in NMR Spectra of the Cyclohomocholestanols (in p.p.m.)

Compound	19-H	Δ
5α-Cholestan-3α-ol[7]	0·77	0
5,7α-Cyclo-B-homo-5α-cholestan-3α-ol[5]	0·82	+0·05
5,7β-Cyclo-B-homo-5β-cholestan-3α-ol[5]	1·05	+0·28
5α-Cholestan-6α-ol[8]	0.78	0
4α,5-Cyclo-A-homo-5α-cholestan-6α-ol (*XXIV*)	0.92	+0·14
4β,5-Cyclo-A-homo-5β-cholestan-6α-ol (*XXI*)	1·04	+0·26

from the 6β-hydroxy derivative of the 4β,5-cyclo series was identical with the acetate obtained on acetolyses of the methanesulphonates derived from the alcohols *II* and *V* respectively. This product is therefore 6β-acetoxy-4β,5-cyclo-A-homo-5β-cholestane (*IX*). Analogous type of reaction was observed when the methanesulphonate *VIII* was dissolved in methanol. After 1 hour at room temperature the ester was completely converted to a methyl ether identical with the methyl ether *X* prepared from the A-homo-6β-hydroxy derivative *XX*.

A comparison of these results with our previous studies on similar topic may be of interest. In the 5β,7β-cyclocholestane series the solvolyses of the 3-substituted methanesulphonates[2] afforded either the 3α-,6α-endomethylene compound, if the stereochemistry was favourable (3β-methanesulphonate), or, in the case of the



3α-methanesulphonyloxy derivative the cation originally formed at $C_{(3)}$ underwent conjugative stabilisation to analogue of *XXIX*. Its subsequent rearrangement may be presented by mechanism analogous to *XXIX* – *XXXII* – *XXXIII* as the product is the corresponding 4,5-unsaturated 6α-acetoxymethyl-B-nor derivative. This was later[3] confirmed when identical B-nor compound was obtained exclusively on acetolysis of 4α-methanesulphonyloxy-5,7β-cyclo-5β-cholestane.

In the 5β,7β-cyclo-B-homo series the situation seems to be different. We have not observed[1] on acetolysis of any of the 3-epimeric methanesulphonates products which would have been expected if the original cation underwent conjugative stabilisation to *XXIX*. In order to gain information about the behaviour of the cation *XXIX* under acetolytic conditions it was therefore necessary to generate it from a 4-substituted compound. Our experimental results show that the participation of the cyclopropane ring proceeds rather through intermediates *XXX* and *XXXI* than through *XXXII* and *XXXIII* as we would expect by analogy with the normal steroid series.

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 with an error of ±1°. The infrared spectra were recorded on the Zeiss UR 10 spectrometer in tetrachloromethane unless otherwise stated. The NMR spectra were recorded on the Varian HA-100 instrument in chloroform and corrected to tetramethylsilane (7·25 p.p.m.) unless otherwise stated. The chemical shift is given in p.p.m. The identity of samples prepared by different routes was checked by mixture melting point determination, by thin-layer chromatography, and by infrared spectra. Ligroin of b.p. 40–60°C was used as solvent. Working up of an ethereal solution means extraction with 5% hydrochloric acid, water, 5% sodium hydrogen carbonate solution, water, drying with magnesium sulphate, and evaporation of the solvent.

5,7β-Cyclo-B-homo-5β-cholestan-4-one (*I*)

The alcohol *II* (25 mg) in acetone (2 ml) was treated with excess Jones' reagent and allowed to stand 5 minutes at room temperature. The excess oxidising agent was removed with methanol (1 ml), the reaction 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 evaporated. The crude product (25 mg) afforded on crystallisation from methanol 11 mg of the ketone *I*, m.p. 118–120°C, $[\alpha]_{20}$ −91° (*c* 1·16), identical with the authentic sample[4].

5,7β-Cyclo-B-homo-5β-cholestan-4β-ol (*II*)

a) *From* 5,7β-*cyclo*-B-*homo*-5β-*cholestan*-4-*one* (I): Elution of the chromatography after isolation of the alcohol *V* under *a*) gave 170 mg of the polar product which on crystallisation from methanol yielded 122 mg of the 4β-hydroxy derivative *II*, m.p. 131–133°C, $[\alpha]_D^{20}$ −37·5° (*c* 0·64). IR: 3610 (hydroxyl), 3060 (cyclopropane) cm^{-1}. NMR: 0·00 (q, one cyclopropane proton), 0·45 (t, one cyclopropane proton), 0·61 (s, 18-H), 0·86 (d, $J = 6$ Hz, 26-H and 27-H), 0·88 (d,

J = 6 Hz, 21-H), 1·28 (s, 19-H), 2·88 (t, J = 3 Hz, 4α-H). For $C_{28}H_{48}O$ (400·7) calculated: 83·93% C, 12·08% H; found: 84·06% C, 12·11% H.

b) *From* 4β-*acetoxy*-5,7β-*cyclo*-B-*homo*-5β-*cholestane* (III): The acetate *III* (85 mg) in methanol (8·5 ml) was treated with a solution of potassium carbonate (100 mg) in water (1·5 ml) and refluxed for 2 hours. The solvent was distilled off under reduced pressure, the product was taken into ether, the ethereal layer was washed with water, dried, and evaporated. The residue on crystallisation from methanol gave 45 mg of the alcohol *II*, m.p. 131—133°C, $[\alpha]_D^{20}$ −35·9° (*c* 1·12).

4β-Acetoxy-5,7β-cyclo-B-homo-5β-cholestane (*III*)

The alcohol *II* (30 mg) in pyridine (1 ml) was acetylated with acetic anhydride (0·6 ml) at room temperature for 24 hours. The reaction mixture was decomposed with ice, the product was extracted with ether, and the solution was worked up. The residue was crystallised from methanol to yield 21 mg of the acetate *III*, m.p. 124—126°C, $[\alpha]_D^{20}$ −61.9° (*c* 0·61). IR: 3065 (cyclopropane), 1730, 1248, 1020 (acetate) cm^{-1}. NMR: 0·12 (dd, J = 4·5 Hz, J' = 9 Hz, one cyclopropane proton), 0·48 (t, J = 4·5 Hz, one cyclopropane proton), 0·70 (s, 18-H), 0·84 (d, J = 6 Hz, 26-H and 27-H), 0·87 (d, J = 6 Hz, 21-H), 1·19 (s, 19-H), 2·03 (s, 4β-acetate), 4·04 (t, J = 3 Hz, 4α-H). For $C_{30}H_{50}O_2$ (442·7) calculated: 81·39% C, 11·38% H; found: 81·53% C, 11·41% H.

4β-Methoxy-5,7β-cyclo-B-homo-5β-cholestane (*IV*)

Diazomethane (150 mg) in ether (8·5 ml) was added to a solution of the alcohol *II* (32 mg) in ether (10 ml) and treated with small portions of aluminium chloride (50 mg). After 4 hours at room temperature the reaction mixture was decomposed with water, the product isolated with ether, and the ethereal solution was worked up. The residue (30 mg) was chromatographed on one plate of silica gel (20 × 20 cm) in ligroin–ether (19 : 1). The corresponding zone was separated, the product eluted with ether, and ether distilled off. The residue (28 mg) was crystallised from methanol to yield 14·5 mg of the methyl ether *IV*, m.p. 93·5—95°C, $[\alpha]_D^{20}$ −28·4° (*c* 0·99). IR: 3070 (cyclopropane), 1104 (methyl ether) cm^{-1}. NMR: −0·16 (dd, J = 4·5 Hz, J' = 9 Hz, one cyclopropane proton), 0·35 (t, J = 4·5 Hz, one cyclopropane proton), 0·60 (s, 18-H), 0·85 (d, J = 6 Hz, 26-H and 27-H), 0·87 (d, J = 6 Hz, 21-H), 1·25 (s, 19-H), 2·38 (t, J = 3 Hz, 4α-H), 3·31 (s, 4β-methyl ether). For $C_{29}H_{50}O$ (414·7) calculated: 84·00% C, 12·16% H; found: 83·95% C, 12·16% H.

5,7β-Cyclo-B-homo-5β-cholestan-4α-ol (*V*)

a) *From* 5,7β-*cyclo*-B-*homo*-5β-*cholestan*-4-*one* (I): The ketone *I* (1 g) in tetrahydrofuran (80 ml) was treated with solid lithium tri-tert-butoxyaluminium hydride (2 g) and allowed to stand at room temperature for 2 hours. The excess hydride was decomposed with water and hydrochloric acid, the product taken into ether, and the ethereal solution was washed with a sodium hydrogen carbonate solution, water, dried, and evaporated. The residue (900 mg) was chromatographed over silica gel (250 g) in ligroin–chloroform (4 : 1). Working up of the corresponding fractions and crystallisation from acetone yielded 310 mg of the alcohol *V*, m.p. 143—146°C, $[\alpha]_D^{20}$ −48·9° (*c* 1·19), identical with the authentic sample[4].

b) *From* 4α-*acetoxy*-5,7β-*cyclo*-B-*homo*-5β-*cholestane* (VI): The acetate *VI* (65 mg) in methanol (10 ml) was treated with a solution of potassium carbonate (100 mg) in water (1·7 ml) and refluxed for 2 hours. Methanol was distilled off under reduced pressure, the product extracted with ether, the solution was washed with water, dried, and evaporated. The residue on crystallisation from

methanol afforded 30 mg of the alcohol *V*, m.p. 142—146°C, $[\alpha]_D^{20}$ −47·9° (*c* 0·73), identical with the autentic sample[4].

4α-Acetoxy-5,7β-cyclo-B-homo-5β-cholestane (*VI*)

The alcohol *V* (200 mg) in pyridine (1 ml) was acetylated with acetic anhydride (0·6 ml) at room temperature for 20 hours. The reaction mixture was decomposed with ice, the product taken into ether, and worked up. The residue was crystallised from methanol to yield 135 mg of the acetate *VI*, m.p. 104—106°C, $[\alpha]_D^{20}$ −27·0° (*c* 1·42). IR: 3065, 3005 (cyclopropane), 1735, 1251, 1240, 1030 cm^{-1} (acetate). NMR: 0·20 (t, $J = 5$ Hz, one cyclopropane proton), 0·50 (dd, $J = 5$ Hz, $J' = 9$ Hz, one cyclopropane proton), 0·70 (s, 18-H), 0·84 (d, $J = 6$ Hz, 26-H and 27-H), 0·87 (d, $J = 6$ Hz, 21-H), 1·10 (s, 19DH), 1·92 (s, 4α-acetate), 5·23 (dd, 4α-H). For $C_{30}H_{50}O_2$(442·7) calculated: 81.39% C, 11·38% H; found: 81·01% C, 11·21% H.

4α-Methoxy-5,7β-cyclo-B-homo-5β-cholestane (*VII*)

Diazomethane (450 mg) in ether (25 ml) was added to a solution of the alcohol *V* (150 mg) in ether (15 ml) and treated within 3 hours with small portions of aluminium chloride (90 mg). The reaction mixture was then poured into water, the product extracted into ether, and the ethereal solution was worked up. The residue (158 mg) was chromatographed on 3 plates of silica gel (20 × 20 cm) in ligroin–ether (4 : 1). The corresponding zones were collected, the product eluted with ether, and worked up. The residue (116 mg) was crystallised from methanol to yield 70 mg of the methyl ether *VII*, m.p. 97—98°C, $[\alpha]_D^{20}$ −41·2° (*c* 0·58). IR: 3075 (cyclopropane), 1121, 1097 (methyl ether) cm^{-1}. NMR: 0·11 (t, $J = 4·5$ Hz, one cyclopropane proton), 0·44 (dd, $J = 9$ Hz, $J' = 4·5$ Hz, one cyclopropane proton), 0·60 (s, 18-H), 0·85 (d, $J = 6$ Hz, 26-H and 27-H), 0·87 (d, $J = 6$ Hz, 21-H), 1·05 (s, 19-H), 3·23 (s, 4α-methyl ether), 3·43 (dd, $J = 11·5$ Hz, $J' = 3·5$ Hz, 4β-H). For $C_{29}H_{50}O$ (414·7) calculated: 84·00% C, 12·16% H; found: 83·91% C, 12·14% H.

4α-Methanesulphonyloxy-5,7β-cyclo-B-homo-5β-cholestane (*VIII*)

A solution of the alcohol *V* (790 mg) in pyridine (12 ml) was treated at +5°C with methanesulphonyl chloride and allowed to stand at the same temperature for 18 hours. The reaction mixture was decomposed with ice and water, the product extracted with ether, and the ethereal solution was worked up. The residue (820 mg) was crystallised from n-heptane to yield 420 mg of the methanesulphonate *VIII*, m.p. 89—91°C, $[\alpha]_D^{20}$ −42·6° (*c* 0·72). IR: 3070 (cyclopropane), 1348, 1180 (mesylate) cm^{-1}. NMR: (deuteriochloroform with tetramethylsilane as internal reference; 80 MHz-Tesla instrument): 0·30 (t, $J = 5$ Hz, one cyclopropane proton), 0·60 (s, 18-H), 0·85 (d, $J = 6$ Hz, 26-H and 27-H), 0·89 (d, $J = 6$ Hz, 21-H), 1·10 (s. 19-H), 2·95 (s, 4α-methanesulphonate), 3·01 (mt, 4β-H). For $C_{30}H_{50}O_3S$ (524·7) calculated: 73·43% C, 10·27% H, 6·52% S; found: 73·50% C, 10·31% H, 6·40% S.

6β-Acetoxy-4β,5-cyclo-A-homo-5β-cholestane (*IX*)

a) *From* 4β,5-*cyclo*-A-*homo*-5β-*cholestan*-6β-*ol* (XX): The alcohol *XX* (30 mg) in pyridine (1 ml) was acetylated with acetic anhydride (0·6 ml) at room temperature for 18 hours. There action mixture was decomposed with ice, the product was isolated with ether, and worked up. The residue (32 mg) was crystallised from methanol to yield 24 mg of the acetate *IX*, m.p. 65—68°C, $[\alpha]_D^{20}$ +22·3° (*c* 0·92). IR: 3075 (cyclopropane), 1734, 1249, 1025 (acetate) cm^{-1}. NMR: 0·14 (dd, $J = 9$ Hz, $J' = 4·5$ Hz, one cyclopropane proton), 0·50 (t, $J = 4·5$ Hz, one cyclopropane proton),

0·70 (s, 18-H), 0·85 (d, $J = 6$ Hz, 26-H and 27-H), 0·90 (d, $J = 6$ Hz, 21-H), 1·18 (s, 19-H), 2·04 (s, 6β-acetate), 4·11 (t, $J = 3$ Hz, 6α-H). For $C_{30}H_{50}O_2$ (442·7) calculated: 81·39% C, 11·38% H; found: 81·60% C, 11·41% H.

b) *From* 4α-*methanesulphonyloxy*-5,7β-*cyclo*-B-*homo*-5β-*cholestane* (VIII): A stirred mixture of the methanesulphonate *VIII* (100 mg) and anhydrous sodium acetate (300 mg) was treated with acetic acid (10 ml) and acetic anhydride (1 ml) and stirring was continued for 2 hours at room temperature. The reaction mixture was poured into water, the product isolated with ether, the ethereal solution was washed with water, a sodium hydrogen carbonate solution, water, dried, and evaporated. The residue (85 mg) was chromatographed on two plates of silica gel (20 × 20 cm) in ligroin–ether (2 : 1). The corresponding zones were collected, the product eluted with ether, and worked up. The residue (73 mg) was crystallised from methanol to yield 56 mg of the acetate *IX*, m.p. 64—67°C, $[\alpha]_D^{20}$ +22° (*c* 0·87).

c) *From* 5,7β-*cyclo*-B-*homo*-5β-*cholestan*-4β-*ol* (II): The alcohol *II* (125 mg) in pyridine (3 ml) was treated at +5°C with methanesulphonyl chloride (0·3 ml) and allowed to stand at the same temperature for 20 minutes. The reaction mixture was decomposed with ice, the product isolated with ether and worked up. The solvent was removed at room temperature, and the residue (70 mg) was mixed with anhydrous sodium acetate (210 mg), treated with acetic acid (7 ml) and acetic anhydride (0·7 ml), and stirred at room temperature for 1 hour. The reaction mixture was diluted with water, the product taken into ether, and the solution was washed with water, a sodium hydrogen carbonate solution, water, dried, and the solvent distilled off. The residue (55 mg) was chromatographed on two plates of silica gel (20 × 20 cm) in ligroin–ether (9 : 1). Working up of the corresponding zones and crystallisation from methanol gave 23 mg of the acetate *IX*, m.p. 63 to 67°C, $[\alpha]_D^{20}$ +19° (*c* 1·14).

6β-Methoxy-4β,5-cyclo-A-homo-5β-cholestane (*X*)

a) *From* 4β,5-*cyclo*-A-*homo*-5β-*cholestan*-6β-*ol* (XX): Diazomethane (600 mg) in ether (24 ml) was added to a solution of the alcohol *X* (100 mg) in ether (10 ml) and treated with aluminium chloride (40 mg) in small portions within 4 hours. The reaction mixture was decomposed with ice and water, the product extracted with ether, and worked up. The residue (90 mg) was chromatographed on silica gel (10 g) in ligroin–ether (99 : 1). Working up of the corresponding fractions, and crystallisation from methanol yielded 45 mg of the methyl ether *X*, m.p. 97—98°C, $[\alpha]_D^{20}$ +17·5° (*c* 1·96). IR: 3065 (cyclopropane), 1103 (methyl ether) cm^{-1}. NMR: (deuteriochloroform with tetramethylsilane as internal reference): 0·68 (s, 18-H), 0·86 (d, $J = 6$ Hz, 26-H and 27-H), 0·90 (d, $J = 6$ Hz, 21-H), 1·22 (s, 19-H), 2·40 (t, $J = 3$ Hz, 6α-H), 3·32 (s, 6β-methyl ether). For $C_{29}H_{50}O$ (414·7) calculated: 84·00% C, 12·16% H; found: 83·97% C, 12·13% H.

b) *From* 4α-*methanesulphonyloxy*-5,7β-*cyclo*-B-*homo*-5β-*cholestane* (VIII): The methanesulphonate *VIII* (100 mg) in methanol (10 ml) was agitated at room temperature for 1 hour. The resulting solution was diluted with water, the product taken into ether, the ethereal solution was washed with water, dried, and ether distilled off. The residue (90 mg) was crystallised from methanol to yield 70 mg of the methyl ether *X*, m.p. 96—98°C, $[\alpha]_D^{20}$ +16° (*c* 1·21).

4-Cholesten-6α-ol (*XIX*)

Cholesterol (*XI*; 100 g) in ether (700 ml) was treated with a solution of perphthalic acid (70 g) in ether (500 ml) and allowed to stand at room temperature for 20 hours. The reaction mixture was poured into water, the excess peracid was extracted with a sodium carbonate solution, the ethereal solution was washed with water, dried, and the solvent distilled off. The residue was dried azeotro-

pically with benzene, the residue (110 mg) was dissolved in pyridine (1000 ml), treated with triethylamine (165 ml) and *p*-toluenesulphonyl chloride (220 g) and allowed to stand at room temperature for 20 hours. The reaction mixture was decomposed with ice and water, the product was isolated with ether, and worked up. The residue (170 g) was dissolved in acetone (3·5 l), treated with 5% perchloric acid (550 ml), and after 20 hours at room temperature about 2/3 of the solvent were distilled off under reduced pressure. The residue was poured into water, and the product isolated with ether, and worked up. The crude diol *XIV* (150 g) was dissolved in *sym*-collidine (700 ml) and refluxed for 1 hour. The raction mixture was then cooled to room temperature, poured into water, and the product extracted into ether. Working up and evaporation of the solvent left 100 g of the olefin *XV* which was dissolved in ethyl acetate (500 ml) and hydrogenated over Adams' catalyst (5 g) until the theoretical amount of hydrogen had been taken up (2 hours). The catalyst was filtered off, washed with ether, and the solvents were distilled off. The diol *XVI* (100 g) was dissolved in ether (2·3 l), treated with methanol (426 ml), water (387 ml) and N-bromosuccinimide (72·4 g), and stirred at room temperature for 1 hour. The reaction mixture was diluted with water, the product taken into ether, the ethereal solution was washed with a sodium hydrogen carbonate solution, water, dried, and solvent distilled off. The hydroxyketone *XVII* (100 g) was dissolved in pyridine (1·5 l), cooled to 0°C, and treated with thionyl chloride (100 ml). After 30 minutes at +5°C the reaction mixture was decomposed with ice and water, the product isolated with ether, and worked up. The residue (80 g) was chromatographed on a silica gel column (800 g) ligroin–ether (19 : 1). Fractions with the unsaturated ketone *XVIII* were combined and evaporated to yield 60 g of the product which was dissolved in ether (600 ml) and treated with a solution of lithium aluminium hydride (60 g) in ether (600 ml) and allowed to stand at room temperature for 15 minutes. The excess hydride was removed with ethyl acetate, the solution diluted with water, washed with hydrochloric acid, water, a sodium hydrogen carbonate solution, water, dried, and evaporated. The product (59 g) was chromatographed on a silica gel column (3 kg) in ligroin–ether (9 : 1). The corresponding fractions were combined and evaporated to yield 39 g of a product which on crystallisation from acetone afforded 32 g of the alcohol *XIX*, m.p. 140—142°C, $[\alpha]_D^{20}$ +61·7° (*c* 1·17), in agreement with the literature[6].

4β,5-Cyclo-A-homo-5β-cholestan-6β-ol (*XX*)

Elution of the chromatography after preparation of the alcohol *XXI* under *b*) afforded fractions with the polar component. Combination, evaporation, and crystallisation from methanol yielded 183 mg of the alcohol *XX*, m.p. 104—106°C, $[\alpha]_D^{20}$ +33° (*c* 0·91). IR: 3625, 1041, 1015 (hydroxyl), 3075 (cyclopropane) cm^{-1}. NMR: 0·01 (dd, $J = 9$ Hz, $J' = 4·5$ Hz, one cyclopropane proton), 0·70 (s, 18-H), 0·86 (d, $J = 6$ Hz, 26-H and 27-H), 0·90 (d, $J = 6$ Hz, 21-H), 1·26 (s, 19-H), 2·91 (t, $J = 3$ Hz, 6α-H). For $C_{28}H_{48}O$ (400·7) calculated: 83·93% C, 12·08% H; found: 84·12% C, 12·07% H.

4β,5-Cyclo-A-homo-5β-cholestan-6α-ol (*XXI*)

a) *From 4-cholesten-6α-ol* (XIX): Elution of the chromatography after isolation of the 4α-alcohol *XXIV* under *a*) and working up of the corresponding fractions afforded 780 mg of the polar product which on crystallisation from methanol yielded 610 mg of the alcohol *XXI*, m.p. 124 to 127°C, $[\alpha]_D^{20}$ +49·4° (*c* 0·56). IR: 3620, 1015 (hydroxyl), 3065 (cyclopropane) cm^{-1}. NMR: 0·16 (t, $J = 4·5$ Hz, one cyclopropane proton), 0·43 dd, $J = 4·5$ Hz, $J' = 9$ Hz, one cyclopropane proton), 0·65 (s, 18-H), 0·84 (d, $J = 6$ Hz, 26-H and 27-H), 0·88 (d, $J = 6$ Hz, 21-H), 1·04 (s, 19-H), 3·95 (dd, $J = 11$ Hz, $J' = 4$ Hz, 6β-H). For $C_{28}H_{48}O$ (400·7) calculated: 83·93% C, 12·08% H; found: 83·84% C, 12·11% H.

b) *From* 4β,5-*cyclo*-A-*homo*-5β-*cholestan*-6-*one* (XXVII): A solution of the ketone *XXVII* (800 mg) in tetrahydrofuran (80 ml) was treated with lithium tri-tert-butoxyaluminium hydride (3·2 g). After 2 hours at room temperature the mixture was poured into water, acidified with hydrochloric acid, and the product isolated with ether. The ethereal solution was worked up to yield 800 mg of a mixture which was chromatographed over silica gel (100 g) in ligroin–ether (49 : 1). Working up of the corresponding fractions and crystallisation of the product (475 mg) from methanol afforded 300 mg of the alcohol *XXI*, m.p. 124—127°C, $[\alpha]_D^{20}$ +47° (*c* 1·54).

6α-Acetoxy-4β,5-cyclo-A-homo-5β-cholestane (*XXII*)

The alcohol *XXI* (230 mg) was acetylated in pyridine (1 ml) with acetic anhydride (0·6 ml) at room temperature for 18 hours. The reaction mixture was decomposed with ice and water, the product taken into ether, and worked up. The residue (240 mg) on crystallisation from methanol yielded 135 mg of the acetate *XXII*, m.p. 130—131°C, $[\alpha]_D^{20}$ +13·4° (*c* 0·67). IR: 3075, 3015 (cyclopropane), 1742, 1246, 1027 (acetate) cm^{-1}. NMR: (deuteriochloroform with tetramethylsilane as internal reference): 0·67 (s, 18-H), 0·86 (d, $J = 6$ Hz, 26-H and 27-H), 0·90 d, $J = 6$ Hz, 21-H), 1·12 (s, 19-H), 1·94 (s, 6α-acetate), 5·16 (dd, $J = 11$ Hz, $J' = 4$ Hz, 6β-H). For $C_{30}H_{50}O_2$ (442·7) calculated: 81·39% C, 11·38% H; found: 81·61% C, 11·75% H.

6α-Methoxy-4β,5-cyclo-A-homo-5β-cholestane (*XXIII*)

A solution of diazomethane (500 mg) in ether (19 ml) was added to the alcohol *XXI* (160 mg) in ether and treated with aluminium chloride (30 mg) in small portions within 4 hours at room temperature. The reaction mixture was decomposed with ice and water, the product taken into ether, and worked up. The residue (150 mg) was chromatographed over silica gel (10 g) in ligroin–ether (99 : 1). Working up of the corresponding fractions afforded a product (105 mg) which on crystallisation from methanol gave 70 mg of the methyl ether *XXIII*, m.p. 42—45°C, $[\alpha]_D^{20}$ +72·4° (*c* 0·61). IR: 3075 (cyclopropane), 1104 (methyl ether) cm^{-1}. NMR: 0·12 (t, $J = 4·5$ Hz, one cyclopropane proton), 0·43 (dd, $J = 9$ Hz, $J' = 4·5$ Hz, one cyclopropane proton), 0·66 (s, 18-H), 0·86 (d, $J = 6$ Hz, 26-H and 27-H), 0·89 (d, $J = 6$ Hz, 21-H), 1·06 (s, 19-H). For $C_{29}H_{50}O$ (414·7) calculated: 84·00% C, 12·16% H; found: 83·69% C, 12·36% H.

4α,5-Cyclo-A-homo-5α-cholestan-6α-ol (*XXIV*)

a) *From* 4-*cholesten*-6α-*ol* (XIX): 0·7% Zn—Cu couple was prepared by adding zinc dust (10·42 g) into a solution of cupric acetate monohydrate (240 mg) in acetic acid (10 ml) at 50—60°C and shaking until the solution decolorised. Fresh acetic acid (10 ml) was added and the sedimented zinc was decanted with eight portions (10 ml each) of ether. The couple was then covered with ether (40 ml), treated with diiodomethane (9·2 ml) and refluxed for 2 hours in a nitrogen atmosphere under stirring. The olefin *XIX* (2·5 g) in ether (120 ml) was then added and refluxed under similar conditions for 2 hours. After cooling off the reaction mixture was poured into 10% sodium hydrogen carbonate solution, the product taken into ether, and the ethereal solution was washed with 5% hydrochloric acid, a sodium hydrogen carbonate solution, water, 10% sodium thiosuphate solution, water, dried, and evaporated. The residue (3 g) was dissolved in ether (30 ml), treated with a solution of perphthalic acid (3 g) in ether (26 ml) and allowed to stand at room temperature for 18 hours. The excess peracid was extracted with a sodium carbonate solution, the ethereal solution was washed with water, dried and evaporated. The residue (2·5 g) was chromatographed over silica gel (750 g) in ligroin–ether (24 : 1). Fractions with the lipophilic product were combined, evaporated, and the residue (850 mg) was crystallised from methanol to yield 715 mg of the alcohol

XXIV, m.p. 114–116°C, $[\alpha]_D^{20}$ +15·5° (*c* 1·27). IR: 3620, 1019 1011 (hydroxyl), 3060 (cyclopropane) cm^{-1}. NMR: 0·16 (t, J = 5 Hz, one cyclopropane proton), 0·66 (s, 18-H), 0·85 (d, J = 6 Hz, 26-H and 27-H), 0·89 (d, J = 6 Hz, 21-H), 0·92 s, 19-H), 3·90 (dd, J = 12 Hz, J' = 4 Hz, 6β-H). For $C_{28}H_{48}O$ (400·7) calculated: 83·93% C, 12·08% H; found: 83·95% C, 11·82% H.

b) *From* 4α,5-*cyclo*-A-*homo*-5α-*cholestan*-6-*one* (XXVIII): The ketone *XXVIII* (120 mg) in tetrahydrofuran (12 ml) was treated with lithium tri-tert-butoxyaluminium hydride (360 mg). After 3 hours at room temperature the reaction mixture was diluted with water, acidified with hydrochloric acid, and the product isolated with ether. Working up afforded a residue (115 mg) which on crystallisation from methanol gave 71 mg of the alcohol *XXIV*, m.p. 114–115°C, $[\alpha]_D^{20}$ +17° (*c* 0·91).

6α-Acetoxy-4α,5-cyclo-A-homo-5α-cholestane (*XXV*)

The alcohol *XXV* (220 mg) in pyridine (1 ml) was acetylated with acetic anhydride (0·6 ml) for 18 hours at room temperature. Working up yielded 225 mg of a product which was chromatographed on silica gel (20 g) in ligroin–ether (33 : 1) Working up of the corresponding fractions afforded 203 mg of the acetate *XXV*, resisting all attempts at crystallisation, $[\alpha]_D^{20}$ +29° (*c* 0·69). IR: 3075 (cyclopropane), 1740, 1244, 1025 (acetate) cm^{-1}. NMR: 0·18 (t, J = 5 Hz, one cyclopropane proton), 0·34 (dd, J = 8·5 Hz, J' = 5 Hz, one cyclopropane proton), 0·66 (s, 18-H), 0·86 (d, J = 6 Hz, 26-H and 27-H), 0·89 (d, J = 6 Hz, 21-H), 0·97 (s, 19-H), 1·94 (s, 6α-acetate), 5·12 (dd, J = 11·5 Hz, J' = 4 Hz, 6β-H). For $C_{30}H_{50}O_2$ (442·7) calculated: 81·39% C, 11·38% H; found: 81·22% C, 11·70% H.

6α-Methoxy-4α,5-cyclo-A-homo-5α-cholestane (*XXVI*)

A solution of diazomethane (900 mg) in ether (35 ml) was added to a solution of the alcohol *XXIV* (180 mg) in ether (20 ml) and treated with small portions of aluminium chloride (50 mg) in the course of 2 hours. The reaction mixture was decomposed with ice and water, the product taken into ether, and worked up. The residue (180 mg) was chromatographed on silica gel in ligroin–ether (99 : 1). Working up of the corresponding fractions yielded 155 mg of the methyl ether *XXVI* resisting all attempts at crystallisation, $[\alpha]_D^{20}$ +44° (*c* 1·09). IR: 3075 (cyclopropane), 2825, 1108 (methyl ether) cm^{-1}. NMR: 0·12 (t, J = 4·5 Hz, one cyclopropane proton), 0·61 (dd, J = 9·5 Hz, J' = 4·5 Hz, one cyclopropane proton), 0·67 (s, 18-H), 0·86 (d, J = 6 Hz, 26-H and 27-H), 0·90 (d, J = 6 Hz, 21-H), 0·93 (s, 19-H), 3·24 (s, 6α-methyl ether), 3·32 (dd, J = 4 Hz, J' = 11 Hz, 6β-H). For $C_{29}H_{50}O$ (414·7) calculated: 84·00% C, 12·16% H; found: 83·73% C, 11·86% H.

4β,5-Cyclo-A-homo-5β-cholestan-6-one (*XXVII*)

a) *From* 4β,5-*cyclo*-A-*homo*-5β-*cholestan*-6α-*ol* (XXI): The alcohol *XXI* (320 mg) in acetone (32 ml) was treated with excess Jones' reagent. After 5 minutes at room temperature the excess reagent was removed with methanol (1 ml), the reaction mixture was poured in water, the product taken into ether, and the ethereal solution was washed with water, a sodium hydrogen carbonate solution, water, dried, and evaporated. The residue (320 mg) was crystallised from methanol to yield 245 mg of the ketone *XXVII*, m.p. 109–110°C, $[\alpha]_D^{20}$ +77° (*c* 1·05). IR: 3070 (cyclopropane), 1704 (carbonyl), 1412 (—CH_2— next to the carbonyl) cm^{-1}. NMR: 0·33 (dd, J = 4·5 Hz, J' = 9 Hz, one cyclopropane proton), 0·74 (t, J = 4·5 Hz, one cyclopropane proton), 0·69 (s, 18-H), 0·85 (d, J = 6 Hz, 26-H and 27-H), 0·90 (d, J = 6 Hz, 21-H), 0·99 (s, 19-H). For $C_{28}H_{46}O$ (398·7) calculated: 84·35% C, 11·63% H; found: 84·50%'C, 11·46% H.

b) *From* 4β,5-*cyclo*-A-*homo*-5β-*cholestan*-6β-*ol* (XX): The alcohol *XX* (45 mg) in acetone (5 ml) was oxidised with Jones' reagent as described in the previous experiment. Similar working up and crystallisation from methanol gave 38 mg of the ketone *XXVII*, m.p. 109—110°C, $[\alpha]_D^{20}$ +80° (*c* 2·12).

4α,5-Cyclo-A-homo-5α cholestan-6-one (*XXVIII*)

The alcohol *XXIV* (310 mg) in acetone (62 ml) was oxidised with Jones' reagent and the reaction mixture was worked up as given in the previous experiments. Crystallisation from methanol afforded 205 mg of the ketone *XXVIII*, m.p. 79—81°C, $[\alpha]_D^{20}$ +18° (*c* 1·20). IR: 3084, 3009 (cyclopropane), 1691 (carbonyl) cm^{-1}. NMR: 0·52 (dd, $J = 6·5$ Hz, $J' = 4$ Hz, one cyclopropane proton), 0·69 (s, 18-H), 0·85 (d, $J = 6$ Hz, 26-H and 27-H), 0·90 (d, $J = 6$ Hz, 21-H), 0·93 (s, 19-H). For $C_{28}H_{46}O$ (398·7) calculated 84·35% C, 11·63% H; found: 84·45% C, 11·52% H.

The analyses were carried out in the Analytical Laboratory of this Institute by Mr V. Štěrba, Mrs V. Rusová and Mrs E. Sýkorová under the direction of Dr J. Horáček. The infrared spectra were recorded by Mr P. Formánek under the direction of Dr J. Smolíková. The NMR spectra were recorded and interpreted by Dr M. Buděšínský. Technical assistence was provided by Mrs J. Mašková.

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