19-HYDROXY STEROIDS SUBSTITUTED IN POSITION 7*

J.FAJKOŠ and J.JOSKA

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

Received September 29th, 1975

Synthesis of 7-oxygenated 19-hydroxycholestane derivatives is described and the structure of the products established by spectral means.

In the course of our studies of the relationship between structure and biological activity of steroids we became interested in 7-oxygenated derivatives. In this paper we describe synthesis of a series of 7-oxygenated 19-hydroxycholestane derivatives required as starting compounds and models for further work.

The key-intermediate, ketone *II*, was prepared from the diacetate *I* by oxidation with tert-butyl chromate in tetrachloromethane at 85°C in about 40% yield. Reduction with lithium tri-tert-butoxyaluminium hydride afforded a mixture of the epimeric alcohols *III* and *IV* in which the equatorial alcohol *IV* predominated. Configurations of the hydroxyl groups in these alcohols follows from their ^{1}H-NMR spectra. Ketone *II* when hydrogenated in ethyl acetate–ethanol over Adams' catalyst yielded about 20% of a lipophilic product and about 80% of a polar component, evidently isomers at $C_{(5)}$. To establish the configuration, the main product was submitted to Huang-Minlon reduction to give the known[1] diol *IX* of 5α-series. The main product is therefore the 5α-isomer *VIII* and the minor product the 5β-isomer *VI*. Both diacetates were also characterised as diols *V* and *VII*. The ketone *VIII* was then reduced with lithium tri-tert-butoxyaluminium hydride in tetrahydrofuran to yield the 7β-epimer *XIII* as the main product. About 20% of the 7α-epimer were also isolated. Structures were again assigned on the basis of ^{1}H-NMR spectra and the compounds were characterised as triols *X* and *XII*.

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 ^{1}H-NMR spectra were recorded on the Varian HA-100 instrument in chloroform and

* Part CLXXXI in the series On Steroids; Part CLXXX: This Journal *41*, 140 (1976).

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 solution, water, drying with magnesium sulphate, and evaporation of the solvent.

3β,19-Diacetoxy-5-cholesten-7-one (*II*)

A solution of the diacetate *I* (5 g) in tetrachloromethane (30 ml) was heated to 85°C and treated dropwise under stirring with a solution of tert-butyl chromate (40 ml) in acetic acid (12·6 ml) and acetic anhydride (5·5 ml). The butyl chromate was added in the course of 30 min, stirring was continued for additional 18 h at 80—85°C. The mixture was cooled with ice and treated in the course of 45 minutes with a solution of oxalic acid (8·5 g) in water (85 ml) and then with solid oxalic acid (6 g) and stirring was continued for 2 h. The organic layer was separated. The upper layer was extracted twice with chloroform and the combined organic extracts were washed with a sodium hydrogen carbonate solution, water, dried, and the solvent was removed. The residue was chromatographed on a silica gel column (250 g) in benzene. Working up of the corresponding fractions gave 2·58 g of the product which was crystallised from methanol–water to yield 1·8 g of the ketone *II*, m.p. 97—98°C, $[\alpha]_D^{20}$ —119° (*c* 1·51). For $C_{31}H_{48}O_5$ (500·7) calculated: 74·36% C, 9·66% H; found: 74·31% C, 9·82% H.

3β,19-Diacetoxy-5-cholesten-7α-ol (*III*)

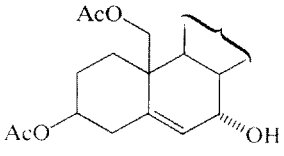
The ketone *II* (2 g) in tetrahydrofuran (50 ml) was treated at room temperature with lithium tri-tert-butoxyaluminium hydride (5 g) and allowed to stand for 30 minutes. The mixture was diluted with ether, the excess hydride was decomposed with dilute hydrochloric acid, and the ethereal layer was worked up. The oily residue contained according to the TLC about 20% of a lipophilic and about 80% of a polar component. The mixture was chromatographed on a silica gel column (350 g) in benzene–ether (19 : 1). Fractions with the lipophilic component were combined, and the solvent removed to yield 320 mg of an oily product $[\alpha]_D^{20}$ —73° (*c* 1·33). ^{1}H-NMR: 0·71 (s, 18-H), 0·86 (d, J = 6 Hz, 26- and 27-H), 0·92 (d, J = 6 Hz, 21-H), 2·02 (s, two acetates), 3·95 and 4·55 (two d, J = 12 Hz, 19-H), 3·90 (q, $J_{7,8}$ = 3·8 Hz, $J_{7,6}$ = 5·4 Hz, 7β-H), 4·68 (mt, 3-H), 5·81 (d, J = 5·4 Hz, 6-H). For $C_{31}H_{50}O_5$ (502·7) calculated: 74·06% C, 10·03% H; found: 74·32% C, 10·09% H.

3β,19-Diacetoxy-5-cholesten-7β-ol (*IV*)

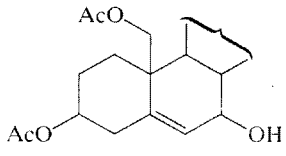
Elution of the chromatography from the foregoing experiment with the same solvent mixture yielded the polar component. Working up of the corresponding fractions and crystallization from methanol–water gave 1·25 g of the alcohol *IV*, m.p. 109—110°C, $[\alpha]_D^{20}$ —33° (*c* 1·28). ^{1}H-NMR: 0·72 (s, 18-H), 0·87 (d, J = 6 Hz, 26- and 27-H), 0·92 (d, J = 6 Hz, 21-H), 1·60 (s, hydroxyl), 2·02 (s, 3-acetate), 2·06 (s, 19-acetate), 3·82 (q, $J_{7,8}$ = 7·5 Hz, $J_{7,6}$ = 2 Hz, 7α-H), 3·98 and 4·52 (two d, J = 12 Hz, 19-H), 4·63 (broad m, 3-H), 5·56 (broad s, 3-H). For $C_{31}H_{50}O_5$ (502·7) calculated: 74·06% C, 10·03% H; found: 74·55% C, 10·18% H.

3β,19-Dihydroxy-5β-cholestan-7-one (*V*)

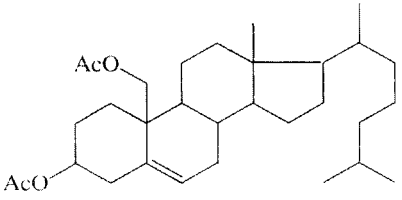
The diacetate *VI* (150 mg) was refluxed with a solution of potassium hydroxide (100 mg) in methanol (10 ml) for 2 h. Methanol was removed under reduced pressure, the residue was diluted



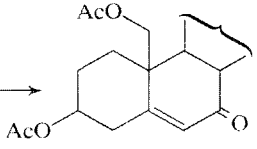
III



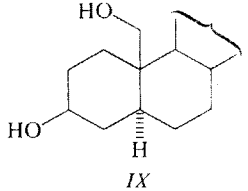
IV



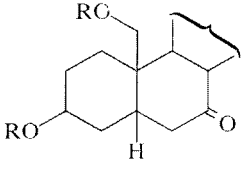
I



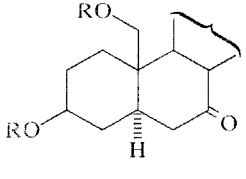
II



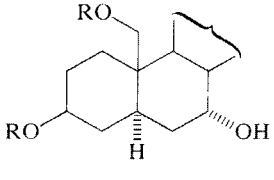
IX



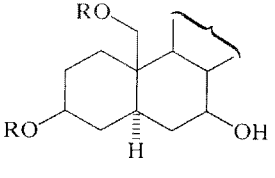
V, R = H
VI, R = Ac



VII, R = H
VIII, R = Ac



X, R = H
XI, R = Ac



XII, R = H
XIII, R = Ac

with water, and the product taken into ether. The ethereal solution was washed with water, dried, and ether distilled off. The residue was crystallised from methanol–water to yield 90 mg of the diol *V*, m.p. 165–166°C, $[\alpha]_D^{20}$ −9° (*c* 1·12). For $C_{27}H_{46}O_3$ (418·6) calculated: 77·46% C, 11·08% H; found: 77·52% C, 11·17% H.

3β,19-Diacetoxy-5β-cholestan-7-one (*VI*)

A solution of the ketone *II* (1·4 g) in ethyl acetate (50 ml) and ethanol (5 ml) was hydrogenated over 5% Pd/$CaCO_3$ catalyst for 3 h. Catalyst was filtered off, washed with ether, and the filtrate was evaporated. The residue contained according to TLC two components, about 20% of the lipophilic and 80% of the polar one. The mixture was chromatographed on a silica gel column (200 g) in benzene. Fractions with the lipophilic component were combined, and the solvent removed. Yield 200 mg of an oily product $[\alpha]_D^{20}$ −69° (*c* 1·09). For $C_{31}H_{50}O_5$ (502·7) calculated: 74·06% C, 10·03% H; found: 73·92% C, 9·95% H.

3β,19-Dihydroxy-5α-cholestan-7-one (*VII*)

The diacetate *VIII* (280 mg) was refluxed with a solution of potassium hydroxide (150 mg) in methanol (20 ml) for 3 h. Methanol was distilled off *in vacuo*, the residue dissolved in ether, the ethereal solution was washed with water, dried, and ether removed. The residue was crystallised from methanol to afford 210 mg of the diol *VII*, m.p. 174–175°C (recrystallisation at 140–145°C), $[\alpha]_D^{20}$ −26° (*c* 1·82). For $C_{27}H_{46}O_3$ (418·6) calculated: 77·46% C, 11·08% H; found: 77·58% C, 11·32% H.

3β,19-Diacetoxy-5α-cholestan-7-one (*VIII*)

Elution of the chromatography after isolation of the 5β-isomer *VI* with the same solvent afforded fractions with the polar compound. Combination and evaporation of the solvent gave 1·03 g of the crude product which on crystallisation from methanol afforded 740 mg of the diacetate *VIII*, m.p. 87–88°C, $[\alpha]_D^{20}$ −32° (*c* 1·54). For $C_{31}H_{50}O_5$ (502·7) calculated: 74·06% C, 10·03% H; found: 74·28% C, 10·21% H.

5α-Cholestan-3β,19-diol (*IX*)

The ketone *VII* (200 mg) was heated with a solution of potassium hydroxide (300 mg) and hydrazin hydrate (98%, 1·8 ml) in triethylene glycol (10 ml) slowly to 190°C and then kept at the same temperature for 3 h. The mixture was diluted with water, the product was taken into ether, and the ethereal solution was washed with dilute hydrochloric acid, a sodium hydrogen carbonate solution, water, dried, and ether removed. The residue was crystallised from methanol to yield 105 mg of the diol *IX*, m.p. 177°C, $[\alpha]_D^{20}$ +34° (1·12), identical with the authentic sample.

5α-Cholestan-3β,7α,19-triol (*X*)

The diacetate *XI* (220 mg) was refluxed with a solution of potassium hydroxide (100 mg) in methanol (15 ml) for 2 h. Methanol was distilled off under reduced pressure, the residue was diluted with water, and the product isolated with ether. The ethereal solution was washed with water, dried, and ether removed. The residue was crystallised from methanol–water to yield 165 mg of the triol *X*, 183–184°C, $[\alpha]_D^{20}$ +16° (*c* 1·43). For $C_{27}H_{48}O_3$ (420·7) calculated: 77·09% C, 11·50% H; found: 77·16% C, 11·43% H.

3β,19-Diacetoxy-5α-cholestan-7α-ol (*XI*)

A solution of the ketone *VIII* (600 mg) in tetrahydrofuran (30 ml) was treated at room temperature. with solid lithium tri-tert-butoxyaluminium hydride (1·5 g) and allowed to stand for 30 minutes The excess hydride was removed with water and dilute hydrochloric acid, and the product was extracted with ether. The ethereal solution was worked up to yield an oily product containing according to the TLC about 30% of a lipophilic and 70% of a polar component. The mixture was chromatographed on a silica gel column (50 g) in benzene–ether (9 : 1). Fractions with the lipophilic component were combined, and solvent removed to yield 180 mg of the oily alcohol *XI*, $[\alpha]_D^{20}$ −21° (*c* 1·18), ^{1}H-NMR: 0·65 (s, 18-H), 0·86 (d, J = 6·5 Hz, 26- and 27-H), 0·89 (d, J = = 6 Hz, 21-H), 1·60 (s, hydroxyl), 1·99 and 2·05 (two s, acetates), 3·86 (mt, W = 10 Hz, 7-H equatorial), 4·21 and 4·37 (two d, J_{gem} = 13 Hz, 19-H), 4·77 (broad m, W = 33 Hz, 3-H axial). For $C_{31}H_{52}O_5$ (504·7) calculated: 73·76% C, 10·39% H; found: 73·82% C, 10·48% H.

5α-Cholestan-3β,7β,19-triol (*XII*)

The diacetate *XIII* (320 mg) was refluxed for 2 h with a solution of potassium hydroxide (120 mg) in methanol (25 ml). Methanol was removed under reduced pressure, the product extracted into ether, and the ethereal solution was washed with water, dried, and ether removed. The residue was crystallised from methanol–water to give 205 mg of the triol *XII*, m. p. 180–181°C, $[\alpha]_D^{20}$ −54° (*c* 2·18). For $C_{27}H_{48}O_3$ (420·7) calculated: 77·09% C, 11·50% H; found: 77·22% C, 11·61% H.

3β,19-Diacetoxy-5α-cholestan-7β-ol (*XIII*)

Elution of the chromatography after isolation of the 7α-epimer *XI* afforded fractions with the polar component. Working up gave 385 mg of the oily alcohol *XIII*, $[\alpha]_D^{20}$ +22° (*c* 2·28). ^{1}H-NMR: 0·68 (s, 18-H), 0·86 (d, J = 6·5 Hz, 26- and 27-H), 0·90 (d, J = 6 Hz, 21-H), 2·01 and 2·07 (two s, acetates), 3·39 (mt, W = 24 Hz, 7-H axial), 4·22 and 4·36 (two d, J_{gem} = 13 Hz, 19-H), 4·71 (broad m, W = 35 Hz, 3-H axial). For $C_{31}H_{52}O_5$ (504·7) calculated: 73·76% C, 10·39% H; found: 74·02% C, 10·31% 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 J. Dr Smolíková. The ^{1}H-NMR spectra were recorded and interpreted by Dr M. Buděšinský.

REFERENCES

1. Watanabe Y., Mizuhata Y., Shiota M.: J. Org. Chem. *31*, 3785 (1966).

Translated by the author (J. F.).