ON STEROIDS. CLX.*

A-HOMOSTEROIDS V: PREPARATION OF SOME FURTHER A-HOMOCHOLESTAN-4-ONE DERIVATIVES

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Synthesis of A-homocholestan-4-one derivatives bearing an oxygen function in the position 4 is reported. Their structure is determined on the basis of chemical correlations and physical methods.

In the foregoing communications of this series[1-4], preparation and structure determination of some 6β-acetoxy-A-homo-5α-cholestan-4-one and 6β-acetoxy-A-homo-5α-cholestan-4a-one derivatives was reported. The present paper deals with further derivatives of A-homocholestane bearing an oxygen function in the position 4.

Mesylation of the previously reported[1] 6β-hydroxy-A-homo-5α-cholestan-4-one (*I*) with methanesulphonyl chloride in pyridine provided the 6β-mesyloxy derivative *II* in 85% yield. The mesylate *II* was reduced with lithium tri-tert-butoxyaluminum hydride to give the alcohols *III* and *V* in 37% and 40% yield, respectively. The reaction mixture contained a small amount of two additional minor products which proved to be the isomeric unsaturated alcohols; their structures were not investigated. The structures of the alcohols *III* and *V* were proved by oxidation with Jones' reagent to the known[1] A-homo-5-cholesten-4-one (*VII*) which could be converted to *III* and *V* in 1 : 1 relation on reduction with lithium tri-tert-butoxyaluminum hydride. The configuration of the hydroxyl group in *III* and *V* was established by the following correlation with the known[2] A-homo-5α-cholestan-4α, 6β-diol 6-monoacetate (*IX*). The acetyl derivative *IX* was subjected to alkaline hydrolysis to give the diol *X* which was acetylated selectively with acetic anhydride in pyridine to furnish the 4α-acetoxy derivative *XI* in 73% yield. Subsequent mesylation lead to the mesyl derivative *XII* which on lithium aluminum hydride reduction gave the alcohol *III* in 83% yield. This reaction sequence provides a direct proof of the α-configuration for the hydroxy derivative *III* and, by implication, of the 4ß-configuration for the epimeric alcohol *V*. Both alcohols were also characterized as corresponding acetyl derivatives *IV* and *VI*.

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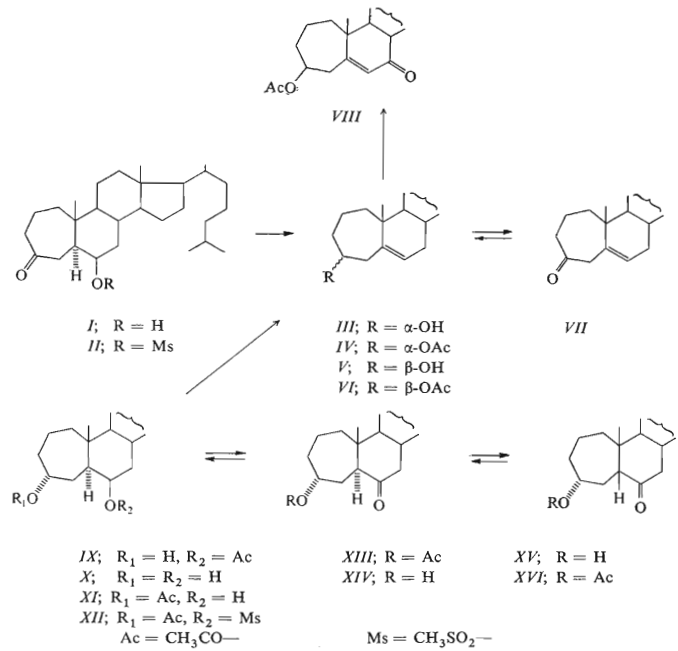

Allylic oxidation of the acetyl derivative *VI* with tert-butyl chromate provided the conjugated ketone *VIII* in 72% yield. This structure is based on NMR data which also rule out the alternative structure of 4a-oxo-Δ^5-unsaturated derivative. The signal of the olefinic proton appears as a singlet which is only compatible with the structure *VIII* where no other proton is located on the adjacent carbon atom. Similarly the width of the $C_{(4)}$-proton signal ($W = 30$ Hz) shows coupling of this proton with more than two protons.

Oxidation of the monoacetate *XI* with chromium trioxide–pyridine complex gave the ketone *XIII*. In the course of this oxidation, the configuration at the $C_{(5)}$-asymmetric center remained preserved. This fact could be demonstrated by reduction of the ketone *XIII* with lithium tri-tert-butoxyaluminum hydride giving the alcohol *XI*. On the other hand, alkaline hydrolysis of the ketone *XIII* with potassium

hydrogen carbonate in refluxing methanol gave a mixture of the alcohols *XIV* and *XV* with 5β-isomer *XV* prepondering in 1 : 4 relation. The same relation of both alcohols is achieved when the alcohol *XV* is equilibrated using methanolic potassium hydroxide. Acetylation of the alcohol *XIV* gave the starting acetate *XIII* whereas a new acetyl derivative *XVI* was obtained from *XV*.

It is interesting to note that contrasting with the normal series, the 5β-isomer preponderates in the equilibrated mixture of the 6-ketones. A difference may also be observed in chiroptical properties. Both acetates *XIII* and *XVI* show negative Cotton effect as analogous 6-ketones in the normal cholestane series but, in contrast to 6-ketones containing a six-membered A-ring, the 5α-isomer shows a stronger negative Cotton effect ($\Delta\varepsilon$ −2·13 for the 5α-isomer *XIII* as compared with $\Delta\varepsilon$ −1·27 for the 5β-isomer *XVI*).

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 tetrachloromethane on Varian HA-100 apparatus using tetramethylsilane as internal standard. The statement "worked up as usual" stands for: The solution was washed with 5% hydrochloric acid, 5% potassium hydrogen carbonate, water, dried over sodium sulfate and the solvent evaporated *in vacuo*. The identity of samples prepared by different routes was checked by a mixture melting point determination and by infrared spectra.

6β-Methanesulphonyloxy-A-homo-5α-cholestan-4-one (*II*)

6β-Hydroxy-A-homo-5α-cholestan-4-one[1] (*I*) (520 mg) in pyridine (10 ml) was treated with methanesulphonyl chloride (1 ml) at 0°C for 4 h. The reaction mixture was decomposed with ice, diluted with water and the product was isolated with ether. The ethereal extract was worked up as usual. After recrystallization from ethanol the residue (700 mg) afforded 525 mg of the mesylate *II*, m.p. 125—126°C, $[\alpha]_D^{22}$ +45·6° (*c* 0·7). The infrared spectrum (tetrachloromethane): 900, 1 175, 1 344, 1 709 cm^{-1}. For $C_{29}H_{50}O_4S$ (494·75) calculated: 70·39% C, 10·16% H, 6·43% S; found: 70·74% C, 9·99% H, 6·42% S.

A-Homo-5-cholesten-4α-ol (*III*)

a) The mesylate *II* (500 mg) in tetrahydrofuran (5 ml) was treated with lithium tri-tert-butoxyaluminum hydride (1 g) at room temperature for 2 h. The reaction mixture was then poured into ice–5% hydrochloric acid and the product was extracted with ether. Usual working up gave 480 mg of the product which was chromatographed on silica gel (40 g) in benzene. The less polar fraction afforded 150 mg of the alcohol *III* which was crystallized from methanol, m.p. 106 to 107·5°C, $[\alpha]_D^{22}$ −2·8° (*c* 0·7). Infrared spectrum (tetrachloromethane): 1 666, 3 020, 3 549 cm^{-1}. For $C_{28}H_{48}O$ (400·7) calculated: 83·93% C, 12·08% H; found: 84·19% C, 12·16% H.

b) The ketone[1] *VII* (80 mg) in tetrahydrofuran (2 ml) was treated with lithium tri-tert-butoxyaluminum hydride (160 mg) at room temperature for 3 h. The same working up as in the case *a*) gave 65 mg of the product which was chromatographed preparatively on one plate of silica gel (20 × 20 cm) using benzene as developing solvent. The corresponding zone was collected, eluted with ether and the solvent evaporated *in vacuo*. The residue (28 mg) was recrystallized from methanol to afford 20 mg of the alcohol *III*, m.p. 106—107°C, $[\alpha]_D^{22}$ −2·5° (*c* 1·0).

c) The acetate *XI* (130 mg) in pyridine (2·5 ml) was treated with methanesulphonyl chloride (0·25 ml) at 0°C and allowed to stand at the same temperature for 16 h. The reaction mixture was decomposed with ice, diluted with water and the product extracted with ether. The ethereal extract was worked up as usual. The oily residue (160 mg) is pure by thin layer chromatography. Infrared spectrum (tetrachloromethane): 1176, 1248, 1344, 1735 cm^{-1}. This oily mesylate *XII* (150 mg) in ether (6 ml) was added to a lithium aluminum hydride (375 mg) solution in ether (12 ml) and the mixture was refluxed for 3 h. The excess hydride was then decomposed successively with ethyl acetate and wet methanol. The reaction mixture was passed through a column of sodium sulfate and the filtrate evaporated *in vacuo*. The residual oil (150 mg) was chromatographed on silica gel (10 g) in benzene solution. The corresponding fractions were combined and evaporated in vacuo to yield 85 mg of the alcohol *III*, which was crystallized from methanol, m.p. 106 to 107°C, $[\alpha]_D^{22}$ −2·5° (*c* 1·0).

4α-Acetoxy-A-homo-5-cholestene (*IV*)

The alcohol *III* (50 mg) was acetylated with acetic anhydride (1·8 ml) in pyridine (2 ml) for 48 h at room temperature. The usual working up gave 50 mg of an oil which was preparatively chromatographed on one plate of silica gel (20 × 20 cm) in benzene. The corresponding zone was collected, eluted with ether and the solvent evaporated *in vacuo*. The residue (42 mg) afforded 34 mg of the acetate *IV* after crystallization from methanol, m.p. 62—63°C, $[\alpha]_D^{22}$ +46·7° (*c* 0·7). Infrared spectrum (tetrachloromethane): 1027, 1240, 1255, 1664, 1731, 3040 cm^{-1}. For $C_{30}H_{50}O_2$ (442·7) calculated: 81·39% C, 11·38% H; found: 81·22% C, 11·08% H.

A-Homo-5-cholesten-4β-ol (*V*)

a) Further elution of the chromatography after isolation of the alcohol *III* with the same solvent afforded three separated fractions. The most polar one gave 165 mg of the alcohol *V*, which was crystallized from methanol, m.p. 123—124°C, $[\alpha]_{22}^{D}$ +10·6° (*c* 0·7). Infrared spectrum (tetrachloromethane): 1030, 1665, 3030, 3615 cm^{-1}. For $C_{28}H_{48}O$ (400·7) calculated: 83·93% C, 12·08% H; found: 83·38% C, 11·78% H.

b) After chromatographic separation of the alcohol *III* from the hydride reduction of the ketone *VII*, the more polar zone was collected, eluted with ether and the solvent evaporated *in vacuo*. On crystallization from methanol the residue (25 mg) gave 19·2 mg of the alcohol *V*, m.p. 123—124°C, $[\alpha]_D^{22}$ +10° (*c* 1·0).

4β-Acetoxy-A-homo-5-cholestene (*VI*)

The alcohol *V* (130 mg) was acetylated with acetic anhydride (0·8 ml) in pyridine (8 ml) for 48 h at room temperature. Usual working up gave 130 mg of a product which after crystallization from methanol afforded 100 mg of the acetate *VI*, m.p. 126—128°C, $[\alpha]_D^{22}$ +8·4° (*c* 0·7). Infrared spectrum (tetrachloromethane): 1024, 1244, 1664, 1732 cm^{-1}. For $C_{30}H_{50}O_2$ (442·7) calculated: 81·39% C, 11·38% H; found: 81·09% C, 11·29% H.

A-Homo-5-cholesten-4-one (*VII*)

a) The alcohol *III* (50 mg) in acetone (3 ml) was treated with excess of Jones' reagent and agitated at room temperature for 5 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 over sodium sulfate and the solvent evaporated *in vacuo*. After crystallization from methanol the oily residue (50 mg) yielded 30 mg of the ketone *VII*, m.p. 108–109°C, $[\alpha]_D^{22}$ +49° (*c* 1·0); literature[1] reports m.p. 108 to 110°C, $[\alpha]_D^{22}$ +49·4° and literature[5] m.p. 108–109°C, $[\alpha]_D$ +59°.

b) The alcohol *V* (50 mg) in acetone (3 ml) was treated with excess of Jones' reagent in the same manner as in the case *a*). The working up gave 50 mg of an oil which after recrystallization from methanol afforded 34 mg of the ketone *VII*, m.p. 108–110°C, $[\alpha]_D^{22}$ +49·5° (*c* 0·7) in accordance with literature[1,5].

A-Homo-5α-cholestan-4α,6β-diol (*X*)

The A-homo-5α-cholestan-4α,6β-diol 6-monoacetate[2] (*IX*) (350 mg) was dissolved in methanol (30 ml), solid potassium hydroxide (350 mg) was added and the mixture was refluxed for 8 h. The reaction mixture was then concentrated to one third of the original volume and the product taken up in ether. The ethereal extract was washed with water, dried over sodium sulfate and the solvent evaporated *in vacuo*. The residue (300 mg) was crystallized from heptane to give 268 mg of the diol, *X*, m.p. 116–118·5°C, $[\alpha]_D^{22}$ ±0° (*c* 0·7). Infrared spectrum (chloroform): 1 024, 1 042, 3 610 cm^{-1}. For $C_{28}H_{50}O_2$ (418·7) calculated: 80·32% C, 12·04% H; found: 79·21% C, 11·97% H.*

A-Homo-5α-cholestan-4α,6β-diol 4-monoacetate (*XI*)

a) The diol *X* (250 mg) was acetylated with acetic anhydride (0·6 ml) in pyridine (10 ml) for 16 h at room temperature. Usual working up gave the crude product (250 mg). Chromatography on silica gel (20 g) in benzene yielded 195 mg of the acetate *XI* which was crystallized from methanol, m.p. 160–161°C, $[\alpha]_{22}^{D}$ +11·3° (*c* 0·7). Infrared spectrum (tetrachloromethane): 1 250, 1 730, 3 620 cm^{-1}. For $C_{30}H_{52}O_3$ (460·7) calculated: 78·20% C, 11·38% H; found: 77·88% C, 11·29% H.

b) To a solution of the ketone *XIII* (80 mg) in tetrahydrofuran (3 ml) lithium tri-tert-butoxyaluminum hydride (160 mg) was added and the mixture was allowed to stand at room temperature for 1 h, then poured into ice–5% hydrochloric acid and the product extracted with ether. The ethereal extract was worked up as usual. After crystallization from methanol the residue (73 mg) yielded 51 mg of the acetate *XI*, m.p. 160–161°C, $[\alpha]_D^{22}$ +11·0° (*c* 0·7).

4β-Acetoxy-A-homo-5-cholesten-7-one (*VIII*)

A stirred solution of the olefine *VI* (80 mg) in tetrachloromethane (3·5 ml) was treated with tert-butyl chromate (0·45 ml), glacial acetic acid (0·17 ml) and acetic anhydride (0·05 ml) and heated to 80°C for 4 h. The reaction mixture was then cooled to room temperature and treated with a solution of oxalic acid (0·1 g) in water (0·15 ml) and with solid oxalic acid (0·05 g). After stirring for 1 h at room temperature the product was extracted with tetrachloromethane, the extract washed with 5% potassium hydrogen carbonate, water, dried over sodium sulfate and the solvent evaporated *in vacuo*. The residual oil (100 mg) was chromatographed on silica gel (15 g) in benzene–ether (99 : 1). The corresponding fractions were combined and evaporated *in vacuo* to yield 60 mg of the ketone *VIII*, which was crystallized from methanol, m.p. 131–133°C,

* Elemental analysis of the compound *X* gave lower value than required. However, the structure of this compound follows from its spectral properties and analytical data of its acetyl derivative *XI*.

$[\alpha]_D^{22}$ −12·6° (*c* 0·07, dioxane). Infrared spectrum (tetrachloromethane): 1026, 1238, 1629, 1675, 1737 cm^{-1}. ORD (dioxane, *c* 0·07, 22°C): $[\phi]_{263}$ +120°, $[\phi]_{267}$ +50°, $[\phi]_{269}$ ±0°, $[\phi]_{275}$ −64°, $[\alpha]_{285}$ −128°, $[\phi]_{296}$ −153°, $[\phi]_{299}$ −153°, $[\phi]_{300}$ −147°, $[\phi]_{310}$ −109°, $[\alpha]_{321}$ ±0°, $[\phi]_{330}$ +109°, $[\phi]_{340}$ +154°, $[\phi]_{344}$ +160°, $[\phi]_{350}$ +120°, $[\phi]_{362}$ ±0°, $[\phi]_{375}$ −50°, $[\phi]_{400}$ −38°. NMR: 1·095 (s, 3 H, 19-CH_3), 0·685 (s, 3 H, 18-CH_3), 0·88 (d, 6 H, $J = 6$ Hz, 26 + 27-CH_3), 0·92 (d, 3 H, 21-CH_3), 1·97 (s, 3H,-OAc), 4·55 (broad unresolved mt, 1 H, $C_{(4)}$-H, $W = 30$ Hz), 5·86 (s, 1 H, $C_{(6)}$-H). Ultraviolet spectrum (ethanol): λ_{max} 238 nm (log ε 4·00). For $C_{30}H_{48}O_3$ (456·7) calculated: 78·90% C, 10·59% H; found: 78·77% C, 10·42% H.

4α-Acetoxy-A-homo-5α-cholestan-6-one (*XIII*)

a) The hydroxy derivative *XI* (400 mg) was oxidized with chromium trioxide (400 mg)–pyridine (2 ml) complex at room temperature for 24 h. Usual workup gave the ketone *XIII* (400 mg) which was crystallized from methanol to give the pure product (285 mg), m.p. 85–87°C, $[\alpha]_{22}^{D}$ −1·9° (*c* 0·7). Infrared spectrum (tetrachloromethane): 1246, 1715, 1736 cm^{-1}. CD (methanol, *c* 0·07, 24°C): Δε −2·13 (291 nm). For $C_{30}H_{50}O_3$ (458·7) calculated: 78·55% C, 10·99% H; found: 78·60% C, 11·01% H.

b) The hydroxy derivative *XIV* (30 mg) was acetylated with acetic anhydride (0·2 ml) in pyridine (1·5 ml) for 24 h at room temperature. The usual workup gave 35 mg of an oil which was purified by preparative chromatography on one plate of silica gel (20 × 20 cm) in benzene–ether (95 : 5). The corresponding zone was collected, eluted with ether and the solvent evaporated *in vacuo*. The residue (21·5 mg) yielded after crystallization from methanol 15 mg of the acetate *XIII*, m.p. 85–87°C, $[\alpha]_D^{22}$ −1·7° (*c* 0·7).

4α-Hydroxy-A-homo-5α-cholestan-6-one (*XIV*)

To a solution of the acetate *XIII* (190 mg) in methanol (19 ml) was added an aqueous solution of potassium hydrogen carbonate (190 mg in 1·9 ml) and the mixture was refluxed for 2 h, then concentrated to one third of the original volume, poured into water and the product was extracted with ether. The ethereal extract was washed with water, dried over sodium sulfate and the solvent evaporated *in vacuo*. The residue (180 mg) was preparatively chromatographed on three plates of silica gel (20 × 20 cm) in benzene–ether (9 : 1); the development was repeated three times, the corresponding zones were collected and eluted with ether to yield an oil (30 mg). Infrared spectrum (KBr): 1074, 1687, 1704 cm^{-1}. For $C_{28}H_{48}O_2$ (416·7) calculated: 80·71% C, 11·61% H; found: 80·35% C, 11·41% H.

4α-Hydroxy-A-homo-5β-cholestan-6-one (*XV*)

The corresponding more polar zones after chromatographic separation of 4α-hydroxy-A-homo-5α-cholestan-6-one (*XIV*) from hydrolysis of the acetate *XIII* were collected, eluted with ether and the solvent evaporated *in vacuo*. The residue (125 mg) yielded after crystallization from heptane 65 mg of the alcohol *XV*, m.p. 142–143°C, $[\alpha]_D^{22}$ +6·6° (*c* 0·7). Infrared spectrum (chloroform): 1031, 1698, 3600 cm^{-1}. For $C_{28}H_{48}O_2$ (416·7) calculated: 80·71% C, 11·61% H; found: 80·48% C, 11·56% H.

Equilibration: The hydroxy derivative *XV* (50 mg) was dissolved in methanol (4 ml) and aqueous solution of potassium hydroxide (25 mg in 0·2 ml) was added and the mixture was allowed to stand at room temperature for 48 h. The usual workup gave 50 mg of the crude product.

Preparative chromatography on one plate of silica gel (20 × 20 cm) in benzene–ether (9 : 1) yielded after three times repeated development 10 mg of the 5α- and 38 mg of the 5β-isomer.

4α-Acetoxy-A-homo-5β-cholestan-6-one (*XVI*)

The alcohol *XV* (33 mg) was acetylated with acetic anhydride (0·2 ml) in pyridine (1·5 ml) for 24 h at room temperature. The usual workup gave 29 mg of a product, which afforded after crystallization from methanol 20 mg of the acetate *XVI*, m.p. 135–136°C, $[\alpha]_D^{22}$ +24·1° (*c* 0·7). Infrared spectrum (tetrachloromethane): 1029, 1239, 1709, 1737 cm^{-1}. CD (methanol, *c* 0·07, 24°C): $\Delta\varepsilon$ −1·27 (291 nm). For $C_{30}H_{50}O_3$ (458·7) calculated: 78·55% C, 10·99% H; found: 78·47% C, 10·81% H.

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