5,7-CYCLOSTEROIDS WITH AN OXYGEN FUNCTION IN POSITION 1*

J.FAJKOŠ and J.JOSKA

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

Received January 1st, 1974

Synthesis of the epimeric 1-hydroxy derivatives of the 5,7β-cyclo-5β-cholestane series is described and their structures established by chemical and spectral means.

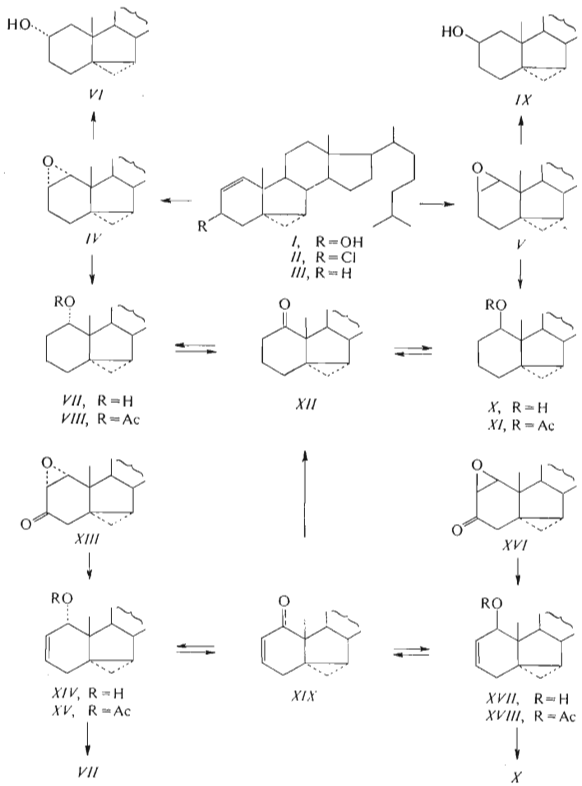
In connection with our studies on solvolysis of methanesulphonyloxy derivatives of the cyclosteroids the 5,7-cyclosteroids with an oxygen function in position 1 were of interest. In this paper we describe the synthesis of such compounds in the 5,7β--cyclo-5β-cholestane series.

We set out from the allylic alcohol *I* the synthesis of which we described recently[1]. Reaction with thionyl chloride led to the chloro derivative *II* which was reduced in crude state with lithium aluminium hydride to the olefin *III*. Its epoxidation afforded mixture of the epimeric epoxides *IV* and *V*. Their configurations follow from the steric course of their reductive cleavage: On reduction with lithium aluminium hydride the α-epoxide *IV* afforded the known[2] equatorial 2α-hydroxy derivative *VI* as the minor product whereas the epimeric epoxide *V* gave under similar condit ons the axial 2β-alcohol[2] *IX* as the main product. Simultaneously, the corresponding 1-substituted alcohols *VII* and *X* were formed on these reactions: The axial 1α-alcohol *VII* as the main product and the equatorial 1β-alcohol *X* as the minor one.

Oxidation of both alcohols gave the same ketone *XII* which in turn was reduced to a mixture of the starting alcohols *VII* and *X*. Though this reaction sequence led to the desired derivatives, the yields were not satisfactory. We therefore worked out an alternative route starting from the epimeric epoxyketones *XIII* and *XVI* the synthesis of which we also described recently[1]. These ketones when heated with hydrazin hydrate underwent reductive elimination[3,4] giving the corresponding allylic alcohols *XIV* and *XVII* in excellent yields. Their oxidation afforded the unsaturated ketone *XIX* which again yielded the starting alcohols *XIV* and *XVII* on metal hydride reduction. These alcohols were hydrogenated over Adams' catalyst in acetic acid to the saturated alcohols *VII* and *X*, identical with the compounds prepared on re-

* Part CLXIX in the series On Steroids; Part CLXVIII: This Journal *39*, 1613 (1974). Part VIII in the series 5,7-Cyclosteroids; Part VII: This Journal *38*, 1406 (1973).

ductive cleavage of the epoxides *IV* and *V*. Configurations as well as conformations of the hydroxyl groups in these saturated alcohols follow from their NMR spectra:



The 1β-proton in the alcohol *VII* shows no large diaxial coupling with any of the neighbouring protons ($W = 5$ Hz; 1α-hydroxyl axial) in contrast to the equatorial 1β-alcohol *X* ($W = 19$ Hz).

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 (TLC), 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, water, drying with magnesium sulphate, and evaporation of the solvent.

5,7β-Cyclo-5β-cholest-1-ene (*III*)

The alcohol[1] *I* (300 mg) in ether (10 ml) was treated at 0°C with thionyl chloride (0·3 ml) and allowed to stand at room temperature for 1 hour. The reaction mixture was diluted with ether, the ethereal solution was washed with a sodium hydrogen carbonate solution, water, dried, and the solvent distilled off. The residue (chloride *II*) was dissolved in ether (30 ml) and refluxed with lithiumaluminium hydride (300 mg) for 2 days. The excess hydride was decomposed with ethyl acetate, the organic layer was washed with dilute hydrochloric acid, and worked up. The residue after evaporation of the solvent contained essentially only the desired olefin (TLC). It was chromatographed over silica gel column (30 g) in ligroin. Fractions containing the olefin were worked up to yield 185 mg of the olefin *III*, $[\alpha]_D^{20}$ −23° (*c* 1·08) which resisted all attempts at crystallisation. For $C_{27}H_{44}O$ (368·6) calculated: 87·97% C, 12·03% H; found: 87·91% C, 12·16% H.

1α,2α-Epoxy-5,7β-cyclo-5β-cholestane (*IV*)

The olefin *III* (150 mg) in ether (7 ml) was treated with a solution of perphthalic acid (100 mg) in ether (1·2 ml) and set aside for 18 hours. The excess peracid was extracted into 5% sodium carbonate, the organic layer was washed with water, dried, and the solvent removed. The residue consisted of two components according to the TLC. It was chromatographed on two plates of silica gel (20 × 20 cm) in benzene. The zones with the lipophilic component were separated, the product eluted with ether, and the solvent distilled off. The residue was crystallised from ether–methanol to yield 48 mg of the epoxide *IV*, m.p. 86–87°C, $[\alpha]_D^{20}$ −33° (*c* 1·23). For $C_{27}.H_{44}O$ (384·6) calculated: 84·31% C, 11·53% H; found: 84·25% C, 11·47% H.

1β,2β-Epoxy-5,7β-cyclo-5β-cholestane (*V*)

The zones containing the polar component from the foregoing experiment were combined, eluted with ether, and the product after evaporation of the solvent was crystallised from ethyl acetate to yield 56 mg of the epoxide *V*, m.p. 139–140°C, $[\alpha]_D^{20}$ −16° (*c* 1·28). For $C_{27}H_{44}O$ (384·6) calculated: 84·31% C, 11·53% H; found: 84·19% C, 11·36% H.

5,7β-Cyclo-5β-cholestan-2α-ol (*VI*)

The epoxide *IV* (100 mg) in tetrahydrofurane (30 ml) was refluxed with lithium aluminium hydride (200 mg) for 5 hours. The excess hydride was decomposed with ethyl acetate, the reaction mix-

ture diluted with ether, and worked up. The residue was chromatographed on three plates of silica gel (20 × 20 cm) in benzene–ether (9 : 1). The zones containing the polar component were separated, eluted with ether, and the solvent removed. The residue was crystallised from methanol to yield 9 mg of the alcohol *VI*, m.p. 141°C, $[\alpha]_D^{20}$ −32° (*c* 1·19) in agreement with the literature[2].

5,7β-Cyclo-5β-cholestan-1α-ol (*VII*)

a) *From* 1α,2α-*epoxy*-5,7β-*cyclo*-5β-*cholestane* (IV): The zones with the lipophilic component from the chromatography of the foregoing experiment afforded after working up and crystallisation from diluted methanol 40 mg of the alcohol *VII*, m.p. 69—71°C, $[\alpha]_D^{20}$ −21° (*c* 1·34). NMR: −0·10 (dd, $J = 8{\cdot}5$ Hz, $J' = 4$ Hz, one cyclopropane proton), 0·64 (s, 18-H), 0·86 (d, $J = 6$ Hz, 26-H and 27-H), 0·89 (s, 19-H), 0·89 (d, $J = 6$ Hz, 21-H), 3·65 (broad t, $W = 5$ Hz, 1β-H). For $C_{27}H_{46}O$ (386·6) calculated: 83·87% C, 11·99% H; found: 83·78% C, 11·93% H.

b) *From* 5,7β-*cyclo*-5β-*cholest*-2-*en*-1α-*ol* (XIV): The alcohol *XIV* (200 mg) in acetic acid (5 ml) was hydrogenated over Adams'catalyst (20 mg) for 1 hour. Catalyst was filtered off, washed with ether (100 ml), the filtrate was washed with a sodium hydrogen carbonate solution, water, dried, and solvent distilled off. The residue was crystallised from methanol–water to yield 165 mg of the alcohol *VII*, m.p. 70—71°C, $[\alpha]_D^{20}$ −20° (*c* 1·48).

c) *From* 5,7β-*cyclo*-5β-*cholestan*-1-*one* (XII): A solution of the ketone *XII* (320 mg) in tetrahydrofuran (8 ml) was treated with lithium tri-tert-butoxyaluminium hydride (700 mg) and allowed to stand at room temperature for 30 minutes. The reaction mixture was diluted with ether (100 ml), the excess hydride decomposed with hydrochloric acid. Usual working up afforded a mixture of the epimeric alcohols *VII* and *X* in which the α-epimer predominated. It was chromatographed over silica gel (50 g) in benzene. Fractions with the lipophilic component were combined, evaporated, and the residue was crystallised from methanol–water to yield 115 mg of the alcohol *VII*, m.p. 69—70°C, $[\alpha]_D^{20}$ −23° (*c* 1·26).

1α-Acetoxy-5,7β-cyclo-5β-cholestane (*VIII*)

The alcohol *VII* (130 mg) was acetylated with acetic anhydride (0·3 ml) in pyridine (0·5 ml) for 18 hours at room temperature. The reaction mixture was decomposed with ice, the product isolated with ether, and the ethereal solution was worked up. The oily product was chromatographed over silica gel (25 g) in ligroin–benzene (1 : 1). Fractions containing the acetate were worked up to yield 115 mg of the acetate *VIII*, $[\alpha]_D^{20}$ −3° (*c* 2·43), resisting all attempts at crystallisation. For $C_{29}H_{48}O_2$ (428·7) calculated: 81·25% C, 11·29% H; found: 81·12% C, 11·23% H.

5,7β-Cyclo-5β-cholestan-2β-ol (*IX*)

The epoxide *V* (320 mg) in tetrahydrofuran (90 ml) was refluxed with lithium aluminium hydride for 5 hours. The excess hydride was removed with ethyl acetate, the reaction mixture was diluted with ether, and the ethereal solution was worked up. The residue was chromatographed over silica gel (40 g) in benzene. Fractions with the lipophilic component were combined, evaporated, and the residue was crystallised from ethanol–water to yield 182 mg of the alcohol *IX*, m.p. 169—171°C, $[\alpha]_D^{20}$ −32° (*c* 1·07) identical with the authentic[2] compound.

5,7β-Cyclo-5β-cholestan-1β-ol (*X*)

a) *From* 1β,2β-*epoxy*-5,7β-*cyclo*-5β-*cholestane* (V): Elution of the chromatography from the foregoing experiment with the same solvent afforded fractions with the polar product. Working

up and crystallisation from methanol–water afforded 42 mg of the alcohol *X*, m.p. 82—83°C, $[\alpha]_D^{20}$ −37° (*c* 1·34). NMR: −26 (dd, $J = 7{\cdot}5$ Hz, $J' = 5$ Hz, one cyclopropane proton), 0·65 (s, 18-H), 0·87 (d, $J = 6$ Hz, 26-H and 27-H), 0·90 (d, $J = 6$ Hz, 21-H), 0·90 (s, 19-H), 3·54 (mt, $W = 19$ Hz, 1α-H). For $C_{27}H_{46}O$ (386·6) calculated: 83·87% C, 11·99% H; found: 83·81% C, 11·95% H.

b) *From* 5,7β-*cyclo*-5β-*cholest*-2-*en*-1β-*ol* (XVII): The alcohol *XVII* (120 mg) in acetic acid (5 ml) was hydrogenated over Adams'catalyst (20 mg) for 1 hour. The reaction mixture was diluted with ether (100 ml) the catalyst was filtered off, washed with water, and the filtrate was washed with a sodium hydrogen carbonate solution, water, dried, and ether distilled off. The residue was crystallised from methanol–water to yield 87 mg of the alcohol *X*, m.p. 85—86°C, $[\alpha]_D^{20}$ −40° (*c* 1·52).

c) *From* 5,7β-*cyclo*-5β-*cholestan*-1-*one* (XII): Elution of the chromatography after isolation of the alcohol *VII* under *c*) with the same solvent afforded fractions with the polar product. Working up and crystallisation from methanol–water afforded 80 mg of the alcohol *X*, m.p. 83—84°C, $[\alpha]_D^{20}$ −38° (*c* 1·45).

1β-Acetoxy-5,7β-cyclo-5β-cholestane (*XI*)

The alcohol *X* (80 mg) was acetylated with acetic anhydride (0·2 ml) in pyridine (0·3 ml) for 18 hours at room temperature. Usual working up and crystallisation from methanol yielded 68 mg of the acetate *XI*, m.p. 89°C, $[\alpha]_D^{20}$ −24° (*c* 1·36). For $C_{29}H_{48}O_2$ (428·7) calculated: 81·25% C, 11·29% H; found: 81·18% C, 11·19% H.

5,7β-Cyclo-5β-cholestan-1-one (*XII*)

a) *From* 5,7β-*cyclo*-5β-*cholestan*-1α-*ol* (VII): The alcohol *VII* (110 mg) in acetone (5 ml) was treated with excess Jones'reagent and allowed to stand at room temperature for 20 minutes. The excess oxidising agent was removed with methanol, the reaction mixture was diluted with water, and the product isolated with ether, the ethereal solution was washed with water, a sodium hydrogen carbonate solution, water, dried, and evaporated. The residue was crystallised from ethanol to yield 90 mg of the ketone *XII*, m.p. 103—104°C, $[\alpha]_D^{20}$ +53° (*c* 1·19). NMR: −0·21 (dd, $J = 8$ Hz, $J' = 5$ Hz, one cyclopropane proton), 0·63 (s, 18-H), 0·85 (d, $J = 6$ Hz, 26-H and 27-H), 0·89 (d, $J = 6$ Hz, 21-H), 1·19 (s, 19-H). For $C_{27}H_{44}O$ (384·6) calculated: 84·31% C, 11·53% H; found: 84·29% C, 11·43% H.

b) *From* 5,7β-*cyclo*-5β-*cholestan*-1β-*ol* (X): The alcohol *X* (90 mg) in acetone (5 ml) was oxidised with Jones' reagent as described in the previous experiment. Similar working up and crystallisation from ethanol gave 65 mg of the ketone *XII*, m.p. 104—105°C, $[\alpha]_D^{20}$ +55° (*c* 1·63).

c) *From* 5,7β-*cyclo*-5β-*cholest*-2-*en*-1-*one* (XIX): The ketone *XIX* (180 mg) in ethyl acetate (10 ml) was hydrogenated over 5% $Pd/CaCO_3$ catalyst (40 mg) for 2 hours. The reaction mixture was diluted with ether, catalyst was filtered off and washed with ether, the filtrate was washed with dilute hydrochloric acid, and worked up. The residue was chromatographed on a silica gel column in benzene. The corresponding fractions were worked up, and the residue was crystallised from ethanol to yield 115 mg of the ketone *XII*, m.p. 104—105°C, $[\alpha]_D^{20}$ +57° (*c* 1·26).

5,7β-Cyclo-5β-cholest-2-en-1α-ol (*XIV*)

a) *From* 1α,2α-*epoxy*-5,7β-*cyclo*-5β-*cholestan*-3-*one* (XIII): The ketone *XIII* (500 mg) was heated with 90% hydrazin hydrate (9 ml) 5 minutes to the boiling point. After cooling off to the

room temperature the mixture was diluted with ether (100 ml) and the ethereal solution was worked up. The oily residue was chromatographed over silica gel (50 g) in benzene. Fractions with the allylic alcohol were combined and evaporated to yield 280 mg of the alcohol *XIV*, $[\alpha]_D^{20}$ +71° (*c* 1·32) which resisted all attempts at crystallisation. NMR (deuteriochloroform with tetramethylsilane as internal reference): 0·67 (s, 18-H), 0·85 (s, 19-H), 0·87 (d, $J = 6$ Hz, 26-H and 27-H), 0·91 (d, $J = 6$ Hz, 21-H), 1·44 (s, hydroxyl), 1·60 (dd, $J_{4,4} = 18$ Hz, $J_{4,3} = 4$ Hz, $J_{4,2} = 0$ Hz, 4β-H), 2·62 (broad d, $J_{4,4} = 18$ Hz, $J_{4,3} = J_{4,2} = 1·5$ Hz, 4α-H), 3·72 (broad d, $J_{1,2} = 4$ Hz, $J_{1,3} = 1·5$ Hz, 1β-H), 5·91 (mt, 2-H and 3-H). For $C_{27}H_{44}O$ (384·6) calculated: 84·31% C, 11·53% H; found: 84·36% C, 11·48% H.

b) *From* 5,7β-*cyclo*-5β-*cholest*-2-*en*-1-*one* (XIX): The ketone *XIX* (200 mg) was dissolved in ether (50 ml) and treated at −30°C with lithium aluminium hydride (40 mg). The reaction mixture was allowed to reach slowly 0°C, then the hydride was decomposed with ice cold saturated solution of sodium sulphate, dry sodium sulphate was added, the solid filtered off and washed with ether. The filtrate was evaporated and the residue was chromatographed on a silica gel column (25 g) in benzene. Fractions with the lipophilic component were combined and evaporated to yield 42 mg of the alcohol *XIV*, $[\alpha]_D^{20}$ +68° (*c* 1·14).

1α-Acetoxy-5,7β-cyclo-5β-cholest-2-ene (*XV*)

The alcohol *XIV* (65 mg) in pyridine (0·2 ml) was acetylated with acetic anhydride (0·15 ml) at room temperature for 18 hours. Usual working up afforded an oily product which was chromatographed on one plate of silica gel (20 × 20 cm) in ligroin–benzene (1 : 1). The corresponding zone was eluted with ether, and the solvent was distilled off to yield 58 mg of the acetate *XV*, $[\alpha]_D^{20}$ +108° (*c* 2·32) resisting all attempts at crystallisation. For $C_{29}H_{46}O_2$ (426·7) calculated: 81·63% C, 10·87% H; found: 81·59% C, 10·75% H.

5,7β-Cyclo-5β-cholest-2-en-1β-ol (*XVII*)

a) *From* 1β,2β-*epoxy*-5,7β-*cyclo*-5β-*cholestan*-3-*one* (XVI): A suspension of the ketone *XVI* (1 g) in 90% hydrazin hydrate (18 ml) was heated to the boiling point for 5 minutes. After cooling off the reaction mixture was diluted with ether and water, and the ethereal solution was worked up. The residue after evaporation of ether was chromatographed on a silica gel column (70 g) in benzene. Fractions with the allylic alcohol were combined, solvent was distilled off, and the residue was crystallised from n-heptane. Yield 720 mg of the alcohol *XVII*, m.p. 120—121°C, $[\alpha]_D^{20}$ −15° (*c* 1·32). NMR: −0·16 (dd, $J = 8$ Hz, $J' = 5·5$ Hz, one cyclopropane proton), (deuteriochloroform with tetramethylsilane as internal reference): 0·65 (s, 18-H), 0·86 (d, $J = 6$ Hz, 26-H and 27-H), 0·88 (s, 19-H), 0·90 (d, $J = 6$ Hz, 21-H), 2·58 (broad d, $J_{4,4} = 17$ Hz, 4-H, one proton), 4·13 (mt, $W = 14$ Hz, 1α-H), 5·52 and 5·81 (two d, $J = 10$ Hz, 2-H and 3-H). For $C_{27}H_{44}O$ (384·6) calculated: 84·31% C, 11·53% H; found: 84·26% C, 11·38% H.

b) *From* 5,7β-*cyclo*-5β-*cholest*-2-*en*-1-*one* (XIX): Elution of the chromatography after isolation of the alcohol *XIV* under *b*) with the same solvent yielded fractions with the lipophilic component. Working up and crystallisation from n-heptane afforded 95 mg of the alcohol *XVII*, m.p. 121—122°C, $[\alpha]_D^{20}$ −14° (*c* 1·65).

1β-Acetoxy-5,7β-cyclo-5β-cholest-2-ene (*XVIII*)

The alcohol *XVII* (110 mg) was acetylated with acetic anhydride (0·2 ml) in pyridine (0·3 ml) for 18 hours at room temperature. Usual working up gave the crude product which was chromato-

graph ed on two plates of silica gel in ligroin–benzene (1 : 1) The corresponding zones afforded working up 95 mg of the acetate *XVIII*, $[\alpha] -23°$ (*c* 1·76) resisting all attempts at crystallisation. For $C_{29}H_{46}O_2$ (426·7) calculated: 81·63% C, 10·87% H; found: 81·58% C, 10·76% H.

5,7β-Cyclo-5β-cholest-2-en-1-one (*XIX*)

a) *From* 5,7β-*cyclo*-5β-*cholest*-2-*en*-1α-*ol* (XIV): The alcohol *XIV* (85 mg) in acetone (4 ml) was treated with excess Jones' reagent. After 15 minutes at room temperature the excess reagent was removed with methanol, the reaction mixture was diluted with water, and the product taken into ether. The ethereal solution was washed with water, a sodium hydrogen carbonate solution, water, dried, and evaporated. The residue was crystallised from methanol to yield 63 mg of the ketone *XIX*, m.p. 114—115°C, $[\alpha]_D^{20} +59°$ (*c* 1·35). UV: λ_{max} 223 nm ($\log \varepsilon$ 3·76; ethanol). IR: 3060, 1685, 1620, 1608 cm^{-1}. For $C_{27}H_{42}O$ (382·6) calculated: 84·75% C, 11·07% H; found: 84·66% C, 11·01% H.

b) *From* 5,7β-*cyclo*-5β-*cholest*-2-*en*-1β-*ol* (XVII): The alcohol *XVII* (100 mg) was oxidised with Jones' reagent in acetone (5 ml) as described in the foregoing experiment. Similar working up and crystallisation from methanol afforded 70 mg of the ketone *XIX*, m.p. 113—115°C, $[\alpha]_D^{20} +61°$ (*c* 1·09).

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 infra red and ultra violet 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.

REFERENCES

1. Fajkoš J., Buděšínský M., Joska J.: This Journal *38*, 1406 (1973).
2. Fajkoš J., Joska J., Šorm F.: This Journal *33*, 3356 (1968).
3. Wharton P. S., Bohlen D. H.: J. Org. Chem. *26*, 3615 (1961).
4. Djerassi C., Williams D. H., Berkoz B.: J. Org. Chem. *27*, 2205 (1962).

Translated by the author (J. F.).