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A-HOMOSTEROIDS II: CONFORMATION OF THE A-RING IN 6β-ACETOXY-4a α-BROMO-A-HOMO-5α-CHOLESTAN-4-ONE

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Syntheses of the derivatives derived from 6β-acetoxy-A-homo-5α-cholestan-4-one are described and their configuration determined. The conformation of the A-homo-ring in the 4aα-bromo derivative is discussed on the basis of ORD, IR and NMR measurements.

Our first paper[1] on A-homosteroids dealt with the preparation and structure proof of 6β-acetoxy-A-homo-5α-cholestan-4-one (*I*) by means of structure correlation of the latter compound with the known A-homo-5α-cholestan-4-one[2]. On the basis of chemical and spectral data, we also discussed the direction of bromination of A-homo-5α-cholestan-4-one leading to 4a-bromo derivative.

In the present paper we publish the preparation of 6β-acetoxy-4aα-bromo-A-homo-5α-cholestan-4-one (*III*) and discuss the configuration of the bromine atom and conformation of the A-homo-ring in the bromo ketone *III* on the grounds of spectral data. Problems concerning preparation and configuration of some additional A-homocholestane derivatives are also dealt with.

Direct bromination of the ketone *I* in acetic acid affords the bromo ketone *III* in 78% yield. In the NMR spectrum, the signal of CHBr proton appears as a doublet ($\delta = 4{\cdot}245$ p.p.m., $J_{4a,5} = 11$ Hz). This fact indicates the presence of one neighboring proton and locates the bromine atom in 4a position which result is in agreement with our earlier observation on the course of bromination of A-homo-5α-cholestan-4-one[1]. The large value of the vicinal coupling constant ($J_{4a,5} = 11$ Hz) shows[3] the dihedral angle between the protons located at $C_{(4a)}$ and $C_{(5)}$ to be near to 180°. In view of the mode of preparation, there is no doubt about the α-configuration of the 5-hydrogen and the value of the dihedral angle is only compatible with

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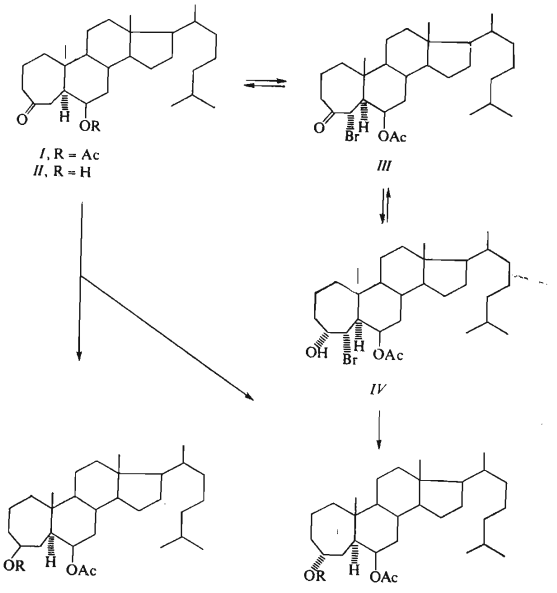
β-configuration of the $C_{(4a)}$-proton. The bromo ketone *III* is thus 6β-acetoxy-4aα-bromo-A-homo-5α-cholestan-4-one.

The same reasons make it now possible to assign the α-configuration of the bromine atom in the previously described[1] 4aα-bromo-A-homo-5α-cholestan-4-one ($J_{4a,5}$ = 10 Hz). A similar, though only alternative, conclusion was arrived at by Snatzke and coworkers[4] in the case of a α-bromo ketone derived from 17β-acetoxy-A-homo-5α-androstan-4-one. Based on the strong positive Cotton effect ($\Delta\varepsilon$ = = 3·25) of the latter, either 3β or 4aα-configuration for the bromine atom was put forward by the German authors. In view of our results, the second possibility is likely for this compound.



I, R = Ac
II, R = H

III

IV

VIa, R = H
VIb, R = Ac

Va, R = H
Vb, R = Ac

Ac = CH_3—CO—

The bromo ketone *III* was reduced with lithium tri-tert-butoxyaluminum hydride to give the bromohydrin *IV*. On oxidation with Jones'reagent, this bromohydrin yields the starting bromo ketone *III* whereas the known ketone *II* results after treatment with methanolic potassium hydroxide. These reactions demonstrate the structure of the bromohydrin *IV* to be 4aα-bromo-4α-hydroxy derivative *IV*. Catalytic dehalogenation of *IV* yields the corresponding 4α-hydroxy derivative *Va*. The epimeric alcohol *VIa* was obtained as the minor product on reduction of the ketone *I* with lithium tri-tert-butoxyaluminum hydride. Both alcohols were characterized as diacetates *Vb* and *VIb*, respectively.

The spectral data, in conjunction with the examination of Dreiding models, provided the possibility of making some conclusions about the preferred conformations of the seven-membered A-ring in the bromo ketone *III* and in 4aα-bromo-A-homo-5α-cholestan-4-one (*VIII*) (ref.[1]). Small shifts in the IR-carbonyl frequencies of the bromo ketones *III* and *VIII* resulting after introducing one bromine atom into the α-position of the keto derivatives *I* and *VII* ($\Delta\nu = 6\ cm^{-1}$ and $\Delta\nu = +7\ cm^{-1}$, respectively) as well as bathochromic shifts of the first extrema in the ORD curves of *III* and *VIII* ($\Delta\lambda = +21$ nm and $\Delta\lambda = +25$ nm, respectively) show that the angle between both dipoles corresponds to that of axial bromine in six-membered α-bromo ketones (*cf.* Table I). The examination of Dreiding models shows that the requirements of the IR, ORD and NMR data are met by following seven conformations of the A-ring: one chair form with a plane of symmetry passing through $C_{(1)}$ atom, one twist chair form with $C_{(4a)}$ in the axis of symmetry, three boat forms with planes of symmetry passing through $C_{(1)}$, $C_{(4)}$, and $C_{(5)}$ and two twist boat forms with $C_{(4a)}$ and $C_{(10)}$ in the axes of symmetry.*

Three of these conformations, *i.e.* $C_{(1)}$-chair, $C_{(1)}$-boat and $C_{(4)}$-boat are rather unlikely owing to substantial strain in such molecules.

Strong positive Cotton effect, observed in both bromo ketones under discussion, is consistent with all remaining conformations, *i.e.* with $C_{(4a)}$-twist chair, $C_{(4a)}$-twist boat, $C_{(10)}$-twist boat and $C_{(5)}$-boat. Thus, the equilibrium mixture of bromo ketone *III*(or *VIII*) conformers should contain significant proportion of all four conformers; in view of the known facts[5,6] the $C_{(4a)}$-twist chair conformer is likely to be the main component of the mixture.

EXPERIMENTAL

Melting points were determined on a Kofler block and are uncorrected. Unless stated otherwise, optical rotations were measured in chloroform. The infrared spectra were measured on a Zeiss UR 10 spectrophotometer and optical rotatory dispersion measurements on a Jasco Model ORD/UV-5. The NMR spectra were measured in deuterated chloroform on Varian HA-100 apparatus using tetramethylsilane as internal standard. The identity of samples prepared by different routes was checked by a mixture melting point determination and by infrared spectra.

* In subsequent text these forms will be designated according to the carbon atom lying in the plane or axis of symmetry.

6β-Acetoxy-4aα-bromo-A-homo-5α-cholestan-4-one (*III*)

a) *From* 6β-*acetoxy*-A-*homo*-5α-*cholestan*-4-*one*(*I*): A solution of bromine (220 mg) in acetic acid (2·2 ml) was added to a solution of the ketone *I* (380 mg) in acetic acid (12·5 ml) containing one drop of hydrobromic acid. The reaction mixture was allowed to stand at room temperature for 15 minutes and then at 0°C for 18 hours. The mixture was poured into ice-water and the product extracted with ether. The ethereal extract was washed with 5% potassium hydrogen carbonate water, dried with sodium sulfate and the solvent evaporated *in vacuo*. The residue (440 mg) after chromatography on silica gel (20 g) in light petroleum–acetone (99 : 1) afforded 350 mg of the bromo ketone *III*, m.p. 125—126°C (methanol), $[\alpha]_D^{26}$ +29·1° (*c* 0·1, methanol). Infrared spectrum (tetrachloromethane): 1 743, 1 712, 1 232 cm^{-1}. NMR: 0·680 (s, 3H, 18-CH_3); 0·820 (s, 3 H, 19-CH_3); 0·860 (d, $J = 6·5$ Hz, 6 H, 26, 27-CH_3); 0·900 (d, $J = 6·0$ Hz, 3 H, 21-CH_3); 2·080 (s, 3 H, OAc); 4·245 (d, 1 H, CH-Br. $J = 11$ Hz); 5·535 (mt, W = 8 Hz, CH—OAc). ORD (methanol, *c* 0·12, 26°C): $[\Phi]_{400}$ +1 050°, $[\Phi]_{350}$ +2 820°, $[\Phi]_{335}$ + 4 580°, $[\Phi]_{327}$ +5 100°, $[\Phi]_{315}$ +3 170°, $[\Phi]_{307}$ ±0°, $[\Phi]_{300}$ −3 340°, $[\Phi]_{290}$ −7 300°, $[\Phi]_{277}$ −8 890°, $[\Phi]_{250}$ −8 010°; a +140. For $C_{30}H_{49}BrO_3$ (537·5) calculated: 67·03%C, 9·19% H; found: 66·88% C, 9·17% H.

b) *From* 6β-*acetoxy*-4aα-*bromo*-A-*homo*-5α-*cholestan*-4α-ol (IV): The bromohydrin *IV* (60 mg) in acetone (3 ml) was treated with excess Jones' reagent and agitated at room temperature for 8 minutes. The excess reagent was removed with methanol, the reaction mixture diluted with water and the product extracted with ether. The ethereal extract was washed with 5% potassium hydrogen carbonate, water, dried with sodium sulfate and the solvent evaporated *in vacuo*. The residue (55 mg) was chromatographed preparatively on one plate of silica gel (20 × 20 cm) in light petroleum–acetone (85 : 15). The corresponding zone was collected with ether and the ether evaporated *in vacuo*. After repeated crystallization from methanol the residue (35 mg) afforded 15 mg of the bromo ketone *III*, m.p. 124—126°C, $[\alpha]_D^{22}$ +28° (*c* 1·0, methanol).

TABLE I

The Spectral Data of the 6β-Acetoxy-A-homo-5α-cholestan-4-one (*I*), A-Homo-5α-cholestan-4-one (*VII*), 6β-Acetoxy-4aα-bromo-A-homo-5α-cholestan-4-one (*III*) and 4aα-Bromo-A-homo-5α-cholestan-4-one (*VIII*)

Compound	IR ν(CO), cm^{-1}	Molecular amplitude $\times 10^{-2}$	ORD first extremum, nm	NMR $J_{4a,5}$, Hz
I	1 706	+114[a]	306[a]	—
III	1 712	+140[a]	327[a]	11
VII (ref.[1])	1 705	+106[b]	310[b]	—
VIII (ref.[1])[c]	1 712	+140[b]	335[b]	10

[a] Methanol; [b] dioxan; [c] In this connection we wish to correct erroneous ORD-values for the bromo ketone *VIII* which have been reported in our previous paper[1]. The correct figures are as follows: ORD (dioxan, *c* 0·17, 27°C): $[\Phi]_{350}$ + 6 430, $[\Phi]_{335}$ + 7 550°, $[\Phi]_{325}$ + 6 980°, $[\Phi]_{306}$ ± 0°, $[\Phi]_{290}$ − 5 590°, $[\Phi]_{283}$ − 6 430°, $[\Phi]_{270}$ − 4 750°, *a* + 140.

6β-Acetoxy-4aα-bromo-A-homo-5α-cholestan-4α-ol (*IV*)

A solution of bromo ketone *III* (550 mg) in tetrahydrofuran (15 ml) was treated with lithium tri-tert-butoxyaluminum hydride (1·2 g) and allowed to stand at room temperature for 2 hours. The reaction mixture was poured into ice–5% hydrochloric acid and the product extracted with ether. The ethereal extract was washed with 5% potassium hydrogen carbonate, water, dried with sodium sulfate and the solvent evaporated *in vacuo*. The residue (500 mg) afforded after chromatography on silica gel (100 g) in light petroleum–acetone (98 : 2) 310 mg of bromohydride *IV*, which was crystallized from methanol at 0°C, m.p. 61–62°C, $[\alpha]_D^{21}$ −10·4° (*c* 0·8), Infrared spectrum (tetrachloromethane): 3571, 1740, 1240, 1028 cm^{-1}. NMR: 0·675 (s, 3 H, 18-CH_3), 0·850 (d, J = 6 Hz, 6 H, 26, 27-CH_3), 0·880 (d, J = 6 Hz, 3 H, 21-CH_3); 0·995 (s, 3 H, 19-CH_3); 2·050 (s, 3 H, 6β-OAc); 4·550 (dublet of dublets, $J_{4a,4}$ = 2 to 3 Hz, $J_{4a,5}$ = 8·5 Hz, 1 H, CH—Br); 4·190 (mt, 1 H, CH—OH). For $C_{30}H_{51}BrO_3.2\,CH_4O$ (603·6) calculated: 63·67% C, 9·85% H; found: 63·26% C, 9·44% H.

Reaction with a base. To a solution of bromohydrin *IV* (100 mg) in methanol (20 ml) was added potassium hydroxide (1·2 g) and the mixture refluxed for 2 hours. After concentrating to one third of the volume *in vacuo* the reaction mixture was poured into water and the product taken up in ether. The ethereal extract was washed with water, dried with sodium sulfate and the solvent evaporated *in vacuo*. The residue (100 mg) afforded after chromatography on silica gel (10 g) in light petroleum–acetone (9 : 1) 61 mg 6β-hydroxy-A-homo-5α-cholestan-4-one (*II*), m.p. 173–174°C, $[\alpha]_D^{20}$ + 35° (*c* 1·0) in accordance with the literature[1].

6β-Acetoxy-A-homo-5α-cholestan-4α-ol (*Va*)

a) *From 6β-acetoxy-A-homo-5α-cholestan-4-one* (I): To a solution of ketone *I* (190 mg) in tetrahydrofuran (4 ml) was added lithium tri-tert-butoxyaluminium hydride (400 mg) and the mixture was allowed to stand at room temperature for 2 hours. The reaction mixture was poured into ice–5% hydrochloric acid and the product was extracted with ether. The ethereal extract was washed with 5% potassium hydrogen carbonate, water, dried with sodium sulfate and the solvent evaporated *in vacuo*. The residue (190 mg) was chromatographed on silica gel (25 g) in light petroleum–acetone (98 : 2). The less polar fractions afforded after recrystallization from heptane 120 mg of the alcohol *Va*, m.p. 154–156°C, $[\alpha]_D^{22}$ −6·3° (*c* 0,6). Infrared spectrum (tetrachloromethane): 3610, 1735 cm^{-1}. For $C_{30}H_{52}O_3$ (460·7) calculated: 78·20% C, 11·38% H; found: 77·93% C, 11·35% H.

b) *From bromohydrin* IV: The bromohydrin *IV* (68 mg) in ethyl acetate (7 ml) and ethanol (3 ml) was shaken in a hydrogen atmosphere with 5% palladium-on-calcium carbonate catalyst (200 mg) for 6 hours. It was then diluted with ether, the catalyst filtered off, washed with ether and the filtrate evaporated *in vacuo*. The residue (50 mg) was chromatographed on one plate of silica gel (20 × 20 cm) in light petroleum–acetone (8 : 2). The corresponding zone was collected, eluted with ether and the ether evaporated *in vacuo*. The residue (22 mg) afforded after recrystallization from heptane 10 mg of alcohol *Va*, m.p. 154·5–156·5°C, $[\alpha]_D^{22}$ −4° (*c* 1·0). The less polar zone afforded after the same work-up 25 mg of the ketone *I*, m.p. 125–127°C, $[\alpha]_D^{22}$ +49·5° (*c* 1·0) in accordance with the literature[1].

4α,6β-Diacetoxy-A-homo-5α-cholestane(*Vb*)

The monoacetate *Va* (20 mg) was acetylated with acetic anhydride (0·1 ml) in pyridine (1 ml) for 48 hours at room temperature. Usual working up gave 22 mg of an oily product which was crystallized from methanol at 0°C (13 mg), m.p. 136–138°C, $[\alpha]_D^{24}$ −9·1° (*c* 0·6). Infrared

spectrum (tetrachloromethane): 1735, 1246, 1022 cm^{-1}. For $C_{32}H_{54}O_4$ (502·75) calculated: 76·44% C, 10·83% H; found: 76·00% C, 10·56% H.

6β-Acetoxy-A-homo-5α-cholestan-4β-ol (*VIa*)

After chromatographic separation of the alcohol *Va* from the hydride reduction of the ketone *I* (see above), chromatography was continued using the same solvent system. Fractions containing the more polar component were combined, evaporated *in vacuo* and the residue (42 mg) was crystallized from heptane to yield 25 mg of the alcohol *VIa*, m.p. 131·5—133·5°C, $[\alpha]_D^{23}$ −2·9° (*c* 0·8). Infrared spectrum (tetrachloromethane): 3615, 1737, 1247, 1029 cm^{-1}. For $C_{30}H_{52}O_3$ (460·7) calculated: 78·20% C, 11·38% H; found: 77·92% C, 11·36% H.

4β,6β-Diacetoxy-A-homo-5α-cholestane (*VIb*)

The monoacetate *VIa* (50 mg) was acetylated with acetic anhydride (0·2 ml) in pyridine (1 ml) for 48 hours at room temperature. Usual working up gave 50 mg of an oily product which was crystallized from methanol at 0°C, (38 mg) m.p. 104—106°C. Infrared spectrum (tetrachloromethane): 1737, 1246, 1022 cm^{-1}. For $C_{32}H_{54}O_4$ (502·75) calculated: 76·44% C, 10·83% H; found: 76·85% C, 10·66% H.

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