SIMMONS–SMITH METHYLENATION OF THE 5,6-DOUBLE BOND IN 19-HYDROXYLATED STEROIDS*

Jan FAJKOŠ and Jiří JOSKA

Institute of Organic Chemistry and Biochemistry, Czechoslovak Academy of Sciences, 166 10 Prague 6

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Simmons–Smith methylenation of 5-cholestene-3β,19-diol 3-monoacetate has been studied and structure of the products established by spectral and chemical means.

In connection with our work on 19-hydroxylated and 19-nor steroids with modified skeleton we became interested in Simmons–Smith methylenation of the variously located double bond in the 19-hydroxylated steroids. Similar compounds proved to be a convenient starting material for steroids with modified skeleton because on participation of the cyclopropane ring in reactions involving carbonium ions new interesting structures are often formed[1–3]. In this paper we describe Simmons–Smith methylenation of 19-hydroxycholesteryl acetate.

When the olefin *I* was submitted to the conditions of the Simmons–Smith methylenation (diiodomethane, Zn–Cu couple, and iodine in ether) three main products were detected in the reaction mixture. They were separated by repeated column chromatography on silica gel. The most polar product was obtained in yields ranging from 50–60% and, according to the spectral evidence, this was the expected addition product *III*. No other product of the same molecular weight was detected. The methylene addition proceeds therefore stereospecifically, from the β-side of the molecule, as the directing influence of the free hydroxyl group on the stereochemistry of the methylene addition is well known[4,5]. We were able to prove the β-configuration of the cyclopropane ring in the alcohol *III* by chemical means: We have oxidized the 19-hydroxyl under mild conditions to the aldehyde *IX* and removed the carbonyl group by Huang–Minlon reduction. The resulting compound was identical in every respect with the known[6] 5,7α-cyclo-B-homo-5α-cholestan-3β-ol (*X*).

Having established the stereochemistry of the cyclopropane ring we turned our attention to the remaining two products of the methylenation reaction. They were obtained in the yields varying from 20–25%. The lower melting, lipophilic compound showed a molecular peak at M^+ 516 with fragmentation pointing to the presence

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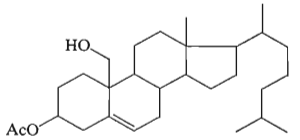
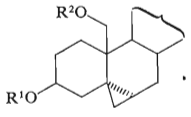
of a 19-ethoxymethoxy grouping. ^{1}H-NMR spectrum is in good agreement with such a structure: It shows an AB pattern for the two 19-protons centered at 3·43 ppm, a singlet at 4·68 ppm for the methylene group attached to two oxygen atoms, as well as the methyl (triplet at 1·23 ppm) and methylene protons (quadruplet at 3·63 ppm) of the terminal ethoxy group. The mass spectrum of the higher melting polar compound showed peaks at *m/e* 868 and 808 which correspond to the loss of one and two molecules of acetic acid from the molecular peak at M^+ 928 which was not detected. ^{1}H-NMR spectrum shows an AB pattern centered at 3·45 ppm for four 19-protons and a singlet at 4·65 ppm for one methylene group (two protons) attached to two oxygen atoms. The lower melting ether is therefore the ethoxymethoxy derivative *VI* and the higher melting one has the structure of the methylenedioxy derivative *VIII*.

The course of the cleavage of these ethers confirm the proposed structures: When treated with zinc dust in acetic acid at 100°C both ethers afforded the 19-hydroxy derivative *III* as the sole product of the reduction (next to some starting material and traces of the diacetate *IV*). On cleavage with boron trifluoride etherate in acetic anhydride the ether *VIII* afforded the diacetate *IV* and a new rearranged product in about equal quantities. The same rearranged compound was obtained as the main product from the ether *VI* and only traces of the diacetate *IV* were isolated. This is also in agreement with the proposed structures for the two ethers.

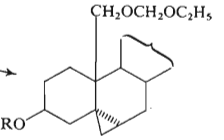
As far as the rearranged product is concerned we suggest for this compound structure *XII* on the basis of the following evidence: The mass spectrum of this compound shows a molecular peak at M^+ 470 corresponding to the empirical formula $C_{31}H_{50}O_3$. An intense peak at *m/e* 410 corresponds to the loss of acetic acid. Further fragmentation showing strong peaks at *m/e* 351 (410 – 59, C_3H_7O), *m/e* 365 (410 – 45, C_2H_5O), and *m/e* 379 (410 – 31, CH_3O) is consistent with the presence of the 19,5-epoxyethane ring. ^{1}H-NMR spectrum shows an AB pattern at 3·68 ppm for the two 19 protons, a multiplet at 3·60 – 3·85 ppm for the two protons of the methylene group adjacent to the oxygen atom, and points to the equatorial character of the 3α proton ($W/2$ = 9 Hz at 5·13 ppm) which is in agreement with the *cis* annelation of the A and B rings in the structure *XII*. The spectrum shows no olefinic or cyclopropane protons but the presence of a double bond has been proved by both epoxidation and catalytic hydrogenation. The compound remained unchanged when treated over Adams' catalyst in ethanol in a hydrogen atmosphere, however in acetic acid a saturated compound of a molecular peak at M^+ 472 was smoothly formed. We may assume therefore that the double bond is located either in position 8(9) or in position 8(14). When oxidized with ruthenium tetroxide according to the method developed by Snatzke[7] and Nakata[8] a product with an intense carbonyl maximum at 1700 cm^{-1} was obtained. This result is compatible only with the structure *XII* with the double bond in position 8(9) because if the double bond were in position 8(14) a product with a carbonyl on a five-membered ring is to be expected. Formation of structure *XII* may be explained by "backbone rearrangement" triggered



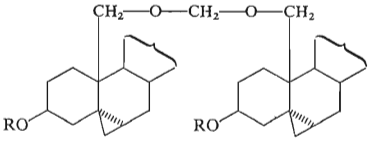
I



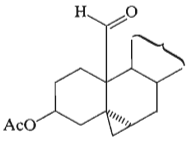
II, $R^1 = R^2 = H$
III, $R^1 = Ac$, $R^2 = H$
IV, $R^1 = R^2 = Ac$



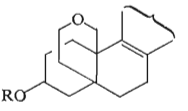
V, R = H
VI, R = Ac



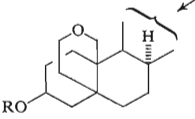
VII, R = H
VIII, R = Ac



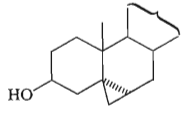
IX



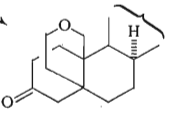
XI, R = H
XII, R = Ac



XIII, R = H
XIV, R = Ac

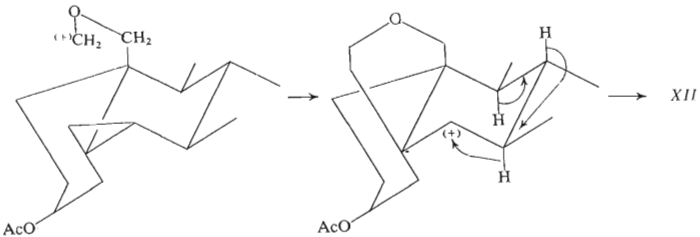


X



XV

off by the carbonium ion generated at $C_{(6)}$ as shown by forms *XVI*–*XVII*. In the cation *XVI* there is a good chance for the overlap of the vacant *p* orbital with the 6,7-bond of the cyclopropane ring to form cation *XVII* which undergoes a type of "backbone rearrangement". There is also a possibility of a change at the C-D ring junction. This will be studied more closely and for present we prefer structure *XII*. As far as the catalytic hydrogenation of the 8(9) double bond and structure of the saturated product *XIV* are concerned we did not study the ability of the double bond to migration to the 8(14) position and we assigned the 8α configuration to the saturated product *XIV* tentatively. Hydrolysis of the acetate *XIV* gave the alcohol *XIII* which was oxidized by Jones' reagent to the ketone *XV*. This ketone showed a carbonyl maximum in IR at 1720 cm^{-1} in agreement with the proposed structure.



XVI *XVII*

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 pm. The mass spectra were recorded on the mass spectrometer AEI MS 902. The UV spectra were recorded on the CF 4 spectrometer in ethanol. 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, 5% aqueous potassium hydrogen carbonate solution, water, drying with sodium sulphate, and evaporation of the solvent *in vacuo*. Ligroin refers to the fraction of b.p. 40–60°C.

5,7α-Cyclo-B-homo-5α-cholestane-3β,19-diol (*II*)

The acetate *III* (200 mg) in methanol (20 ml) was treated with a solution of potassium hydroxide (100 mg) in water (2 ml) and refluxed for 15 min. Methanol was distilled off under reduced pressure, the residue was treated with water, and the product taken into ether. The ethereal solution was washed with water, dried, and solvent removed. The residue was crystallized from methanol–water to yield 130 mg of the diol *II*, m.p. 150–151°C, $[\alpha]_D^{20}$ −9° (*c* 1·16). For $C_{28}H_{48}O_2$ (416·7) calculated: 80·71% C, 11·61% H; found: 80·45% C, 11·52% H.

5,7α-Cyclo-B-homo-5α-cholestane-3β,19-diol 3-Monoacetate (*III*)

a) *From* 5-*cholestene*-3β,19-*diol* 3-*monoacetate* (I): 0·5% Zn–Cu couple was prepared by adding zinc dust (24·6 g; Baker 60–200 mesh) into a solution of cupric acetate monohydrate (400 mg) in acetic acid (60 ml) at 50–60°C and shaking until the solution decolorized. The solvent was poured off, the metal was washed first with acetic acid (60 ml) and then decanted with eight portions of ether (60 ml each). The metal was covered with ether (200 ml), iodine (400 mg) and diiodomethane (40 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 *I* (10 g) in ether (150 ml) was added. The mixture was stirred under nitrogen at room temperature for 3 h, diluted with ether, poured into 5% sodium hydrogen carbonate, the ethereal layer was washed with 5% sodium thiosulphate, water, dried, and the solvents were removed *in vacuo*. The residue was chromatographed on a silica gel column (700 g) in benzene–ether (33 : 1). Fractions with the most polar component were combined, solvents removed, and the residue was crystallized from ethanol–water to yield 3·8 g of the acetate *III*, m.p. 97–98°C, $[\alpha]_D^{20}$ −2·5° (*c* 1·32). Mass spectrum: M^+ 458. IR spectrum: 3645, 3610 (hydroxyl), 3065 (cyclopropane), 1735, 1250 cm^{-1} (acetate). ^{1}H-NMR spectrum: 0·14 (q, $J_1 = 4·5$ Hz, $J_2 = 9$ Hz, one cyclopropane proton), 0·45 (t, $J = 4·5$, one cyclopropane proton), 0·59 (s, 18-H), 0·83 (d, $J = 6$ Hz, 26-H and 27-H). 0·85 (d, $J = 6$ Hz, 21-H), 1·97 (s, acetate), 3·48 (s, 19-H), 4·90 (broad mt, $W = 60$ Hz, 3α-H). For $C_{30}H_{50}O_3$ (458·7) calculated: 78·55% C, 10·99% H; found: 78·39% C, 10·87% H.

b) *From* 19,19′-*methylenedioxy*-5,7α-*cyclo*-B-*homo*-5α-*cholestane*-3β-*ol* 3-*acetate* (VIII): The acetate *VIII* (1 g) was dissolved in acetic acid (60 ml), zinc dust (15 g) was added, and the mixture was heated in a boiling water bath under stirring for 40 min. Zinc was filtered off, washed with acetic acid (20 ml), the filtrate was diluted with water, and the product taken into ether. The ethereal solution was washed with a sodium hydrogen carbonate solution, water, dried, and solvent removed. The residue contained according to the TLC the starting material and a new polar compound in about equal quantities. It was chromatographed on a silica gel column (70 g) in benzene–ether (9 : 1). Fractions with the lipophilic component yielded 320 mg of the starting compound, further elution with the same solvent mixture gave fractions with the polar component. Working up and crystallization from ethanol–water yielded 360 mg of the acetate *III*, m.p. 96–97°C, $[\alpha]_D^{20}$ −3° (*c* 1·31), identical with the compound prepared as under *a*).

c) *From* 19-*ethoxymethoxy*-5,7α-*cyclo*-B-*homo*-5α-*cholestane*-3β-*ol* 3-*acetate* (VI): The ether *VI* (1 g) was treated with zinc dust in acetic acid for 1 h as described in the previous experiment. Similar working up afforded a mixture which was chromatographed over silica gel (130 g) in benzene–ether (20 : 1). The lipophilic fractions gave 270 mg of the starting material, followed by fractions with traces of the diacetate *IV*. Fractions with the polar component were worked up and the product crystallized from ethanol–water to yield 430 mg of the acetate *III*, m.p. 95–96°C, $[\alpha]_D^{20}$ −3° (*c* 1·09).

5,7α-Cyclo-B-homo-5α-cholestane-3β,19-diol 3,19-Diacetate (*IV*)

a) *From* 5,7α-*cyclo*-B-*homo*-5α-*cholestane*-3β,19-*diol* 3-*monoacetate* (III): The alcohol *III* (220 mg) was acetylated with acetic anhydride (2 ml) in pyridine (2·5 ml) for 20 h at room temperature. The mixture was decomposed with ice, diluted with water, and the product taken into ether. The ethereal solution worked up, and the residue after evaporation of ether was crystallized from chloroform–methanol to yield 203 mg of the diacetate *IV*, m.p. 89—90°C, $[\alpha]_D^{20}$ +8° (*c* 1·19). For $C_{32}H_{52}O_4$ (500·7) calculated: 76·75% C, 10·47% H; found: 76·68% C, 10·31% H.

b) *From* 19,19′-*methylenedioxy*-5,7α-*cyclo*-B-*homo*-5α-*cholestane*-3β-*ol* 3-*acetate* (VIII): The acetate *VIII* (250 mg) in acetic anhydride (5 ml) was treated with boron trifluoride etherate (0·5 ml) and agitated for 5 h at room temperature. The mixture was decomposed with pyridine and ice, diluted with water, and the product extracted with ether. The ethereal solution was worked up and the oily residue containing two products according to the TLC was chromatographed over silica gel (80 g) in benzene–ether (49—1). Fractions with the lipophilic components were worked up, solvents removed, and the residue was crystallized from methanol to yield 110 mg of the diacetate *IV*, m.p. 89—90°C, $[\alpha]_D^{20}$ +8° (*c* 1·23), identical with the compound prepared as under *a*).

c) *From* 19-*ethoxymethoxy*-5,7α-*cyclo*-B-*homo*-5α-*cholestane*-3β-*ol* 3-*acetate* (VI): The ether *VI* (2 g) in acetic anhydride (40 ml) was treated with boron trifluoride etherate (1·3 ml) and allowed to stand at room temperature for 4 h. The mixture was cooled to 0°C, pyridine was added (4 ml) and the excess anhydride was decomposed with ice and water. The product was taken into ether, the ethereal solution was worked up, and ether removed. The residue (1·65 g) was chromatographed on a silica gel column in benzene–ether (20 : 1). Fractions with the lipophilic compound were combined, solvents removed, and the residue was crystallized from methanol to yield 420 mg of the diacetate *IV*, m.p. 88—90°C, $[\alpha]_{20}^{D}$ +7° (*c* 1·09).

19-Ethoxymethoxy-5,7α-cyclo-B-homo-5α-cholestane-3β-ol (*V*)

The acetate *VI* (200 mg) in methanol (8 ml) was treated with a solution of potassium hydroxide (150 mg) in the minimum amount of water and kept at 50°C for 1 h. The excess alkali was neutralized with acetic acid, solvents were distilled off under reduced pressure, and the residue was diluted with water. The product was taken into ether, the solution was worked up, and ether removed. The oily residue was pure on TLC, resisted all attempts at crystallization, and on acetylation gave the starting acetate. Yield 135 mg of the alcohol *V*, $[\alpha]_D^{20}$ 0° (*c* 1·05). For $C_{31}H_{54}O_3$ (474·7) calculated: 78·42% C, 11·47% H; found: 78·12% C, 10·95% H.

19-Ethoxymethoxy-5,7α-cyclo-B-homo-5α-cholestane-3β-ol 3-Acetate (*VI*)

Fractions with the lipophilic products after isolation of the acetate *III* under *a*) were worked up to yield 4·5 g of a crystalline product which showed one spot on TLC in benzene–ether (9 : 1). However, in ligroin–ether (7 : 1) the mixture separated in two products. It was chromatographed on a silica gel column (500 g) in ligroin–ether (33 : 1). Fractions with the lipophilic component were combined, solvents removed, and the residue was crystallized from methanol to yield 1·5 g of the ether *VI*, m.p. 47—48°C, $[\alpha]_D^{20}$ 0° (*c* 1·43). Mass spectrum: $M^+ = 516$, $[456]^+ = M^+ - 60$, $[427]^+ = 456 - C_2H_5$, $[410]^+ = 456 - C_2H_5OH$, $[397]^+ = 456 - CH_3CH_2O - CH_2$. IR spectrum: 3070 (cyclopropane), 1736, 1249, 1020 (acetate), 1115, 1100 cm^{-1}(ether.) ^{1}H-NMR spectrum: 0·01 (q, $J_1 = 4·5$ Hz, $J_2 = 9$ Hz, one cyclopropane proton), 0·56 (t, $J = 4·5$ Hz, one cyclopropane proton), 0·63 (s, 18-H), 0·85 (d, $J = 6·5$ Hz, 26-H and 27-H), 0·88 (d, $J = 6$ Hz, 21-H), 1·23 (t, $J = 7$ Hz, —O—CH_2—$\underline{HC}_3$), 2·00 (s, acetate), 3·43 (d, 3·33, d, 3·48, AB syst.,

$J = 10$ Hz, 19-H), 3·63 (q, $J = 7$ Hz), —O—$\underline{CH_2}$—CH_3), 4·68 (s, O—CH_2—O), 4·93 (mt, $W = 60$ Hz, 3α-H). For $C_{33}H_{56}O_4$ (516·8) calculated: 76·69% C, 10·71% H; found: 76·41% C, 10·71% H.

19,19′-Methylenedioxy-5,7α-cyclo-B-homo-5α-cholestane-3β-ol (*VII*)

The acetate *VIII* (300 mg) was suspended in ethanol (8 ml), treated with a solution of potassium hydroxide (200 mg) in the minimum amount of water and ethanol (5 ml) and refluxed for 30 min. Methanol was distilled off *in vacuo*, the residue was diluted with water, and the product taken into ether. The ethereal solution was washed with water, dried, and ether removed. The residue was crystallized from methanol to yield 205 mg of the alcohol *VII*, m.p. 134—137°C, $[\alpha]_D^{20}$ −7·5° (*c* 0·98). For $C_{57}H_{96}O_4$ (845·3) calculated: 80·98% C, 11·45% H; found: 80·63% C, 11·28% H.

19,19′-Methylenedioxy-5,7α-cyclo-B-homo-5α-cholestane-3β-ol 3-Acetate (*VIII*)

Fractions with the polar component from the chromatography after isolation of the acetate *VI* obtained on elution with ligroin–ether (33 : 1) were combined, solvents removed, and the residue was crystallized from chloroform–methanol to yield 2·2 g of the ether *VIII*, m.p. 153—155°C, $[\alpha]_D^{20}$ −1° (*c* 1·46). Mass spectrum: $[868]^+ = M^+ - 60$, $[808]^+ = M^+ - 120$, IR spectrum: 3 070 (cyclopropane), 1 735, 1 730, 1 247, 1 035, 1 025 (acetate), 1 115, 1 100 cm^{-1} (ether). ^{1}H-NMR spectrum: 0·03(mt, one cyclopropane proton), 0·72 (mt, one cyclopropane proton), 0·64 (s, 18-H), 0·86 (d, $J = 6·5$ Hz, 26-H and 27-H), 0·89 (d, $J = 6$ Hz, 21-H), 2·00 (s, acetate), 3·35 and 3·54 (two d, AB syst., $J = 10$ Hz, 19-H, —O$\underline{H}$—O, two groups), 4·65 (s, O—$C\underline{H_2}$—O, one group), 4·96 (mt, $W = 60$ Hz, 3α-H). For $C_{61}H_{100}O_6$ (929·4) calculated: 78·83% C, 10·85% H; found: 78·67% C, 10·59% H.

3β-Hydroxy-5,7α-cyclo-B-homo-5α-cholestane-19-al 3-Acetate (*IX*)

The alcohol *II* (500 mg) in acetone (20 ml) was treated at 0°C with excess Jones' reagent. After 3 min methanol was added, the mixture was diluted with water, and the product extracted into ether. The ethereal solution was worked up and ether removed to yield 480 mg of the oily aldehyde *IX*, pure on TLC. $[\alpha]_D^{20}$ −65° (*c* 1·72). For $C_{30}H_{48}O_3$ (456·7) calculated: 78·90% C, 10·59% H; found: 78·73% C, 10·38% H.

5,7α-Cyclo-B-homo-5α-cholestane-3β-ol (*X*)

The aldehyde (500 mg) in triethylene glycol (30 ml) was treated with potassium hydroxide (800 mg) and 98% hydrazine hydrate (4 ml) and heated to 200°C for 3 h. After cooling off the mixture was diluted with water, the product extracted with ether, and the ethereal solution was worked up. The residue after evaporation of the solvent was chromatographed over silica gel (40 g) in benzene–ether (20 : 1). Fractions with the required compound were combined, solvent distilled off, and the residue was crystallized from methanol to yield 105 mg of the alcohol *X*, m.p. 101—102°C, $[\alpha]_D^{20}$ −4° (*c* 1·08), identical in every respect with the described compound.

19,5-Epoxyethane-5β-cholest-8-en-3β-ol (*XI*)

The acetate *XII* (100 mg) in methanol (3 ml) was refluxed with a solution of potassium hydroxide (100 mg) in methanol (2 ml) for 2 h. The excess alkali was removed with acetic acid, solvents were distilled off *in vacuo*, and the product isolated with ether. The ethereal solution was washed

with a sodium hydrogen carbonate solution, water, dried, and the residue after evaporation of ether was crystallized from methanol to yield 65 mg of the alcohol *XI*, m.p. 157–158°C, $[\alpha]_D^{20}$ 0° (*c* 1·76). IR spectrum: 3615 (hydroxyl), 1663 (double bond), 1092, 1039, 996, 926 cm^{-1} (ether). For $C_{29}H_{48}O_2$ (428·7) calculated: 81·25% C, 11·29% H; found: 81·15% C, 11·08% H.

19,5-Epoxyethane-5β-cholest-8-en-3β-ol 3-Acetate (*XII*)

a) *From* 19-*ethoxymethoxy*-5,7α-*cyclo*-B-*homo*-5α-*cholestane*-3β-*ol* 3-*acetate* (VI): Elution of the chromatography after isolation of the diacetate *IV* under *c*) with the same solvent mixture yielded after working up of the corresponding fractions and crystallization from methanol 380 mg of the epoxide *XII*, m.p. 141–142°C, $[\alpha]_D^{20}$ +20° (*c* 1·87). Mass spectrum: M^+ 470, $[410]^+ = 470-60$, $[351]^+ = 410-59$ (C_3H_7O), $[365]^+ = 410-45$ (C_2H_5O), $[379]^+ = 410-31$ (CH_3O). IR spectrum: 1671 (double bond), 1740, 1256, 1242, 1228, 1021 (acetate), 1092 cm^{-1} (ether). ^{1}H-NMR spectrum: 0·66 (s, 18-H), 0·86 (d, J = 6·5 Hz, 26-H and 27-H), 0·93 (d, J = 6·5 Hz, 21-H), 2·02 (s, acetate), 3·34 and 4·01 (two d, AB syst., J = 11 Hz, 19-H), 3·60–3·85 (mt, O—C<u>H</u>$_2$—C<u>H</u>$_2$—), 5·13 (mt, W = 18 Hz, 3α-H equatorial). For $C_{31}H_{50}O_3$ (470·7) calculated: 79·10% C, 10·71% H; found: 79·28% C, 10·69% H.

b) *From* 19,19′-*methylenedioxy*-5,7α-*cyclo*-B-*homo*-5α-*cholestane*-3β-*ol* 3-*acetate* (VIII): Elution of the chromatography after isolation of the acetate *IV* under *b*) with the same solvent mixture afforded fractions with the polar component. Combination and evaporation left a residue (105 mg) which on crystallization from methanol gave 76 mg of the oxide *XII*, m.p. 140 to 141°C, $[\alpha]_D^{20}$ +18° (*c* 1·16).

c) *From* 19,5-*epoxyethane*-5β-*cholest*-8-*en*-3β-*ol* (XI): The alcohol *XI* (150 mg) was acetylated with acetic anhydride (1·2 ml) in pyridine (2 ml) at room temperature for 18 h. Usual working up and crystallization from methanol afforded 90 mg of the acetate *XII*, m.p. 142–143°C, $[\alpha]_D^{20}$ +20° (*c* 1·45).

19,5-Epoxyethane-5β,8α-cholestane-3β-ol (*XIII*)

The acetate *XIV* (200 mg) in methanol (5 ml) was treated with a solution of potassium hydroxide (100 mg) in methanol (2 ml) and refluxed for 4 h. The excess alkali was neutralized with acetic acid, solvent was removed *in vacuo*, and the residue was treated with water. The product was taken into ether, the ethereal solution was worked up, and ether distilled off. The residue was crystallized from methanol to yield 115 mg of the alcohol *XIII*, m.p. 156–157°C, $[\alpha]_D^{20}$ +60° (*c* 1·14). IR spectrum: 3615 (hydroxyl), 1096, 986, 940 cm^{-1} (ether). ^{1}H-NMR spectrum: 0·82 (s, 18-H), 0·86 (d, J = 6·5 Hz, 26-H and 27-H), 0·86 (d, J = 6·5 Hz, 21-H), 1·74 (s, OH), 3·75 and 4·41 (two d, AB syst., J = 11 Hz, 19-H). 3·40–3·90 (mt, O—C<u>H</u>$_2$—C<u>H</u>$_2$—), 4·19 (mt, W = 18 Hz, 3α-H equatorial). For $C_{29}H_{50}O_2$ (430·7) calculated: 80·87% C, 11·70% H; found: 80·76% C, 11·54% H.

19,5-Epoxyethano-5β,8α-cholestane-3β-ol 3-Acetate (*XIV*)

The acetate *XII* (200 mg) in acetic acid (20 ml) was hydrogenated over Adams' catalyst (100 mg) for 3 h. The catalyst was filtered off, washed with ether and the filtrate was diluted with ether (150 ml). Acetic acid was removed with 3% sodium carbonate, the ethereal solution was dried, and ether removed, the residue was crystallized from methanol to yield 145 mg of the acetate *XIV*, m.p. 161–162°C, $[\alpha]_D^{20}$ +61° (*c* 1·23). Mass spectrum: M^+ 472. IR spectrum: 1740, 1250, 1235 (acetate), 1096, 927 cm^{-1} (ether). ^{1}H-NMR spectrum: 0·83 (s, 18-H), 0.86 (d, J = 6·5 Hz,

26-H and 27-H), 0·87 (d, J = 6·5 Hz, 21-H), 2·03 (s, acetate), 3·74 and 4·15 (two d, AB syst., J = = 11 Hz, 19-H), 3·40–3·90 (mt, —O—$\underline{CH}_2$—CH_3—). 5·14 (mt, W = 18 Hz, 3α-H equatorial). For $C_{31}H_{52}O_3$ (472·7) calculated: 78·76% C, 11·09% H; found: 78·63% C, 10·87% H.

19,5-Epoxyethano-5β,8α-cholestane-3-one (*XV*)

The alcohol *XIII* (200 mg) in acetone (12 ml) was oxidized with Jones' reagent at room temperature for 20 min. The excess reagent was removed with methanol, the mixture was diluted with ether and water. The ethereal solution was worked up, and the residue after evaporation of ether was crystallized from methanol to yield 120 mg of the ketone *XV*, m.p. 107–108°C, $[\alpha]_D^{20}$ +47° (*c* 1·16). Mass spectrum: M^+ 428. IR spectrum: 1720 (carbonyl), 1096, 963 cm^{-1} (ether). For $C_{29}H_{48}O_2$ (428·7) calculated: 81·25% C, 11·29% H, found: 81·14% C, 11·18% H.

Oxidation of 19,5-Epoxyethano-5β-cholest-8-en-3β-ol 3-Acetate (*XII*) with Ruthenium Tetroxide

Ruthenium dioxide hydrate (Merck) (200 mg) was added to a stirred solution of sodium metaperiodate (3·2 g) in water (50 ml) covered with tetrachloromethane (50 ml). The mixture was stirred at 0°C for 1 h, organic layer was separated, filtered through a glass filter, and washed with a solution of sodium metaperiodate (1 g) in water (50 ml). The lower layer was poured into a solution of the acetate *XI* (70 mg) in tetrachloromethane (5 ml) and allowed to stand at 20°C for 1 g. The mixture was washed with 2% sodium sulphite, the organic layer was dried, and solvents removed *in vacuo*. The residue was purified by preparative TLC (2 plates 20 × 20 cm) in benzene–ether (1 : 1). The zone with the product (R_F 0·8) was collected, extracted with ether, and ether removed to yield 39 mg of an oily product, pure on TLC. IR spectrum: 1741, 1237 (acetate), 1096, 924 (ether), 1700 cm^{-1} (carbonyl).

The analyses were carried out in the Analytical Laboratory of this Institute by Mrs E. Sýkorová and Mrs E. Šípová under the direction of Dr J. Horáček. The IR *and* UV *spectra were recorded by Mr P. Formánek under the direction of Dr J. Smolíková. The mass spectra were recorded by Dr J. Kohoutová under the direction of Dr J. Dolejš.* ^{1}H-NMR *spectra were recorded by Dr M. Synáčkova.*

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