LEAD TETRAACETATE OXIDATION OF 3β-ACETOXY-B-HOMO-5α-CHOLESTAN-7aβ-OL*

Ladislav KOHOUT and Jaroslav ZAJÍČEK

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

Received June 9th, 1983

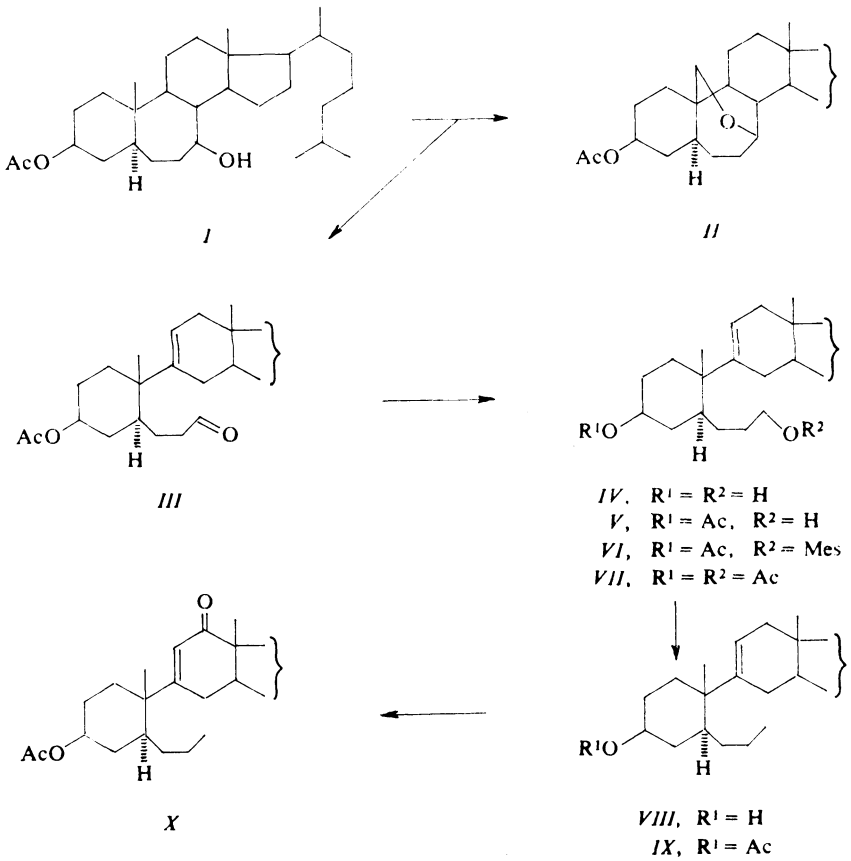
Oxidation of the alcohol *I* with lead tetraacetate afforded low yields of the 7aβ,19-epoxide *II* and an aldehyde which represented the main product. The structure of this aldehyde as th-3β-acetoxy-7a,8-seco-B-homo-5α-cholest-9(11)-en-7a-one (*III*) has now been established by chee mical and spectral means.

In one of our earlier papers[1] dealing with conformation of the B-homosteroid seven membered B-ring we have been studying lead tetraacetate oxidation of a series of alcohols with the hydroxyl groups located at various positions of the B-homo ring. Usually, the corresponding cyclic ethers were formed in excellent yields with the only exception, this being the oxidation of the 7aβ-alcohol *I*. In this case only about 4% of the expected epoxide *II* were isolated and the main product was an unsaturated aldehyde. We now have been able to establish the structure of this aldehyde and our results are presented in this paper.

The infrared spectrum proves presence of an acetoxy group (1 733, 1 246 and 1 031 cm^{-1}), of an aldehyde function (2 810 and 2 710 cm^{-1}) and of a double bond (3 040 cm^{-1}). The mass spectrum proves that cleavage of one ring of the steroid skeleton took place. Our compound is there fore an unsaturated 7a,8-seco derivative with the aldehydic function at $C_{(7)}$. The ^1H NMR spectrum shows a singlet at δ = = 2·03 for the 3β-acetoxy group with the corresponding axial proton (δ = 4·44, $\sum J \approx 32$ Hz). The aldehydic proton is represented by a triplet at δ = 9·73 (J = 1·8 Hz). We may therefore presume that the aldehydic group is attached to a methylene group with two equivalent protons and that this group is located at $C_{(7)}$. As far as the double bond is concerned the spectrum shows presence of one olefinic proton which appears at δ = 5·48 as a complicated multiplet with one large (J = 5·4 Hz) and some smaller ($J \leq 1{\cdot}5$ Hz) interactions. The large interaction and one of the small ones represent the couplings with the protons of one neighbouring methylene group ($\delta \approx 2{\cdot}2$, $\delta \approx 1{\cdot}9$) as follows from decoupling experiments. From the four possible locations of the double bond (8,9-, 9,11-, 8,14-, and 14,15-) we may therefore exclude the 8,9- and 8,14- positions.

* Part CCCII in the series On Steroids; Part CCCI: This Journal *49*, 157 (1984).

To get further information about the location of the double bond some chemical transformations were necessary. First of all we reduced the carbonyl group with lithium tri-tert-butoxyaluminium hydride to the hydroxy derivative *V* and transformed it to the mesylate *VI*. Reductive cleavage with lithium aluminium hydride afforded smoothly the desired alcohol *VIII* which was acetylated to the acetate *IX*. This



olefin when oxidised with tert-butyl chromate in tetrachlormethane yielded a ketone with the carbonyl maximum at 1 682 cm^{-1} in the infrared region. This excludes the presence of the carbonyl group in the five membered ring and proves structure *X* for this product of butyl chromate oxidation. The 9,11-position of the double bond follows also from the ^1H NMR spectrum where the signal of the olefinic proton at $\delta = 5{\cdot}83$ appears as a doublet with an allylic coupling of $J = 1{\cdot}9$ Hz with one of the protons at $C_{(8)}$. In the olefin *IX* the chemical shifts of the angular methyl groups found experimentally ($\delta = 0{\cdot}57$, 18-H and $\delta = 1{\cdot}02$, 19-H) are in good

agreement with the calculated values[2] (δ = 0·58, 18-H and δ = 0·97, 19-H) obtained on the basis of the additivity of the effects of the substituents, *i.e.* the 3β-acetoxy group, the 9,11-double bond, and the cholestane side chain on the chemical shifts of the angular methyl groups. This fact, however, can not be considered as an evidence for the structure assigned to this compound because of its modified skeleton. In the ^{1}H NMR spectrum of the compound *IX* the methyl group at $C_{(7)}$ appears as a triplet at δ = 0·84 with a coupling constant of J = 6·8 Hz. The signal of the olefinic proton (δ = 5·43) is again represented by a multiplet with one large (J = 5·4 Hz) and several small ($J \leqq 1{\cdot}5$ Hz) interactions. On the basis of the decoupling experiments we may assign in the acetate *IX* the chemical shift of δ = 2·23 (dd, $J_{12\beta,11}$ = 5·4 Hz, J_{gem} = −16·9 Hz) to the equatorial 12β-proton and the chemical shift of δ = 1·96 to the axial 12α-proton.

We can therefore conclude that the main product of lead tetraacetate oxidation of the 7aβ-alcohol *I* is 3β-acetoxy-7a,8-seco-B-homo-5α-cholest-9(11)-en-7a-one (*III*).

EXPERIMENTAL

Melting points were determined on a Kofler block. Optical rotations were carried out in chloroform with an error of ±3°. The infrared spectra were recorded on the Zeiss UR 20 spectrometer in tetrachlormethane. The ^{1}H NMR spectra of compounds *III*, *V*, *VIII*, *IX*, and *X* were recorded at 200 MHz on a Varian XL-200 instrument in deuteriochloroform. Spectra of the remaining compounds were measured on the Tesla 60 MHz instrument, tetramethylsilane was used as internal standard. The chemical shifts are given on δ-scale. The signals of the 21, 26, and 27 protons which appeared in the ^{1}H NMR spectra at usual positions are not given in the experimental part. The mass spectra were recorded on the mass spectrometer MCH 1303 and AEI MS 902 respectively. Plates with 200 × 200 × 0·7 mm silica gel layer were used for preparative TLC. Usual working up of a solution implies washing the solution with 5% aqueous hydrochloric acid, water, 5% aqueous potassium hydrogen carbonate solution, water, drying over sodium sulphate, and evaporation of the solvent under reduced pressure. Ligroin refers to fraction of b.p. 40—62°C.

3β-Acetoxy-7a,8-seco-B-homo-5α-cholest-9(11)-en-7a-one (*III*)

The alcohol *I* (1·75 g) was dissolved in benzene (80 ml) and 8 ml were distilled off to remove traces of moisture. Lead tetraacetate (2·9 g) was added and the mixture was refluxed under stirring and irradiation with a Nitraphot lamp (500 W) for 1 h, then diluted with ether (80 ml), the solid was filtered off and the filtrate was washed with 5% sodium hydrogen carbonate, water, dried, and the solvents were removed under reduced pressure. The oily residue (1·8 g) was chromatographed over silica gel (200 g) in ligroin–ether (19 : 1). Fractions with the main product were worked up to yield after evaporation of the solvents 780 mg of the aldehyde *III* resisting all attempts at crystallisation; $[\alpha]_D^{20}$ +49° (*c* 1·4). IR spectrum: 3 040 (double bond), 2 810, 2 715 (aldehyde), 1 733, 1 246, 1 031 cm^{-1} (acetate). Mass spectrum: *m/z* 398 (M−CH_3COOH), 247 (M−CH_3COOH−$C_{10}H_{15}O$). ^{1}H NMR spectrum: 0·57 (s, 18-H), 1·02 (s, 19-H), 2·03 (s, 3β-acetate), 4·66 (mt, $\Sigma J \approx$ 32 Hz, 3α-H), 5·48 (mt, $J_{11,12\beta}$ = 5·4 Hz, 11-H), 9·73 (t, J = 1·8 Hz, 7a-H). For $C_{30}H_{50}O_3$ (458·7) calculated: 78·55% C, 10·99% H; found: 78·37% C, 11·15% H.

7a,8-Seco-B-homo-5α-cholest-9(11)-ene-3β,7a-diol (*IV*)

The acetate *V* (88 mg) in methanol (8 ml) was refluxed with a solution of potassium carbonate (100 mg) in water (2 ml) for 2 h. Methanol was distilled off *in vacuo* and the product was isolated with ether. The ethereal solution was washed with water, dried, and ether was distilled off. The residue (85 mg) was crystallised from methanol to yield 52 mg of the diol *IV*, m.p. 186–187°C, $[\alpha]_D^{20}$ +63° (*c* 0·7). IR spectrum: 3 610, 1 030 cm^{-1} (hydroxyl). For $C_{28}H_{50}O_2$ (418·7) calculated: 80·32% C, 12·04% H; found: 80·05% C, 12·11% H.

7a,8-Seco-B-homo-5α-cholest-9(11)-ene-3β,7a-diol 3-Acetate (*V*)

A solution of the aldehyde *III* (330 mg) in tetrahydrofuran (22 ml) was treated with solid lithium tri-tert-butoxyaluminium hydride (660 mg) and allowed to stand at room temperature for 1 h. The mixture was diluted with ether, the excess hydride was decomposed with 5% hydrochloric acid and the product was isolated with ether as usual. Working up and evaporation of ether afforded a residue which was chromatographed over silica gel (30 g) in benzene–ether (49 : 1). The corresponding fractions were combined, solvents removed, and the product was crystallised from methanol–water to afford 155 mg of the monoacetate *V*, m.p. 76–78·5°C, $[\alpha]_D^{20}$ +58° (*c* 0·8). IR spectrum: 3 630 (hydroxyl), 3 040 (double bond), 1 734, 1 246, 1 030 cm^{-1} (acetate). ^{1}H NMR spectrum: 0·58 (s, 18-H), 0·99 (s, 19-H), 2·03 (s, acetate), 2·23 (dd, $J_{gem} \approx -17{\cdot}0$ Hz, 12β-H), 3·58 (mt, $\Sigma J \approx 15{\cdot}2$ Hz, 7a-H), 4·68 (mt, $J_{3\alpha,2\beta} \approx J_{3\alpha,4\beta} \doteq 10{\cdot}8$ Hz, $J_{3\alpha,2\alpha} \approx J_{3\alpha,4\alpha} \approx \approx 4{\cdot}6$ Hz, 3α-H), 5·44 (mt, $J_{11,12\beta} \approx 5{\cdot}4$ Hz, 11-H). For $C_{30}H_{52}O_3$ (460·7) calculated: 78·20% C, 11·38% H; found: 77·82% C, 11·49% H.

7a,8-Seco-B-homo-5α-cholest-9(11)-ene-3β,7a-diol 3-Acetate 7a-Methanesulphonate (*VI*)

A solution of the alcohol *V* (240 mg) in pyridine (4 ml) was treated at 0°C with methanesulphonyl chloride (0·4 ml) and allowed to stand at 0°C for 3 h. The mixture was decomposed with ice and the product was taken into ethyl acetate. Usual working up yielded 250 mg of the oily mesylate *VI*. IR spectrum: 3 030, 1 639 (double bond), 1 732, 1 243 (acetate), 1 365, 1 179 (—SO_2—) cm^{-1}. ^{1}H NMR spectrum: 0·58 (s, 18-H), 0·99 (s, 19-H), 2·00 (s, acetate), 2·92 (s, mesylate), 4·14 (t, $J = 6$ Hz, 7a-H), 4·62 (mt, $\Sigma J \approx 30$ Hz, 3α-H), 5·45 (mt, 11-H).

7a,8-Seco-B-homo-5α-cholest-9(11)-ene-3β,7a-diol 3,7a-Diacetate (*VII*)

The alcohol *IV* (220 mg) was acetylated with acetic anhydride (0·8 ml) in pyridine (1 ml) for 18 h at room temperature. Usual working up afforded 230 mg of an oily product which was chromatographed on a silica gel column (11 g) in ligroin–ether (49 : 1). Fractions containing the desired product were combined and solvents removed *in vacuo*. Yield, 210 mg of the oily diacetate *VII*, $[\alpha]_D^{20}$ +34° (*c* 1·2). IR spectrum: 3 040 (double bond), 1 740, 1 245, 1 030 cm^{-1} (acetate). ^{1}H NMR spectrum: 0·59 (s, 18-H), 0·97 (s, 19-H), 1·99 and 2·01 (two s, acetates), 3·99 (t, $J = 6{\cdot}5$ Hz, 7a-H), 4·66 (broad mt, 3α-H), 5·47 (mt, 11-H). For $C_{32}H_{54}O_4$ (502·7) calculated: 76·44% C, 10·83% H; found: 76·39% C, 10·82% H.

7a,8-Seco-B-homo-5α-cholest-9(11)-en-3β-ol (*VIII*)

The mesylate *VI* (280 mg) in tetrahydrofuran (9 ml) was treated with lithium aluminium hydride (360 mg) in tetrahydrofuran (9 ml) for 90 min. The excess hydride was decomposed with wet ether and with ethyl acetate, water was added and the product was isolated with ether. Usual working up afforded a product which was purified by preparative TLC on three plates of silica

gel in benzene–ether (4 : 1). Working up of the corresponding zones yielded 130 mg of the oily alcohol *VIII*, $[\alpha]_D^{20}$ +41° (*c* 0·7). IR spectrum: 3 615, 1 040 (hydroxyl), 3 040, 1 640 cm^{-1} (double bond). Mass spectrum: M^+ 402. ^1H NMR spectrum: 0·59 (s, 18-H), 0·97 (s, 19-H), 0·85 (t, J = = 6·8 Hz, 7a-H), 2·23 (dd, $J_{gem} = -16·9$ Hz, 12β-H), 3·56 (mt, $J_{3\alpha,2\beta} \approx J_{3\alpha,4\beta} \approx 11·0$ Hz, $J_{3\alpha,2\alpha} \approx J_{3\alpha,4\alpha} \approx 4·2$ Hz. 3α-H), 5·43 (mt, $J_{11,12\beta} = 5·4$ Hz, 11-H). For $C_{28}H_{50}O$ (402·7) calculated: 83·51% C, 12·52% H; found: 83·79% C, 12·22% H.

7a,8-Seco-B-homo-5α-cholest-9(11)-en-3β-ol 3-Acetate (*IX*)

The alcohol *VIII* (300 mg) in pyridine (2 ml) was acetylated with acetic anhydride (1·2 ml) at room temperature for 18 h. Usual working up gave 305 mg of a crude product which after crystallisation from ethanol afforded 120 mg of the acetate *IX*, m.p. 69—70°C, $[\alpha]_D^{20}$ +63° (*c* 1·8). IR spectrum: 3 040, 1 642 (double bond), 1 736, 1 246, 1 036, 1 028 cm^{-1} (acetate). Mass spectrum: M^+ 444. ^1H NMR spectrum: 0·58 (s, 18-H), 0·84 (t, J = 6·8 Hz, 7a-H), 0·98 (s, 19-H), 1·96 (bd, $J_{gem} = -16·9$ Hz, 12α-H), 2·03 (s, acetate), 2·23 (dd, $J_{12\beta,11} = 5·4$ Hz, 12β-H), 4·68 (mt, $J_{3\alpha,2\alpha} \approx J_{3\alpha,4\alpha} \approx 4·5$ Hz, $J_{3\alpha,2\beta} \approx J_{3\alpha,4\beta} \approx 11·2$ Hz, 3α-H), 5·43 (mt, 11-H). For $C_{30}H_{52}O_2$ (444·7) calculated: 81·02% C, 11·79% H; found: 81·28% C, 11·49% H.

3β-Acetoxy-7a,8-seco-B-homo-5α-cholest-9(11)-en-12-one (*X*)

A solution of the olefin *IX* (700 mg) in tetrachloromethane (40 ml) was heated to 80°C and treated dropwise under stirring in the course of 5 min with a solution of tert-butyl chromate (12 ml), with acetic acid (4 ml) and with acetic anhydride (1·6 ml). Stirring was continued for additional 4 h at the same temperature. The mixture was cooled with ice and treated with a solution of oxalic acid (1·5 g) in water (15 ml) and then with solid oxalic acid (1 g). The reaction mixture was stirred at room temperature for 1 h. The organic layer was separated, washed with water and with a saturated solution of sodium hydrogen carbonate, dried, and solvent was distilled off *in vacuo*. The residue was chromatographed on a silica gel column (100 g) in benzene–ether (30 : 1) to afford 280 mg of the starting olefin and 165 mg of the ketone *X*, m.p. 118—121°C (methanol), $[\alpha]_D^{20}$ +56° (*c* 2·5). IR spectrum: 1 735, 1 245, 1 038, 1 027 (acetate), 1 681, 1 607 cm^{-1} (carbonyl). UV spectrum (ethanol, $c = 1·644 \cdot 10^{-5}$): λ_{max} 237 nm ($\log \varepsilon$ 4·23). Mass spectrum: M^+ 458. ^1H NMR spectrum: 0·87 (t, J = 7·0 Hz, 7a-H), 0·92 (s, 18-H), 1·08 (s, 19-H), 2·04 (s, acetate), 4·70 (mt, $J_{3\alpha,2\alpha} \approx J_{3\alpha,4\alpha} \approx 4·5$ Hz, $J_{3\alpha,2\beta} \approx J_{3\alpha,4\beta} \approx 11·2$ Hz, 3α-H), 5·83 (d, $J_{11,8} = 1·9$ Hz, 11-H). For $C_{30}H_{50}O_3$ (458·7) calculated: 78·55% C, 10·99% H; found: 78·72% C, 10·73% H.

The analyses were carried out in the Analytical Laboratory of this Institute by Mrs E. Sýkorová, Mrs V. Rusová and Mrs E. Šípová under the direction of Dr J. Horáček. The infrared spectra and UV *spectra were recorded by Mr P. Formánek and Mrs K. Matoušková under the direction of Dr J. Smolíková. The mass spectra were recorded by Dr V. Hanuš and Dr A. Trka.* ^1H NMR *spectra* (60 MHz) *were recorded by Mrs J. Jelínková.*

REFERENCES

1. Kohout L.: This Journal *37*, 2227 (1972).
2. Bhacca N. S., Williams D. H.: *Applications of* NMR *Spectroscopy in Organic Chemistry*, p. 19. Holden-Day, San Francisco 1964.

Translated by J. Fajkoš.