SIMMONS–SMITH METHYLENATION OF THE 4,5-DOUBLE BOND IN 19-HYDROXYLATED STEROIDS*

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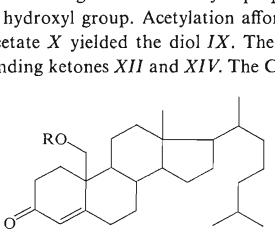
Simmons–Smith methylenation of 4-cholestene-3α,19-diol 19-monoacetate and of 4-cholestene--3β,19-diol 19-monoacetate has been studied and structure of the products established by spectral means.

In the course of our studies[1] on participation of the cyclopropane ring in solvolytic reactions 19-hydroxylated steroid derivatives with the cyclopropane ring in position 4,5 became of interest. In this paper we describe syntheses of all four isomeric 3--hydroxy-4,5-cyclopropano derivatives of 19-hydroxycholestane.

The starting[2] alcohol *I* was transformed to the acetate *II* which on reduction with sodium borohydride afforded the alcohols *III* and *V*. They were characterized also as the acetates *IV* and *VI*. The epimeric alcohols were submitted to the Simmons–Smith methylenation. In both cases the stereochemistry of the addition was directed by the configuration of the hydroxyl at $C_{(3)}$ and afforded the cyclopropano derivatives *VII* and *X*, respectively, with the configuration of the cyclopropane ring corresponding to the configuration of the hydroxyl group. Acetylation afforded the acetates *VIII* and *XI*, hydrolysis of the acetate *X* yielded the diol *IX*. The alcohols *VII* and *X* were oxidized to the corresponding ketones *XII* and *XIV*. The CD spectra of these ketones



I, R = H
II, R = Ac

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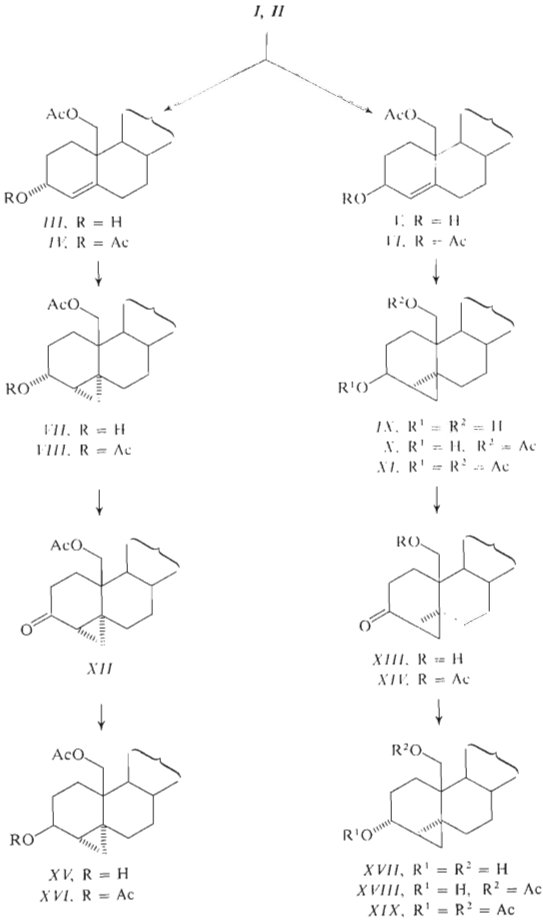
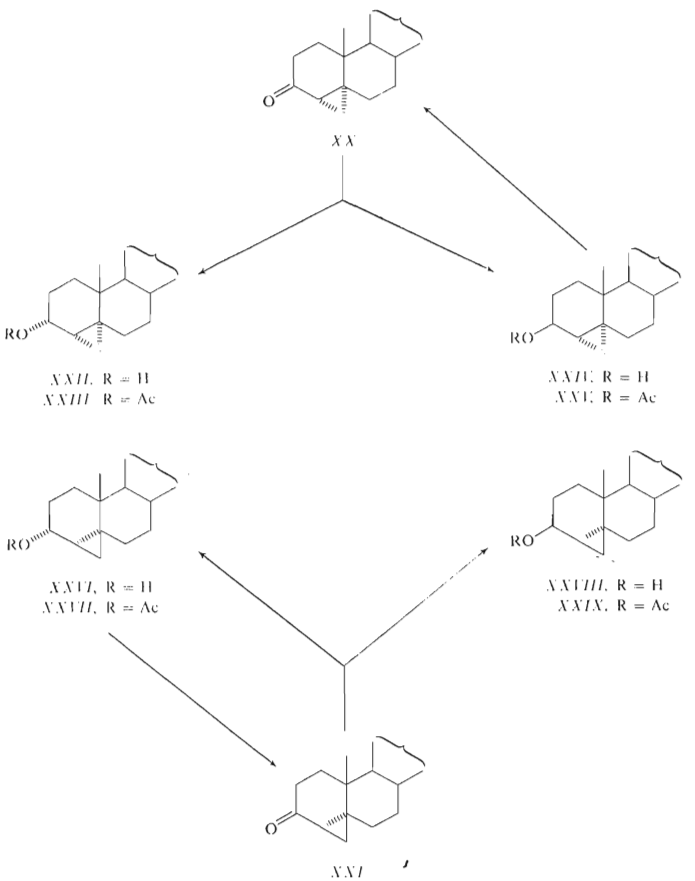

I, II
AcO
RO
III, R = H
IV, R = Ac
V, R = H
VI, R = Ac
VII, R = H
VIII, R = Ac
R²O
R¹O
IX, R¹ = R² = H
X, R¹ = H, R² = Ac
XI, R¹ = R² = Ac
O
XII
XIII, R = H
XIV, R = Ac
XV, R = H
XVI, R = Ac
XVII, R¹ = R² = H
XVIII, R¹ = H, R² = Ac
XIX, R¹ = R² = Ac



confirm the configuration of the cyclopropane ring: Ketone *XII* shows $\Delta\varepsilon$ −3·64, the isomeric ketone *XIV* shows $\Delta\varepsilon$ +3·43 in agreement with the octant rule. Similar situation exists in the known[3] 10-methyl analogues *XX* ($\Delta\varepsilon$ −2·98) and *XXI* ($\Delta\varepsilon$ +3·10). Hydride reduction of the ketones *XII* and *XIV* afforded, as expected, the

alcohols *XV* and *XVIII* with the equatorial conformation of the hydroxyl groups at $C_{(3)}$. They were also characterized as the diacetates *XVI* and *XIX* and diol *XVII*. For spectral studies all the four isomeric alcohols *XXII*, *XXIV*, *XXVI* and *XXVIII* without the substituent at $C_{(19)}$ were required. They were prepared from the known[3] ketones *XX* and *XXI* by metal hydride reduction and were characterized as the corresponding acetates.

EXPERIMENTAL

Melting points were determined on a Kofler block. Optical measurements were carried out in chloroform with an error of ±2°. The infrared spectra were recorded on the Zeiss UR 20 spectrometer in tetrachloromethane. The ^{1}H-NMR spectra were recorded on the Varian HA-100 instrument in deuteriochloroform and corrected to tetramethylsilane (7·25 ppm). The chemical shift is given in ppm. The CD spectra were recorded on a Dichrographe II (Jouan–Roussel) in methanol 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 spectral evidence. Usual working up of a solution implies washing the solution with 5% aqueous hydrochloric acid, water, drying over sodium sulphate, and evaporation of the solvent under reduced pressure. Ligroin refers to the fraction of b.p. 40–60°C.

19-Acetoxy-4-cholesten-3-one (*II*)

The alcohol[2] *I* (3·7 g) in pyridine (15 ml) was treated with acetic anhydride (12 ml) and allowed to stand at room temperature for 20 h. The mixture was decomposed with ice and water, the product was taken into ether, and the ethereal solution was worked up. The residue after evaporation of the solvent (4·2 g) was purified by column chromatography over silica gel (200 g) in benzene. Working up of the corresponding fractions afforded 3·9 g of the acetate *II* $[\alpha]_D^{20}$ +122° (*c* 1·58) which resisted all attempts at crystallization. For $C_{29}H_{46}O_3$ (442·7) calculated: 78·68% C, 10·48% H; found: 78·39% C, 10·31% H.

4-Cholestene-3α,19-diol 19-Monoacetate (*III*)

The ketone *II* (1·2 g) in methanol (30 ml) and ethyl acetate (10 ml) was treated with sodium borohydride (500 mg). The mixture was stirred at room temperature for 2 h, the excess hydride was decomposed with acetic acid and the solvents were distilled off under reduced pressure. The residue was dissolved in ether, washed with a sodium hydrogen carbonate solution, water, dried, and ether was distilled off. The product was chromatographed on a silica gel column (100 g) in benzene–ether (4 : 1). Fractions with the lipophilic component were combined, solvents removed, and the residue was crystallized from methanol–water to yield 140 mg of the alcohol *III*, m.p. 61–63°C, $[\alpha]_D^{20}$ +126° (*c* 1·39). IR spectrum: 3620 (hydroxyl), 3045, 1661 (double bond), 1745, 1238, 1037 cm^{-1} (acetate). ^{1}H-NMR spectrum: 0·68 (s, 18-H). 0·86 (d, J = 6·5 Hz, 26-H and 27-H), 0·89 (d, J = 6·5 Hz, 21-H), 2·03 (s, acetate), 4·07 and 4·43 (two d, J = 11·5 Hz, 19-H), 4·14 (m, 44-H), 5·63 (broad d, 4-H). For $C_{29}H_{48}O_3$ (444·7) calculated: 78·33% C, 10·88% H; found: 78·09% C, 10·72% H.

4-Cholestene-3α,19-diol 3,19-Diacetate (*IV*)

The alcohol *III* (120 g) in pyridine (1 ml) was acetylated with acetic anhydride (0·5 ml) for 20 h at room temperature. The mixture was decomposed with ice and water, the product was taken into

ether, and the ethereal solution was worked up. The residue after evaporation of the solvent (170 mg) was chromatographed over silica gel (20 g) in ligroin–benzene (2 : 1). The corresponding fractions were worked up to yield 95 mg of the diacetate *IV*, $[\alpha]_D^{20}$ +185° (*c* 1·24) which resisted all attempts at crystallization. For $C_{31}H_{50}O_4$ (486·7) calculated: 76·50% C, 10·36% H; found: 76·32% C, 10·29% H.

4-Cholestene-3β,19-diol 19-Monoacetate (*V*)

Elution of the chromatography after isolation of the alcohol *III* with the same solvent mixture afforded fractions with the polar component. Working up gave 1 g of a crude product which on crystallization from methanol yielded 800 mg of the alcohol *V*, m.p. 114–116°C, $[\alpha]_D^{20}$ +70° (*c* 1·46). IR spectrum: 3625, 3610 (hydroxyl), 1742, 1240, 1035 (acetate), 1660 cm^{-1} (double bond). ^{1}H-NMR spectrum: 0·67 (s, 18-H), 0·86 (d, J = 6·5 Hz, 26-H and 27-H), 0·89 (d, J = = 6·5 Hz, 21-H), 2·06 (s, acetate), 4·15 (m, 3α-H), 4·15 and 4·46 (two d, J = 11·5 Hz, 19-H), 5·52 (broad d, W = 11 Hz, 4-H). For $C_{29}H_{48}O_3$ (444·7) calculated: 78·33% C, 10·88% H; found: 78·20% C, 10·64% H.

4-Cholestene-3β,19-diol 3,19-Diacetate (*VI*)

The alcohol *V* (1 g) was acetylated with acetic anhydride (3 ml) in pyridine (4 ml) for 20 h at room temperature. The mixture was decomposed with ice, diluted with water, and the product was isolated with ether. Usual working up and crystallization from methanol yielded 900 mg of the diacetate *VI*, m.p. 88–89°C, $[\alpha]_D^{20}$ +31° (*c* 1·55). For $C_{31}H_{50}O_4$ (486·7) calculated: 76·50% C, 10·36% H; found: 76·81% C, 10·11% H.

4α,5-Cyclopropano-5α-cholestane-3α,19-diol 19-Monoacetate (*VII*)

The Zn–Cu couple (0·5%) was prepared by adding zinc dust (750 mg; Baker 60–200 mesh) into a solution of cupric acetate monohydrate (13 mg) in acetic acid (4 ml) at 50–60°C and shaking until the solution decolorized. The solvent was poured off, the metal was washed first with acetic acid (10 ml) and then decanted with eight portions of ether (10 ml each). The metal was covered with ether (10 ml), iodine (4 mg) and diiodomethane (1 ml) were added and the mixture was refluxed in a nitrogen atmosphere under stirring for 3 h. After cooling off to the room temperature a solution of the alcohol *III* (330 mg) in ether (3 ml) was added and the mixture was stirred under nitrogen at room temperature for 3 h, diluted with ether, poured into 5% sodium hydrogen carbonate solution, the ethereal layer was washed with 5% sodium thiosulphate, water, dried, and the solvents were removed under reduced pressure. The residue was chromatograhped on a silica gel column (30 g) in benzene–ether (6 : 1). The corresponding fractions were worked up and the product was crystallized from methanol to yield 120 mg of the alcohol *VII*, m.p. 182–183°C, $[\alpha]_D^{20}$ +83° (*c* 1·44). IR spectrum: 3606 (hydroxyl), 1728, 1249, 1031 (acetate), 3075 cm^{-1} (cyclopropane). For $C_{30}H_{50}O_3$ (458·7) calculated: 78·55% C, 10·99% H; found: 78·31% C, 10·90% H.

4α,5-Cyclopropano-5α-cholestan-3α,19-diol 3,19-Diacetate (*VIII*)

The alcohol *VII* (150 mg) was acetylated with acetic anhydride (1·2 ml) in pyridine (2 ml) for 20 h at room temperature. The mixture was decomposed with ice, diluted with water, and the product was isolated with ether. Usual working up and crystallization from methanol yielded 110 mg of the diacetate *VIII*, m.p. 121–122°C, $[\alpha]_D^{20}$ +108° (*c* 1·29). ^{1}H-NMR spectrum: 0·155 (dd, J_1 = 9 Hz, J_2 = 5 Hz) and 0·73 (dt, $J_{1,2}$ = 5 Hz, J_3 = 2 Hz, two cyclopropane protons)

0·54 (m, 6-H), 0·66 (s, 18-H), 0·86 and 0·87 (two d, J = 6·5 Hz, 26-H amd 27-H), 0·89 (d, J = = 6·5 Hz, 21-H), 2·04 and 2·10 (two s, acetates), 4·24 and 4·41 (two d, J = 11·5 Hz, 19-H) 5·31 (m, W = 17 Hz, 3β-H). For $C_{32}H_{52}O_4$ (500·7) calculated: 76·75% C, 10·47H %; found: 72·04% C, 10·22% H.

4β,5-Cyclopropano-5β-cholestane-3β,19-diol (*IX*)

The acetate *X* (100 mg) in methanol (15 ml) was refluxed with a solution of potassium hydroxide (200 mg) in 50% methanol (1 ml) for 1 h. The excess alkali was removed with acetic acid , the solvents were distilled off under reduced pressure, and the product was taken into ether. The ethereal solution was washed with a sodium hydrogen carbonate solution, water, dried, and ether removed. The residue was crystallized from ethyl acetate to yield 45 mg of the diol *IX*, m.p. 105—107°C, $[\alpha]_D^{20}$ 0° (*c* 1·35). For $C_{28}H_{48}O_2$ (416·7) calculated: 80·17% C, 11·61% H; found: 80·65% C, 11·60% H.

4β,5-Cyclopropano-5β-cholestane-3β,19-diol 19-Monoacetate (*X*)

The Zn–Cu couple (0·5%) was prepared from zinc dust (21 g) and cupric acetate monohydrate (360 mg) in acetic acid (100 ml) as described for the preparation of the cyclopropano derivative *VII*. The metal was washed with acetic acid (100 ml), ether (450 ml) and covered with absolute ether (240 ml). Iodine (80 mg) and diiodomethane (30 ml) were added, the mixture was refluxed under similar conditions for 3 h. After cooling off the alcohol *V* (9·9 g) in ether (90 ml) was added and treated for 3 h as described above. Similar working up yielded a crude product which was chromatographed on a silica gel column (400 g) in benzene–ether (19 : 1). The corresponding fractions containing the desired alcohol *X* contaminated with the starting material were worked up and the residue (5·7 g) was dissolved in ether and treated with a solution of perphthalic acid (3 g) in ether (40 ml). After 12 h at room temperature the mixture was diluted with ether and the excess peracid was extracted into 5% sodium carbonate. The ethereal solution was washed with water, dried, and the solvent removed. The residue was chromatographed over silica gel (400 g) in benzene–ether (9 : 1). The fractions with the lipophilic component were combined, solvents removed, and the residue was crystallized from methanol–water to yield 4·5 g of the alcohol *X*, m.p. 91—93°C, $[\alpha]_D^{20}$ +11° (*c* 1·32). IR spectrum: 3 620 (hydroxyl), 3 075 (cyclopropane). 1 740, 1 240, 1 035 cm^{-1} (acetate). For $C_{30}H_{50}O_3$ (458·7) calculated: 78·55% C, 10·99% H; found: 78·40% C, 10·79% H.

4β,5-Cyclopropano-5β-cholestane-3β,19-diol 3,19-Diacetate (*XI*)

The alcohol *X* (100 mg) was acetylated with acetic anhydride (0·3 ml) in pyridine (0·5 ml) for 20 h at room temperature. The mixture was decomposed with ice, diluted with water, and the product isolated with ether. Usual working up and crystallization from methanol gave 70 mg of the diacetate *XI*, m.p. 84—86°C, $[\alpha]_D^{20}$ −22° (*c* 1·37). ^{1}H-NMR spectrum: 0·24 (dd, J_1 = 9·5 Hz, J_2 = 5 Hz, one cyclopropane proton), 0·55 (m, 6-H), 0·665 (s, 18-H), 0·86 (d, J = 6·5 Hz, 26-H and 27-H), 0·89 (d, J = 6·5 Hz, 21-H), 2·04 and 2·08 (two s, acetates), 4·06 and 4·46 (two d, J = = 11·5 Hz, 19-H), 5·28 (broad t, W = 15 Hz, 3α-H). For $C_{32}H_{52}O_4$ (500·7) calculated: 76·75% C, 10·47% H; found: 76·60% C, 10·30% H.

19-Acetoxy-4α,5-cyclopropano-5α-cholestan-3-one (*XII*)

A solution of the alcohol *VII* (200 mg) in acetone (80 ml) was treated with excess Jones' reagent and allowed to stand at room temperature for 15 min. The excess reagent was removed with

methanol and the solvents were partly distilled off *in vacuo*. The residue was diluted with water, the product was extracted with ether, and the ethereal solution was washed with a sodium hydrogen carbonate solution, water, dried and solvents removed. The residue was crystallized from methanol to yield 165 mg of the ketone *XII*, m.p. 76–78°C, $[\alpha]_D^{20}$ +38° (*c* 1·25) IR spectrum:: 3085, 3015 (cyclopropane), 1745, 1235, 1040 (acetate), 1695 cm^{-1} (carbonyl). Mass spectrum; $M^{+\cdot}$ 456. CD spectrum: $\Delta\varepsilon_{276}$ −3·64. For $C_{30}H_{48}O_3$ (456·7) calculated: 78·90% C, 10·59% H; found: 78·72% C, 10·48% H.

19-Hydroxy-4β,5-cyclopropano 5β-cholestan-3-one (*XIII*)

The acetate *XIV* (100 mg) was dissolved in methanol (25 ml), treated with a solution of potassium hydroxide (150 mg) in the same solvent and heated to 50°C for 45 min. The excess alkali was removed with acetic acid, solvents were distilled off under reduced pressure, the residue was diluted with water, and the product isolated with ether. The ethereal solution was washed with a sodium hydrogen carbonate solution, water, dried, and ether removed. The crude product was crystallized from ethyl acetate to yield 40 mg of the alcohol *XIII*, m.p. 189–191°C, $[\alpha]_D^{20}$ +74° (*c* 1·25). IR spectrum: 3630 (hydroxyl), 3095 (cyclopropane), 1675 cm^{-1} (carbonyl). For $C_{28}H_{46}O_2$ (414·6) calculated: 81·10% C, 11·18% H; found: 80·90% C, 11·08% H.

19-Acetoxy-4β,5-cyclopropano-5β-cholestan-3-one (*XIV*)

The alcohol *X* (2·2 g) in acetone (120 ml) was treated with excess Jones' reagent and allowed to stand at room temperature for 15 min. The excess reagent was removed with methanol, the mixture was diluted with water, and the product isolated with ether. The ethereal solution was worked up and the residue after evaporation of ether was chromatographed on a silica gel column (150 g) in benzene–ether (19 : 1). The corresponding fractions were worked up and the residue was crystallized from methanol to yield 1·7 g of the ketone *XIV*, m.p. 85–87°C, $[\alpha]_D^{20}$ +85° (*c* 1·30). Mass spectrum: $M^{+\cdot}$ 456. CD spectrum: $\Delta\varepsilon_{285}$ +3·43. For $C_{30}H_{48}O_3$ (456·7) calculated: 78·90% C, 10·59% H; found: 78·71% C, 10·38% H.

4α,5-Cyclopropano-5α-cholestane-3β,19-diol 19-Monoacetate (*XV*)

A solution of the ketone *XII* (170 mg) in 1,2-dimethoxyethane (4 ml) was treated with solid lithium tri-tert-butoxyaluminium hydride. After 2 h at room temperature the excess hydride was decomposed with acetic acid, the mixture was diluted with water, and the product taken into ether. The ethereal solution was worked up and the residue was chromatographed over silica gel (35 g) in benzene–ether (2 : 1). The corresponding fractions were worked up and the residue was crystallized from methanol to yield 95 mg of the alcohol *XV*, m.p. 81–82°C, $[\alpha]_D^{20}$ +47° (*c* 1·28). IR spectrum: 3620 (hydroxyl), 3065 (cyclopropane), 1740, 1241, 1033 cm^{-1} (acetate). For $C_{30}H_{50}O_3$ (458·7) calculated: 78·55% C, 10·99% H; found: 78·40% C, 10·81% H.

4α,5-Cyclopropano-5α-cholestane-3β,19-diol 3,19-Diacetate (*XVI*)

The alcohol *XV* (50 mg) in pyridine (0·5 ml) was acetylated with acetic anhydride (0·4 ml) for 20 h at room temperature. The mixture was decomposed with ice, diluted with water, and the product isolated with ether. Usual working up and crystallization from methanol gave 35 mg of the diacetate *XVI*, m.p. 121–123°C, $[\alpha]_D^{20}$ +39° (*c* 1·56). ^{1}H-NMR spectrum: 0·19 (dd, J_1 = 9·5 Hz, J_2 = 5 Hz, one cyclopropane proton), 0·47 (dt, $J_1 = J_2$ = 5 Hz, J_3 = 2 Hz, one cyclopropane proton), 0·54 (m, 6-H), 0·66 (s, 18-H), 0·86 (d, *J* = 6·5 Hz, 26-H and 27-H), 0·89 (d, *J* = 6·5 Hz,

21-H), 2·05 and 2·09 (two s, acetates), 4·38 and 4·66 (two d, $J = 1·5$ Hz, 19-H), 5·09 (m, $W = 6$ Hz, 3α-H). For $C_{32}H_{52}O_4$ (500·7) calculated: 76·75% C, 10·47% H; found: 76·61% C, 10·20% H.

4β,5-Cyclopropano-5β-cholestane-3α,19-diol (*XVII*)

A solution of the diacetate *XIX* (300 mg) in methanol (50 ml) was heated to 50°C with a solution of potassium hydroxide (400 mg) in methanol (15 ml) for 1 h. The excess alkali was removed with acetic acid and the solvents were distilled off *in vacuo*. The residue was diluted with water, the product taken into ether, and the ethereal solution was worked up. The residue after evaporation of ether was crystallized from methanol to yield 210 mg of the diol *XVII*, m.p. 198–200°C, $[\alpha]_D^{20}$ +31° (*c* 1·29). For $C_{28}H_{48}O_2$ (416·7) calculated: 80·71% C, 11·61% H; found: 80·59% C, 11·35% H.

4β,5-Cyclopropano-5β-cholestane-3α,19-diol 19-Monoacetate (*XVIII*)

The ketone *XIV* (700 mg) in 1,2-dimethoxyethane (15 ml) was reduced with lithium tri-tert-butoxyaluminium hydride (1·5 g) as described above for the alcohol *XV*. Similar working up and chromatography over silica gel (120 g) in benzene–ether (9 : 1) afforded 630 mg of the alcohol *XVIII*, $[\alpha]_D^{20}$ +55° (*c* 1·31) which resisted all attempts at crystallization. IR spectrum: 3625 (hydroxyl), 3070 (cyclopropane), 1741, 1242 cm^{-1} (acetate). For $C_{30}H_{50}O_3$ (458·7) calculated: 78·55% C, 10·99% H; found: 78·30% C, 10·82% H.

4β,5-Cyclopropano-5β-cholestane-3α,19-diol 3,19-Diacetate (*XIX*)

The alcohol *XVIII* (600 mg) was acetylated with acetic anhydride (1·6 ml) in pyridine (3 ml) for 20 h at room temperature. The mixture was decomposed with ice, diluted with water, and the product was isolated with ether. Working up afforded a product which was chromatographed on a silica gel column (50 g) in benzene. The corresponding fractions were worked up to yield 510 mg of the diacetate *XIX*, $[\alpha]_D^{20}$ +45° (*c* 1·48) resisting all attempts at crystallization. ^{1}H-NMR spectrum: 0·32 (dd, $J_1 = 10$ Hz, $J_2 = 5$ Hz, one cyclopropane proton), 0·53 (t, $J_1 = 5$ Hz, $J_2 = 5·5$ Hz, one cyclopropane proton), 0·55 (m, 6-H), 0·67 (s, 18-H), 0·86 (d, $J = 6·5$ Hz, 26-H and 27-H), 0·89 (d, $J = 6·6$ Hz, 21-H), 2·07 and 2·09 (two s, acetates), 4·03 and 4·46 (two d, $J = 11·5$ Hz, 19-H), 4·49 (m, $W = 17$ Hz, 3β-H). For $C_{32}H_{52}O_4$ (500·7) calculated: 76·75% C, 10·47% H; found: 76·61% C, 10·25% H.

4α,5-Cyclopropano-5α-cholestan-3-one (*XX*)

The alcohol *XXIV* (60 mg) in acetone (5 ml) was treated with excess Jones' reagent and allowed to stand at room temperature for 15 min. The excess reagent was removed with methanol, the mixture was diluted with water, and the product was isolated with ether. Working up and chromatography over silica gel (6 g) in benzene–ether (33 : 1) afforded a product which on crystallization from methanol yielded 40 mg of the ketone *XX*, m.p. 137–138°C, $[\alpha]_D^{20}$ +13° (*c* 1·27) in accordance with the literature[3]. IR spectrum: 3085, 3015 (cyclopropane), 1693 cm^{-1} (carbonyl). CD spectrum: ε_{279} −2·98.

4β,5-Cyclopropano-5β-cholestan-3-one (*XXI*)

The alcohol *XXVI* (100 mg) in acetone (5 ml) was oxidized with Jones' reagent as described in the previous experiment. Similar working up, chromatography, and crystallization from ether–

–methanol yielded 55 mg of the ketone *XXI*, m.p. 81–82°C, $[\alpha]_D^{20}$ +70° (*c* 1·36) in accordance with the literature[3]. IR spectrum: 3080, 3015 (cyclopropane), 1688 cm^{-1} (carbonyl). CD spectrum: $\Delta\varepsilon_{284}$ +3·10.

4α,5-Cyclopropano-5α-cholestan-3α-ol (*XXII*)

The ketone *XX* (160 mg) in 1,2-dimethoxyethane (5 ml) was treated with solid lithium tri-tert-butoxyaluminium hydride and allowed to stand at room temperature for 2 h. The mixture was poured into 1% acetic acid, the product was extracted into ether, and the ethereal solution was washed with a sodium hydrogen carbonate solution, water, dried, and ether was distilled off. The residue (180 mg) was chromatographed on a silica gel column (30 g) in benzene and the fractions with the minor and polar product were combined, and solvent removed. The residue (15 mg) was crystallized from methanol to yield 8 mg of the alcohol *XXII*, m.p. 105–106°C, $[\alpha]_D^{20}$ +85° (*c* 0·97) in accordance with the literature[3].

4α,5-Cyclopropano-5α-cholestan-3α-ol 3-Acetate (*XXIII*)

The alcohol *XXII* (50 mg) was acetylated with acetic anhydride (0·2 ml) in pyridine (1 ml) for 20 h at room temperature. Decomposition with ice, isolation of the product with ether and working up of the ethereal solution afforded a product which on crystallization from methanol gave 35 mg of the acetate *XXIII*, m.p. 91–92°C, $[\alpha]_D^{20}$ +118° (*c* 1·31). IR spectrum: 3075, 3010 (cyclopropane), 1732, 1251, 1026, 1018 cm^{-1} (acetate). ^{1}H-NMR spectrum: 0·14 (dd, $J_1 = 8$ Hz, $J_2 =$ = 5 Hz, one cyclopropane proton), 0·74 (dt, $J_1 = J_2 = 5$ Hz, $J_3 = 2$ Hz, one cyclopropane proton), 0·51 (m, 6–H), 0·67 (s, 18-H), 0·87 (d, $J = 6{\cdot}5$ Hz, 26-H and 27-H), 0·90 (d, $J = 6{\cdot}5$ Hz, 21-H), 1·02 (s, 19-H), 2·04 (s, acetate), 5·31 (m, $W = 18$ Hz, 3β-H). For $C_{30}H_{50}O_2$ (442·7) calculated: 81·39% C, 11·38% H; found: 81·20% C, 11·18% H.

4α,5-Cyclopropano-5α-cholestan-3β-ol (*XXIV*)

Fractions with the lipophilic component from the chromatography after isolation of the alcohol *XXII* were worked up and the product was crystallized from methanol to yield 110 mg of the alcohol *XXIV*, m.p. 131–132°C, $[\alpha]_{20}^{D}$ +49° (*c* 1·34). IR spectrum: 3625, 1031, 1019, 996 (hydroxyl), 3065 cm^{-1} (cyclopropane). For $C_{28}H_{48}O$ (400·7) calculated: 83·93% C, 12·08% H; found: 83·78% C, 11·95% H.

4α,5-Cyclopropano-5α-cholestan-3β-ol 3-Acetate (*XXV*)

The alcohol *XXIV* (60 mg)was acetylated with acetic anhydride (0·4 ml) in pyridine (0·8 ml) for 20 h at room temperature. Usual working up and crystallization from methanol afforded 40 mg of the acetate *XXV*, m.p. 143–144°C, $[\alpha]_D^{20}$ +34° (*c* 1·21). Mass spectrum: $M^{+\cdot}$ 442. ^{1}H-NMR spectrum: 0·16 (dd, $J_1 = 9{\cdot}5$ Hz, $J_2 = 5$ Hz, one cyclopropane proton), 0·41 (dt, $J_1 = J_2 = 5$ Hz, $J_3 = 2$ Hz, one cyclopropane proton), 0·51 (m, 6-H), 0·67 (s, 18-H), 0·86 (d, $J = 6{\cdot}5$ Hz, 26-H and 27-H), 0·90 (d, $J = 6{\cdot}5$ Hz, 21-H), 1·15 (s, 19-H), 2·06 (s, acetate), 5·07 (m, $W = 16{\cdot}$Hz, 3β-H). For $C_{30}H_{50}O_2$ (442·7) calculated: 81·39% C, 11·38% H; found: 81·27% C, 11·25% H.

4β,5-Cyclopropano-5β-cholestan-3α-ol (*XXVI*)

The ketone *XXI* (400 mg) was reduced with lithium tri-tert-butoxyaluminium hydride (800 mg) in 1,2-dimethoxyethane (10 ml) as described for the reduction of the 5α-isomer *XX*. Similar working

up yielded a product which was chromatographed on a silica gel column (35 g) in benzene–ether (33 : 1). Fractions with the lipophilic component were worked up to yield 225 mg of the alcohol *XXVI*, $[\alpha]_D^{20}$ +26° (*c* 1·45) resisting all attempts at crystallization. IR spectrum: 3620, 1043, 1026, 1008 (hydroxyl), 3060 cm^{-1} (cyclopropane). $C_{28}H_{48}O$ (400·7) calculated: 83·93% C, 12·08% H; found: 83·70% C, 12·01% H.

4β,5-Cyclopropano-5β-cholestan-3α-ol 3-Acetate (*XXVII*)

The alcohol *XXVI* (500 mg) was acetylated with acetic anhydride (1·5 ml) in pyridine (2 ml) for 20 h at room temperature. Usual working up gave 600 mg of a product which was chromatographed over silica gel (50 g) in benzene to yield after crystallization from methanol 380 mg of the acetate *XXVII*, m.p. 75–76°C, $[\alpha]_D^{20}$ +31° (*c* 1·31). ^{1}H-NMR spectrum: 0·19 (dd, J_1 = 10 Hz, J_2 = 5 Hz, one cyclopropane proton), 0·33 (t, J_1 = 5·5 Hz, J_2 = 5 Hz, one cyclopropane proton), 0·55 (m, 6-H), 0·67 (s, 18-H), 0·71 (dd, J_1 = 10 Hz, J_2 = 5·5 Hz, 4-H), 0·86 and 0·87 (two d, J = 6·5 Hz, 26-H and 27-H), 0·91 (d, J = 6·5 Hz, 21-H), 0·95 (s, 19-H), 2·08 (s, acetate), 4·95 (m, W = 17 Hz, 3β-H). For $C_{30}H_{50}O_2$ (442·7) calculated: 81·39% C, 11·38% H; found: 81·20% C, 11·21% H.

4β,5-Cyclopropano-5β-cholestan-3β-ol (*XXVIII*)

Fractions from the chromatography after isolation of the alcohol *XXVI* containing the polar component were worked up and the product was crystallized from acetone to yield 17 mg of the alcohol *XXVIII*, m.p. 80–82°C, $[\alpha]_D^{20}$ −9° (*c* 1·11) in accordance with the literature[3].

4β,5-Cyclopropano-5β-cholestan-3β-ol 3-Acetate (*XXIX*)

The alcohol *XXVIII* (100 mg) was acetylated with acetic anhydride (0·5 ml) in pyridine (1 ml) for 20 h at room temperature. The mixture was decomposed with ice, diluted with water, and the product was isolated with ether. Usual working up and crystallization from ether–methanol yielded 75 mg of the acetate *XXIX*, m.p. 86–87°C, $[\alpha]_D^{20}$ −80° (*c* 1·53). IR spectrum: 3075, 3010 (cyclopropane), 1732, 1253, 1231, 1019 cm^{-1} (acetate). ^{1}H-NMR spectrum: 0·12 (dd, J_1 = = 9·5 Hz, J_2 = 5 Hz, one cyclopropane proton), 0·68 (t, $J_1 = J_2$ = 5 Hz, one cyclopropane proton), 0·55 (m, 6-H), 0·67 (s, 18-H), 0·86 and 0·87 (two d, J = 6·5 Hz, 26-H and 27-H), 0·90 (d, J = 6·5 Hz, 21-H), 0·97 (s, 19-H), 2·04 (s, acetate), 5·26 (m, W = 15 Hz, 3α-H). For $C_{30}H_{50}O_2$ (442·7) calculated: 81·39% C, 11·28% H; found: 81·70% C, 11·50% H.

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REFERENCES

1. Fajkoš J., Joska J., Tureček F.: This Journal, in press.
2. Mousseron-Canet M., Labeeuw B., Lanet J. C.: Bull. Soc. Chim. Fr. *1968*, 2125.
3. Dauben W. G., Lang P., Berezin G. H.: J. Org. Chem. *31*, 3869 (1966).

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