ON STEROIDS. CXXXVIII.*
B-HOMOSTEROIDS. V.**
CYCLIC OXIDES IN THE B-HOMOSTEROID SERIES

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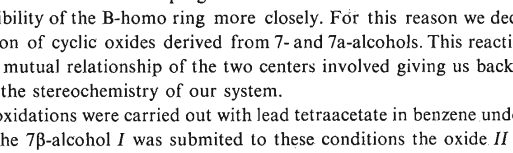
Lead tetraacetate oxidation of the four epimeric 7- and 7a-hydroxy derivatives of the B-homocholestane series has been studied and the structure of oxides as well as their stereochemistry are discussed.

In our previous work on B-homosteroids[1-4] we have dealt with the chemistry and stereochemistry of B-homosteroids. We have shown[2-4] that the preferred conformation of the seven-membered B-homo ring is the twist chair with the axis of symmetry passing through the carbon atom 7. It has further been shown[3,4] that the limited flexibility allows this ring to take up modified conformations as a result of non-bonded interactions. In the progress of this work we became interested in studying the flexibility of the B-homo ring more closely. For this reason we decided to study formation of cyclic oxides derived from 7- and 7a-alcohols. This reaction requires a defined mutual relationship of the two centers involved giving us back the information of the stereochemistry of our system.

The oxidations were carried out with lead tetraacetate in benzene under irradiation. When the 7β-alcohol *I* was submited to these conditions the oxide *II* was obtained in good yield. Its structure follows from the NMR spectrum in which instead of the



I *II*

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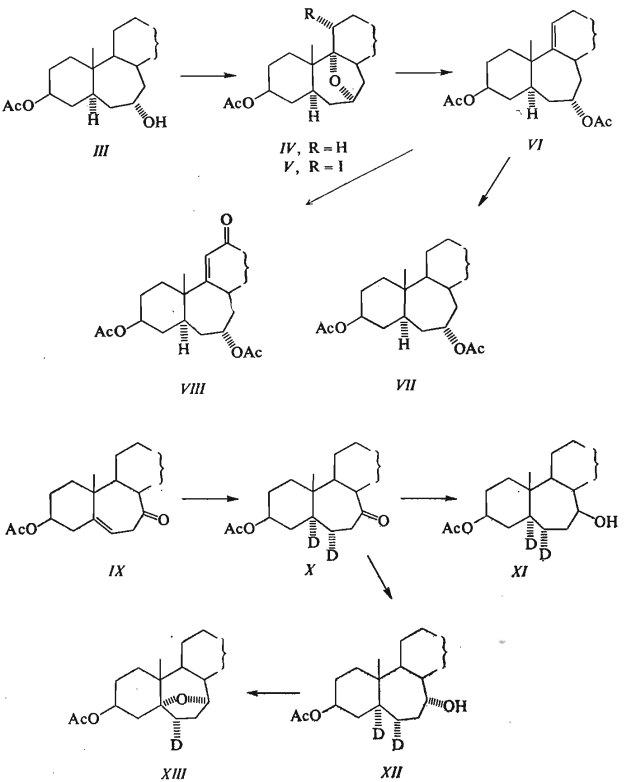
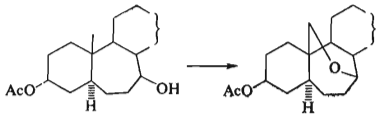
19-methyl signal the two remaining 19-protons appear at 3·68 p.p.m. and at 3·64 p.p.m. The epimeric 7α-hydroxy derivative *III* gave under indentical conditions also an oxide as followed from its mass spectrum. The NMR spectrum showed presence of all methyl groups and a triplet of one proton at 4·24 p.p.m. (J = 8·0 Hz). This points to the fact that one of the tertiary α-protons on the skeleton was attacked – most probably the 9α-proton. The 14α-proton is sterically inconvenient and in the case of the 5α-proton a four membered ring would have been formed. In agreement with



this assumption the structure of the 7α,9α-oxide *IV* was proved by chemical means for this compound as follows: Reaction with boron trifluoride etherate in acetanhydride transformed this oxide to an unsaturated acetoxy derivative in which the double bond is not in allylic position excluding the structure of the 7α,5α-oxide. This unsaturated acetoxy derivative on catalytic hydrogenation gave the known[1] diol diacetate *VII* and its NMR spectrum shows one olefinic proton. Oxidation with tert-butyl chromate yielded an α,β-unsaturated oxocompound with the carbonyl maximum at 1 686 cm^{-1}. The carbonyl group must therefore be attached to a six-membered ring and the only possibility is structure *VIII* for this product of chromate oxidation and structure *VI* for the olefin; this proves back the structure *IV* for the oxide. The same oxide was also prepared on reaction with lithium aluminium hydride from the iodo compound *V* which was obtained from the alcohol *III* when the oxidation was carried out under the presence of iodine. The structure of the iodo derivative *V* follows from its NMR spectrum. The 11-proton appears at 4·550 p.p.m. as a quartet with J_{AB} = 13·0 Hz and $(J_{AX} + J_{BX})$ = 19·0 Hz; it has therefore axial conformation and β-configuration.

Our next concern were the epimeric 7a-hydroxy derivatives. In the 7aα-ol the expected center to be attacked was the 5α-hydrogen and we therefore started the reaction sequence with the labelled compound *X* obtained on catalytic deuteration of the unsaturated ketone *IX*. Hydride reduction gave a mixture of both epimeric alcohols *XI* and *XII* from which the required 7aα-ol *XII* was separated by chromatography. Oxidation with lead tetraacetate gave an oxide containing according to the mass spectroscopic data only one deuterium atom in the molecule in contrast to the starting dideuteriated alcohol *XII*. This – together with NMR data – proves unambiguously the structure *XIII* for this 5α,7aα-oxide. The last alcohol we dealt with was the 7aβ-ol *XIV*. The oxidation was carried out as usual but, the expected 7aβ,19-oxide *XV* was only the minor product (4% yield) formed on this reaction. The main product was an unsaturated aldehyde the structure of which will be studied in future.

Fig. 1 shows the different conformations of the B-homo ring in the four oxides. The oxides in which the cycloheptane ring is allowed to take up the convenient $C_{(7)}$-twist chair or a conformation derived by slight distorsion are formed in good yields (about 60%) whereas the yield of the 7aβ,19-oxide in which this ring is forced into the unfavourable twist boat conformation are extremely low (4%). These results



XIV *XV*

prove the previous findings on the preferred conformations of the B-homo ring as well as its relative flexibility.

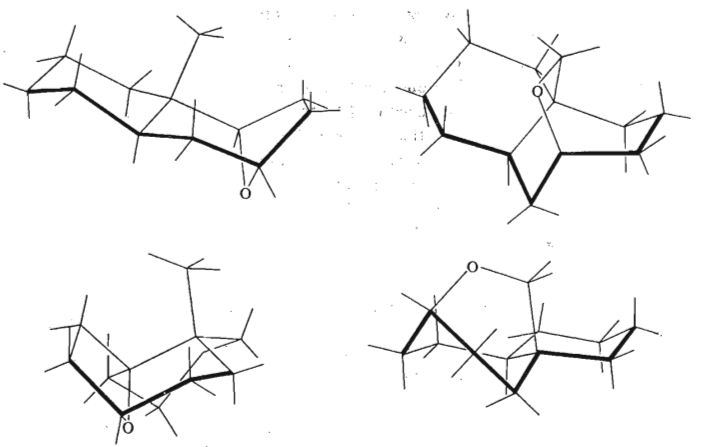


FIG. 1
Conformation of the B-homo Ring in the Oxides

EXPERIMENTAL

Melting points were determined on 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. The mass spectra were recorded on the mass spectrometer MCH 1303 with the direct inlet system. The NMR spectra were recorded on Varian HA-100 instrument in deuteriochloroform with tetramethylsilane as internal reference. 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 and by infrared spectra.

3β-Acetoxy-7β,19-oxido-B-homo-5α-cholestane (*II*)

The alcohol *I* (2 g) was dissolved in benzene (80 ml), and about 8 ml of the solvent were removed by distillation. The solution was treated with lead tetraacetate (3·2 g) and refluxed under stirring and irradiation (500 W, Nitraphot) for 4 hours. The reaction mixture was then diluted with wet ether (80 ml), filtered, and the filtrate washed with 5% sodium hydrogen carbonate solution, water, dried, and the solvent evaporated. The oily residue (1·85 g) was chromatographed on a silica gel column (100 g) in benzene–ether (30 : 1). The crude product (1·323 g) afforded after crystallisation from methanol 1·035 g of the oxide *II*, m.p. 116–118°C, $[\alpha]_D^{20}$ +1° (*c* 3·33); NMR: 0·68 (s, 18-H), 0·83 (d, *J* 6·0 Hz, 26 and 27-H), 0·85 (d, *J* 6·0 Hz, 21-H), 1·98 (s, $COOCH_3$), 3·64 and 3·68

(2d, *J* 10·0 Hz, 19-H), 4·02 (t, *J* 7·0 Hz, 7α-H), 4·56 (m, 3α-H). For $C_{30}H_{50}O_3$[1] (458·7) calculated: 78·55% C, 10·99% H; found: 78·62% C, 10·69% H.

3α-Acetoxy-7α,9α-oxido-B-homo-5α-cholestane (*IV*)

a) *From* 3β-*acetoxy*-B-*homo*-5α-*cholestan*-7α-*ol* (III): The alcohol *III* (500 mg) was oxidised with lead tetraacetate as described for the acetate *II*; after reflux for 6 hours and working up reaction mixture yielded 500 mg of oil product, which was chromatographed on a silica gel column (50 g) in benzene–ether (99 : 1). The crude product (380 mg) on crystallisation from methanol gave 292 mg of the oxide *IV*, m.p. 111–113°C, $[\alpha]_D^{20}$ −5° (*c* 1·37); NMR: 0·61 (s, 18-H), 0·94 (s, 19-H), 0·86 (d, *J* 6·0 Hz, 21-H), 0·83 (d, *J* 6·0 Hz, 26 and 27-H), 1·98 (s, $COOCH_3$), 4·24 (t, *J* 8·0 Hz, 7β-H), 4·65 (m, 3α-H). For $C_{30}H_{50}O_3$ (458·7) calculated: 78·55% C, 10·99% H; found: 78·51% C, 10·37% H.

b) *From* 3β-*acetoxy*-7α,9α-*oxido*-11α-*iodo*-B-*homo*-5α-*cholestane* (V): A solution of the iodo derivative *V* (850) in tetrahydrofuran (150 ml) was treated at room temperature with a solution of lithium aluminum hydride (2 g) in tetrahydrofurane (50 ml). After 30 minutes at room temperature the excess hydride was decomposed with ethyl acetate, the reaction mixture diluted with water, acidified with hydrochloric acid, and extracted with ether. The ethereal solution was washed with diluted hydrochloric acid, a sodium hydrogen carbonate solution, water, dried and evaporated. The oily residue (800 g) was acetylated with acetic anhydride (2·4 ml) in pyridine (4 ml) at room temperature for 20 hours. Usual working up gave the crude acetate which was chromatographed on a silica gel column (80 g) in benzene–ether (99 : 1) to yield 550 mg of a product. Crystallisation from methanol gave the oxide *IV*, m.p. 111–112°C, $[\alpha]_D^{20}$ −4° (*c* 1·42).

3β-Acetoxy-7α,9α-oxido-11α-iodo-B-homo-5α-cholestane (*V*)

A solution of the alcohol *III* (200 mg) in benzene (8 ml) was treated with iodine (60 mg) and lead tetraacetate (320 mg) and refluxed under irradiation (500 W, Nitraphot) for 3 hours. The reaction mixture was filtered, washed with a sodium thiosulphate solution and water and the solvent evaporated. The residue (243 mg) was chromatographed on a silica gel column (15 g) in benzene–ether (4 : 1) to yield 143 mg of the crude product which on crystallisation from ethanol gave 118 mg of the oxide *V*, m.p. 130–131°C, $[\alpha]_D^{20}$ −45·6° (*c* 1·78). NMR 0·58 (s, 18-H), 0·82 (d, *J* 6·0 Hz, 21-H), 0·87 (d, *J* 6·0 Hz, 26 and 27-H), 1·98 (s, $COOCH_3$), 4·35 (t, *J* 8·0 Hz 7β-H), 4·55 (q, $|J_{AX} + J_{BX}| = 19$ Hz, J_{AB} 13·0 Hz, 11β-H), 4·77 (m, 3α-H). For $C_{30}H_{51}IO_3$ (584·5) calculated: 61·63% C, 8·45% H, 21·71% I; found: 61·77% C, 8·35% H, 21·13% I.

3β,7α-Diacetoxy-B-homo-5α-cholest-9(11)-ene (*VI*)

The oxide *IV* (1·39 g) in acetanhydride (40 ml) was treated with boron trifluoride-etherate (1 ml) and allowed to stand at room temperature for 1 hour. The reaction mixture was decomposed with ice, the product extracted with ether and the ethereal solution washed with a sodium hydrogen carbonate solution and worked up. The residue (1·41 g) was chromatographed on a silica gel column (50 g) in benzene–ether (49 : 1). The product (1·22 g) was crystallised from methanol to yield 1·05 g of the olefin *VI*, m.p. 60–62°C, $[\alpha]_D^{20}$ +14° (*c* 1·53). IR 3050, 1735, 1245, 1028 cm^{-1}; NMR: 0·56 (s, 18-H), 0·85 (d, *J* 6·5 Hz, 26 and 27-H), 0·87 (d, *J* 6·0 Hz, 21-H), 0·97 (s, 19-H), 1·98 and 2·00 (2 s, $COOCH_3$), 4·70 and 5·02 (2 m, 3α- and 7β-H), 5·56 (d, *J* 6·0 Hz, 11-H). For $C_{32}H_{52}O_4$ (500·7) calculated: 76·75% C, 10·47% H; found: 76·80% C, 10·41% H.

3β,7α-Diacetoxy-B-homo-5α-cholestane (*VII*)

The olefin *VI* (65 mg) was hydrogenated in glacial acetic acid (5 ml) over platinum catalyst (100 mg) for 6 hours. The reaction mixture was diluted with ether, the catalyst filtered off, washed with ether and the filtrate washed with a sodium hydrogen carbonate solution, water, dried, and evaporated. The residue oil (65 mg) was chromatographed on two silica gel plates (20 × 20 cm) in benzene–ether (9 : 1). Working up to the corresponding zones and crystallisation from methanol gave 49 mg of the diacetate *VII*, m.p. 75—76°C, $[\alpha]_D^{20}$ −10° (*c* 1·45), identical with the authentic sample[1].

3β,7α-Diacetoxy-B-homo-5α-cholest-9(11)-en-12-one (*VIII*)

A stirred solution of the olefin *VI* (250 mg) in tetrachloromethane (5 ml) was treated with tert-butyl chromate (1·8 ml), glacial acetic acid (0·6 ml) and acetanhydride (0·25 ml) and heated to 80°C for 5 hours. The reaction mixture was then cooled to room temperature and treated with a solution of oxalic acid (400 mg) in water (4 ml) and with oxalic acid (300 mg). After stirring for 2 hours at room temperature the organic layer was separated and worked up. The residual oil (290 mg) was chromatographed over silica gel (29 g) in light petroleum (b.p. 40—60°C)–ether (9 : 1). The corresponding fractions were combined and evaporated to yield 204 mg of the ketone *VIII* which resisted all attempts at crystallisation; $[\alpha]_D^{20}$ +33·1° (*c* 1·47). IR: 1738, 1686, 1596, 1242, 1043 cm^{-1}; UV λ_{max} 239, log ε 3·98 (ethanol); NMR: 0·86 (d, *J* 6·2 Hz, 26 and 27-H), 0·90 and 1·13 (2 s, 18 and 19-H), 0·96 (d, *J* 6·0 Hz, 21-H), 1·94 and 2·02 (2d, $COOCH_3$), 4·73 (m, 3α-H), 5·08 (m, 7β-H), 5·87 (m, 11-H). For $C_{32}H_{50}O_5$ (514·7) calculated: 74·67% C, 9·78% H; found: 74,47% C, 10,02% H.

3β-Acetoxy-B-homo-5α-cholestan-7a-one-[5α,6α-$^2H_2$] (*X*)

The unsaturated ketone *IX* (2 g) in mono-deuteriated acetic acid (CH_3COO^2H, 50 ml) was deuteriated over platinum oxide catalyst (200 mg) for 1 hour. Catalyst was filtered off, washed with ether, the filtrate diluted with ether and washed with water, a sodium hydrogen carbonate solution, water, dried, and evaporated. The residue was crystallised from methanol to give 1·44 g of the dideuteriated ketone *X*, m.p. 144°C, $[\alpha]_D^{20}$ +74° (*c* 1·35). Mass spectrum: M^+ 460. For $C_{30}H_{48}{}^2H_2O_3$ (460·7) calculated: 78·20% C, 11·38% H; found: 78·25% C, 11·34% H.

3β-Acetoxy-B-homo-5α-cholestan-7aα-ol-[5α,6α-$^2H_2$] (*XII*)

The ketone *X* (2·05) in tetrahydrofuran (160 ml) was treated at room temperature with lithium borohydride (4·1 g) and refluxed for 2 hours. The excess hydride was then decomposed with wet ether, water, and diluted hydrochloric acid. The product was taken into ether and the ethereal layer worked up as usual. The oily residue was acetylated with acetic anhydride (6 ml) in pyridine (10 ml) at room temperature for 2 hours. Usual working up afforded according to the thin layer chromatography a mixture of the two epimeric acetates *XI* and *XII* which was chromatographed on silica gel column (200 g) in benzene–ether (99 : 1) to yield 802 mg of the more polar alcohol *XII*, m.p. 121—123°C (methanol), $[\alpha]_D^{20}$ +8° (*c* 1·04); Mass spectrum: M^+ 462. For $C_{30}H_{50}{}^2H_2O_3$ (462·7) calculated: 77·86% C, 11·76% H; found: 78·02% C, 11·78% H. The fractions containing the less polar component from the chromatography of the foregoing experiment gave after working up and crystallisation from methanol 650 mg of 3β-acetoxy-B-homo-5α-cholestan-7aβ-ol-[5α,6α-$^2H_2$] (*XI*), m.p. 128—130°C, $[\alpha]_D^{20}$ +18° (*c* 1·19); Mass spectrum: M^+ 462. For $C_{30}H_{50}{}^2H_2O_3$ (462·7) calculated: 77·86% C, 11·76% H; found: 77·94% C, 11·80% H.

3β-Acetoxy-5,7aα-oxido-B-homo-5α-cholestane-[6α-^{2}H] (*XIII*)

The alcohol *XII* (1·8 g) was oxidised with lead tetraacetate as described for the acetate *II* to yield 1·7 g of product which was chromatographed on a silica gel column (85 g) in benzene to yield after crystallisation from ethanol–water 885 mg of the oxide *XIII*, m.p. 68—70°C, $[\alpha]_D^{20}$ −12·6° (*c* 1·16); Mass spectrum: M^+ 459; NMR: 0·62 (s, 18-H), 0·80 (s, 19-H), 0·86 (d, *J* 6·0 Hz, 26 and 27-H), 0·89 (d, *J* 6·0 Hz, 21-H), 1·99 (s, $COOCH_3$), 3·94 (m, 7aβ-H), 4·88 (m, 3α-H). For $C_{30}H_{49}.^2HO_3$ (459·7) calculated: 78·37% C, 11·19% H; found: 78·60% C, 11·19% H.

3α-Acetoxy-7aβ,19-oxido-B-homo-5α-cholestane (*XV*)

The alcohol *XVI* (1·75 g) was oxidised with lead tetraacetate as described for the acetate *II*; after the reflux for 1 hour and working up reaction mixture yielded 1·8 g of oil product which was chromatographed over silica gel (200 g) in light petroleum (b.p. 40—60°C)–ether (19 : 1). Next to the main product (780 mg) — 66 mg of the oxide *XV* were isolated, m.p. 136—137°C (methanol), $[\alpha]_D^{20}$ +31° (*c* 1·86); Mass spectrum: M^+ 458; IR: 1738, 1247, 1032 cm^{-1}; NMR: 0·73 (s, 18-H), 0·86 (d, *J* 6·0 Hz, 26 and 27-H), 0·90 (d, *J* 6·0 Hz, 21-H), 2·01 (s, $COOCH_3$), 3·93 (m, 7aα-H), 3·56 and 4·04 (2 d, *J* 11·0 Hz, 19-H), 4·64 (m, 3α-H).

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