SYNTHESIS AND SOME REACTIONS OF THE EPIMERIC 5,7α-CYCLO-B-HOMO-5α-CHOLESTAN-4-OLS*

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Synthesis and some reactions of the epimeric 5,7α-cyclo-B-homo-5α-cholestan-4-ols are described and structures of the products established by chemical and spectral means.

In our previous papers[1,2] we dealt with the preparation and reactions of 5,7β-cyclo--B-homo-5β-cholestane derivatives substituted with and oxygen function in position 4. In this paper we present a similar study in the 5,7α-cyclo-B-homo-5α-cholestane series.

The ketone[1] *I* was reduced with lithium tri-tert-butoxyaluminium hydride to a mixture of two alcohols in a relation of about 1 : 10. Surprisingly, only the main product afforded on reoxidation the starting ketone *I*. It was therefore the 4-hydroxy compound *IV*; the 4α configuration follows from the NMR spectrum. The minor product contained a double bond instead of the cyclopropane ring and spectral evidence pointed to structure *II*. Authentic alcohol *II* was prepared by acid catalysed rearrangement of the alcohol[2] *VI* and both compounds proved to be identical; alcohol *II* was prepared recently in our Laboratories by unambigous route[3]. Formation of the A-homo derivative *II* from the ketone *I* under metal hydride reduction conditions is an interesting observation and we intend to study this reaction more closely in future.

Alcohol *IV* when oxidised with chromic acid in pyridine gave exclusively the ketone *I*. Oxidation with Jones' reagent, on the other hand, afforded next to the ketone *I* the rearranged B-homoketone *VII*. Evidently, the alcohol *IV* underwent partly acid catalysed rearrangement to the alcohol *VIII* prior to oxidation. In fact, alcohol *IV* rearranged smoothly to the B-homoalcohol *VIII* when exposed to 4M sulphuric acid. Our attempts to prepare the epimeric 4β-alcohol *X* from the ketone *I* failed as metal hydride reduction led exclusively to the 4α-epimer, and catalytic hydrogenation caused fission of the cyclopropane ring leading to the alcohol *III*.

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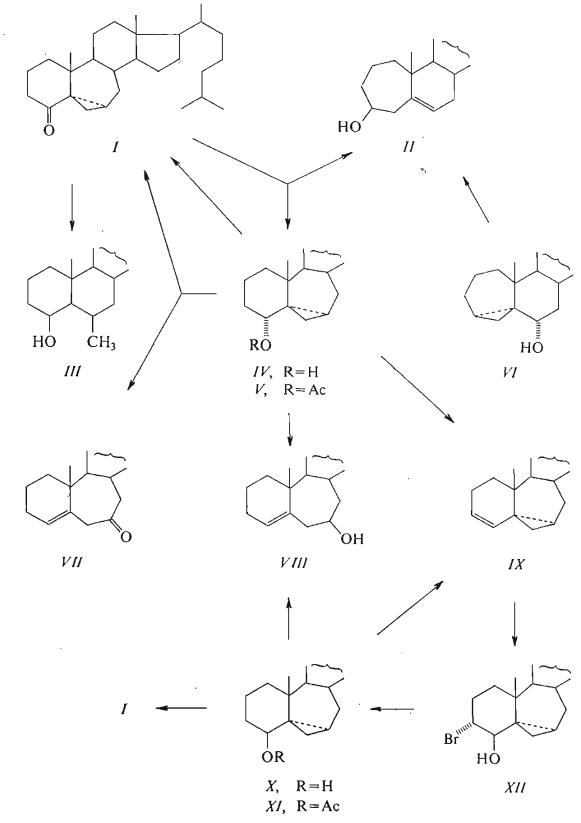
We therefore set out from the known[4] olefin *IX* which after hypobromous acid addition followed by catalytic removal of the halogen atom gave the desired 4β--alcohol *X*. This alcohol, like the 4α-epimer *IV*, afforded on oxidation with chromic acid in pyridine the ketone *I*, on oxidation with Jones'reagent a mixture of the ketones *I* and *VII*, and rearranged to the alcohol *VIII* when exposed to 4M sulphuric



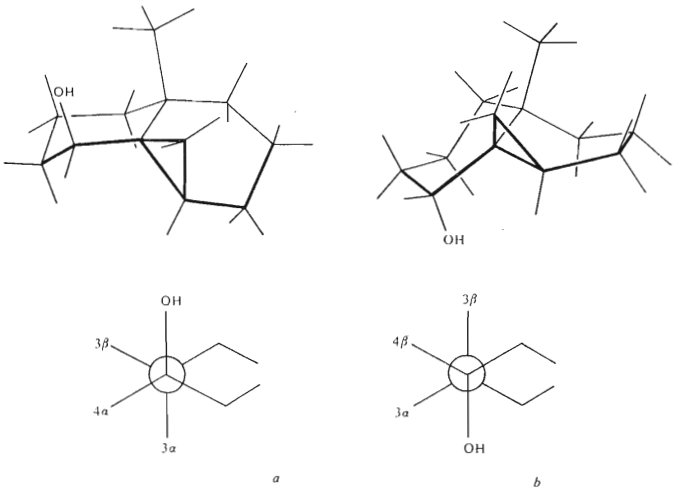


FIG. 1

Conformations of the 5,7β-Cyclo-β-homo-5β-cholestane Skeleton in Alcohols *IV*(b) and *X*(a)

acid. Both alcohols *IV* and *X* underwent elimination of the hydroxyl group when treated with methanesulphonyl chloride in pyridine the only product being the olefin[4] *IX*.

The NMR spectra of the epimeric alcohols *IV* and *X* require some discussion. The upfield shift the 19-methyl signal (Table I) in the alcohol *X* points clearly to the 4β-configuration of the hydroxyl group. The coupling constants point to an

TABLE I

Characteristic Chemical Shift Values (p.p.m.) in the Epimeric 5,7α-Cyclo-B-homo-5α-cholestan--4-ols[a]

Compound	4-H	18-H	19-H
4α-ol (*IV*)	3·25 (t, $J = 4$ Hz)	0·61	0·86
4β-ol (*X*)	2·85 (t, $J = 3$ Hz)	0·62	0·99

[a] Solvent chloroform corrected to tetramethylsilane.

equatorial conformation of both at $C_{(4)}$ epimeric protons in these alcohols. Figure 1 shows the probable skeletal conformations where both alcohols have an axial hydroxyl group. However, it is difficult to explain the preference of these conformations on the basis of the non-bonded interactions drawn from the Dreiding models.

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 NMR spectra were recorded on the Varian HA-100 instrument in chloroform and 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, 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.

5,7α-Cyclo-B-homo-5α-cholestan-4-one (*I*)

a) *From 5,7α-cyclo-*B-*homo-5α-cholestan-4α-ol* (IV) *with Jones' reagent*: Elution of the chromatography after isolation of the ketone *VII* with the same solvent mixture, and working up of the corresponding fractions afforded 890 mg of a product which after crystallisation from methanol yielded 630 mg of the ketone *I*, m.p. 108—110°C, $[\alpha]_D^{20}$ +50° (*c* 1·42), in agreement with the literature[1].

b) *From 5,7α-cyclo-*B-*homo-5α-cholestan-4α-ol with chromic acid in pyridine*: A solution of the alcohol *IV* (70 mg) in pyridine (7 ml) was treated with a solution of chromic acid (70 mg) in pyridine (7 ml). After 2 hours at room temperature the reaction mixture was poured into 5% sodium hydrogen carbonate, the product taken into ether, and the ethereal solution was worked up. The residue was chromatographed on two plates of silica gel (20 × 20 cm) in ligroin–ether (9 : 1). The corresponding zones were collected, the product eluted with ether, and the solvent distilled off. The residue (48 mg) was crystallised from methanol–water to yield 35 mg of the ketone *I*, m.p. 107—109°C, $[\alpha]_D^{20}$ +51° (*c* 1·19), in accordance with the literature[1].

c) *From 5,7α-cyclo-*B-*homo-5α-cholestan-4β-ol* (X): The alcohol *X* (40 mg) in pyridine (4 ml) was oxidised with chronic acid (40 mg) in pyridine (4 ml) as given in the foregoing experiment. Similar working up and crystallisation from diluted metanol yielded 21 mg of the ketone *I*, m.p. 107—109°C, $[\alpha]_D^{20}$ +51° (*c* 0·87) in agreement with the literature[1].

A-Homo-5-cholesten-4β-ol (*II*)

a) *From 5,7α-cyclo-*B-*homo-5α-cholestan-4-one* (I): Elution of the chromatography after isolation of the alcohol *IV* under *a*) with the same solvent mixture afforded fractions with the polar component. Combination and evaporation of the solvent gave 300 mg of a product which on crystallisation from methanol yielded 180 mg of the A-homo derivative *II*, m.p. 127—128°C, $[\alpha]_D^{20}$ +9° (*c* 0·60) in accordance with the literature[3]. IR: 3615, 1029 (hydroxyl), 3020, 1659 cm^{-1} (double bond). NMR: 0·68 (s, 18-H), 0·87 (d, J = 6 Hz, 26-H and 27-H), 0·91 (d, J = 6 Hz, 21-H), 0·91 (s, 19-H), 3·95 (broad mt, 4α-H), 5·45 (broad d, 6-H).

b) *From 4α,5-cyclo-*A-*homo-5α-cholestan-6α-ol* (VI): A solution of the alcohol *VI* (100 mg) in acetone (10 ml) was treated with 4M-H_2SO_4 (1 ml) and allowed to stand a room temperature for 1 hour. The reaction mixture was diluted with water, the product taken into ether, the ethereal

solution was washed with 5% sodium hydrogen carbonate, water, dried and evaporated. The residue (95 mg) was crystallised from methanol to yield 63 mg of the alcohol *II*, m.p. 126–128°C, $[\alpha]_D^{20}$ +10° (*c* 1·77).

6β-Methyl-5α-cholestan-4β-ol (*III*)

a) *From* 5,7α-*cyclo*-B-*homo*-5α-*cholestan*-4-*one* (I) *in ethanol*: The ketone *I* (100 mg) in ethanol (10 ml) was hydrogenated over Adams' catalyst (100 mg) for 2 hours at room temperature. Catalyst was filtered off, washed with ether and solvents removed. The residue (100 mg) was chromatographed on three silica gel plates (20 × 20 cm) in ligroin–ether (9 : 1). The corresponding zones were collected, the product eluted with ether, and the solvent was distilled off. The residue (55 mg) was crystallised from methanol to yield 35 mg of the alcohol *III*, m.p. 108–109°C, $[\alpha]_D^{20}$ +23° (*c* 0·78). IR: 3615 cm^{-1} (hydroxyl). NMR (deuteriochloroform with tetramethylsilane as internal reference): 0·71 (s, 18-H), 0·89 (d, J = 6 Hz, 26-H and 27-H), 0·93 (d, J = 6 Hz, 21-H), 1·24 (s, 19-H), 1·29 (d, J = 6·5 Hz, 6β-methyl), 4·01 (mt, W = 8 Hz, 4α-H). For $C_{28}H_{50}O$ (402·7) calculated: 83·51% C, 12·52% H; found: 83·70% C, 12·76% H.

b) *From* 5,7α-*cyclo*-B-*homo*-5α-*cholestan*-4-*one in acetic acid*: The ketone *I* (100 mg) in acetic acid (10 ml) was hydrogenated over Adams' catalyst (100 mg) for 30 minutes. Catalyst was filtered off, washed with ether, the filtrate was washed with water, a sodium hydrogen carbonate solution, water, dried, and evaporated. The residue was chromatographed on three plates of silica gel (20 × 20 cm) in ligroin–ether (9 : 1). The corresponding zones were collected, the product eluted with ether, and the solvent distilled off to yield 60 mg of a product which on crystallisation from methanol gave 39 mg of the alcohol *III*, m.p. 108–109°C, $[\alpha]_D^{20}$ +21° (*c* 0·65).

5,7α-Cyclo-B-homo-5α-cholestan-4α-ol (*IV*)

a) *From* 5,7α-*cyclo*-B-*homo*-5α-*cholestan*-4-*one* (I): A solution of the ketone *I* (3·5 g) in tetrahydrofuran (150 ml) was treated with lithium tri-tert-butoxyaluminium hydride (8 g) and allowed to stand at room temperature for 4 hours. The reaction mixture was poured into 1% hydrochloric acid and the product was isolated with ether. The ethereal solution was washed with a sodium hydrogen carbonate solution, water, dried, and evaporated. The residue (3·5 g) was chromatographed on a silica gel column (350 g) in ligroin–ether (9 : 1). Fractions with the lipophilic product were worked up and the residue (2·3 g) was crystallised from acetone to yield 2·03 g of the alcohol *IV*, m.p. 115–118°C, $[\alpha]_D^{20}$ −32° (*c* 0·68). IR: 3610, 1025 (hydroxyl), 3065 cm^{-1} (cyclopropane). NMR: 0·30 (mt, two cyclopropane protons), 0·61 (s, 18-H), 0·85 (d, J = 6 Hz, 26-H and 27-H), 0·86 (s, 19-H), 0·88 (d, J = 6 Hz, 21-H), 3·25 (t, J = 4 Hz, 4β-H). For $C_{28}H_{40}O$ (400·7) calculated: 83·93% C, 12·08% H; found: 84·01% C, 12·07% H.

b) *From* 4α-*acetoxy*-5,7α-*cyclo*-B-*homo*-5α-*cholestane* (V): A solution of the acetate *V* (150 mg) in methanol (15 ml) was treated with a solution of potassium carbonate (150 mg) in water (2 ml) and refluxed for 2 hours. The reaction mixture was poured in water, the product isolated with ether, and the ethereal solution was washed with water, dried, and evaporated. The residue (135 mg) was chromatographed over silica gel (10 g) in ligroin–ether (9 : 1). The corresponding fractions afforded after working up 115 mg of a product which on crystallisation from acetone gave 77 mg of the alcohol *IV*, m.p. 115–116°C, $[\alpha]_D^{20}$ −31° (*c* 1·14).

4α-Acetoxy-5,7α-cyclo-B-homo-5α-cholestane (*V*)

The alcohol *IV* (165 mg) was acetylated with acetic anhydride (0·6 ml) in pyridine (1 ml) for 18 hours at room temperature. The reaction mixture was decomposed with water, the product isolated with ether, and the ethereal solution was worked up. The residue (170 mg) was crystallised from

methanol to yield 110 mg of the acetate *V*, m.p. 70–73°C, $[\alpha]_D^{20}$ −10° (*c* 1·05). IR: 3065 (cyclopropane), 1729, 1248, 1020 cm^{-1} (acetate). NMR: 0·30 (broad mt, two cyclopropane protons), 0·60 (s, 18-H), 0·85 (d, J = 6 Hz, 26-H and 27-H), 0·87 (s, 19-H), 0·88 (d, J = 5·5 Hz, 21-H), 1·99 (s, acetate), 4·44 (t, J = 3·5 Hz, 4β-H). For $C_{30}H_{50}O_2$ (442·7) calculated: 81·39% C, 11·38% H; found: 81·44% C, 11·36% H

B-Homo-4-cholesten-7-one (*VII*)

A solution of the alcohol *IV* (1·5 g) in acetone (200 ml) was treated with excess Jones' reagent and allowed to stand at room temperature for 10 minutes. The excess reagent was removed with methanol, the reaction mixture was poured in water, and the product was isolated with ether. The ethereal solution was washed with water, a sodium hydrogen carbonate solution, water, dried, and evaporated. The residue was chromatographed over silica gel (250 g) in ligroin–ether (49 : 1). Fractions with lipophilic component were worked up and the residue (370 mg) was crystallised from methanol to yield 240 mg of the ketone *VII*, m.p. 88–89°C, $[\alpha]_D^{20}$ +15° (*c* 1·76) in accordance with the literature[4].

B-Homo-4-cholesten-7β-ol (*VIII*)

a) *From* 5,7α-*cyclo*-B-*homo*-5α-*cholestan*-4α-*ol* (IV): A solution of the alcohol *IV* (80 mg) in acetone (8 ml) was treated with 4M-H_2SO_4 (0·8 ml) and set aside at room temperature for 60 minutes. The reaction mixture was diluted with water, the product taken into ether, the ethereal solution was washed with sodium hydrogen carbonate, water, dried, and evaporated. The product (75 mg) was chromatographed on two plates of silica gel (20 × 20 cm) in ligroin–ether (2 : 1). The corresponding zones were collected, the product eluted with ether, and the solvent distilled off to yield 36 mg of the alcohol *VIII*, $[\alpha]_D^{20}$ −21° (*c* 0·94) which resisted all attempts at crystallisation and was identical with the product described in the literature[4].

b) *From* 5,7α-*cyclo*-B-*homo*-5α-*cholestan*-4β-*ol* (X): Alcohol *X* (55 mg) in acetone (5 ml) when treated similarly with 4M-H_2SO_4 acid (0·5 ml) as described in the foregoing experiment afforded after working up 22 mg of the alcohol *VIII*, $[\alpha]_D^{20}$ −20° (*c* 1·11).

5,7α-Cyclo-B-homo-5α-cholest-3-ene (*IX*)

a) *From* 5,7α-*cyclo*-B-*homo*-5α-*cholestan*-4α-*ol* (IV) *with phosphorus oxychloride*: The alcohol *IV* (100 mg) in pyridine (10 ml) was treated at −20°C dropwise with phosphorus oxychloride (0·2 ml) and allowed to stand at room temperature for 20 hours. The reaction mixture was poured on ice, the product taken into ether, and worked up. The residue was chromatographed on three silica gel plates (20 × 20 cm) in ligroin. The corresponding zones were collected, the product eluted with ether, and after evaporation of the solvent the residue was crystallised from methanol to yield 44 mg of the olefin *IX*, m.p. 70–72°C, $[\alpha]_D^{20}$ +17° (*c* 0·39), in agreement with the literature[4].

b) *From* 5,7α-*cyclo*-B-*homo*-5α-*cholestan*-4α-*ol* (IV) *with methanesulphonyl chloride*: The alcohol *IV* (220 mg) in pyridine (3 ml) was treated at 0°C with methanesulphonyl chloride (0·3 ml) and allowed to stand at room temperature for 3 hours. The reaction mixture was decomposed with ice, the product extracted with ether, and the extract worked up. The residue (180 mg) was chromatographed on two plates of silica gel (20 × 20 cm) in n-heptane. The corresponding zones were collected, the product eluted with ether, and the solvent distilled off, to leave 135 mg of a product which on crystallisation from methanol afforded 85 mg of the olefin *IX*, m.p. 70–72°C, $[\alpha]_D^{20}$ +16° (*c* 0·74).

c) *From* 5,7α-*cyclo*-B-*homo*-5α-*cholestan*-4β-*ol* (X): The alcohol *X* (100 mg) in pyridine (1·5 ml) was treated with methanesulphonyl chloride (0·15 ml) as given in the previous experiment. Similar working up gave 60 mg of a crude product which was purified by preparative thin-layer chromatography to yield 26 mg of a product. Crystallisation from methanol afforded 11 mg of the olefin *IX*, m.p. 70—72°C, $[\alpha]_D^{20}$ +15° (*c* 1·18).

5,7α-Cyclo-B-homo-5α-cholestan-4β-ol (*X*)

The bromohydrin *XII* (60 mg) in ethyl acetate (5 ml) and ethanol (5 ml) was hydrogenated over 5% Pd/$CaCO_3$ catalyst (100 mg) under the presence of ammonium acetate (50 mg) for 12 hours. The catalyst was filtered off, washed with ethanol and the solvent distilled off under reduced pressure. The residue was dissolved in ether and the ethereal solution was worked up. The product was chromatographed on two plates of silica gel (20 × 20 cm) in ligroin–ether (2 : 1). The corresponding zones were worked up to yield next to the starting material (15 mg) 35 mg of a bromine free product which after crystallisation from methanol yielded 22 mg of the alcohol *X*, m.p. 93—95°C, (recrystallisation at 62—65°C), $[\alpha]_D^{20}$ 0° (*c* 0·65). IR: 3650 (hydroxyl), 3060 cm^{-1} (cyclopropane). NMR: 0·21 (dd, $J = 5$ Hz, $J' = 9$ Hz, one cyclopropane proton), 0·40 (t, $J = 5$ Hz, one cyclopropane proton), 0·62 (s, 18-H), 0·85 (d, $J = 6$ Hz, 26-H and 27-H), 0·88 (d, $J = 6$ Hz, 21-H), 0·99 (s, 19-H), 2·85 (t, $J = 3$ Hz, 4α-H), 3·45 (s, hydroxyl). For $C_{28}H_{48}O$ (400·7) calculated: 83·93% C, 12·08% H; found: 83·71% C, 12·11% H.

4β-Acetoxy-5,7α-cyclo-B-homo-5α-cholestane (*XI*)

The alcohol *X* (130 mg) in pyridine (1 ml) was acetylated with acetic anhydride (0·6 ml) at room temperature for 18 hours. Usual working up afforded a product which was chromatographed on two plates of silica gel (20 × 20 cm) in ligroin–ether (9 : 1). The corresponding zones were worked up and the product crystallised from methanol to yield 70 mg of the acetate *XI*, m.p. 86—87°C, (recrystallisation at 79—81°C), $[\alpha]_D^{20}$ −12° (*c* 1·02). IR: 3065 (cyclopropane), 1730, 1248 cm^{-1} (acetate). NMR: 0·18—0·45 (mt, two cyclopropane protons), 0·61 (s, 18-H), 0·85 (d, $J = 6$ Hz, 26-H and 27-H), 0·88 (d, $J = 6$ Hz, 21-H), 0·95 (s, 19-H), 2·02 (s, acetate), 3·08 (broad d, 4α-H). For $C_{30}H_{50}O_2$ (442·7) calculated: 81·39% C, 11·38% H; found: 81·42% C, 11·43% H.

3α-Bromo-5,7α-cyclo-B-homo-5α-cholestan-4β-ol (*XII*)

A solution of the olefin *IX* (450 mg) in dioxane (70 ml) and water (1·5 ml) was treated with 0·9% perchloric acid (1·1 ml) and N-bromoacetamide (180 mg). After 2 hours at room temperature the reaction mixture was poured in water, the product taken into ether, the ethereal solution was washed with a sodium hydrogen carbonate solution, water, dried, and evaporated. The oily residue was chromatographed on ten plates of silica gel (20 × 20 cm) in ligroin–ether (2 : 1). Working up of the corresponding zones afforded 140 mg of the bromohydrin *XII*. A sample was dissolved in the minimum amount of methanol at room temperature and allowed to crystallise at −5°C to yield crystalls of the bromohydrin *XII*, m.p. 82—85°C, $[\alpha]_D^{20}$ −26° (*c* 0·72). IR: 3600, 1030, 1010 (hydroxyl), 3065 cm^{-1} (cyclopropane). NMR (deuteriochloroform with tetramethylsilane as internal reference): 0·40 (mt, two cyclopropane protons), 0·63 (s, 18-H), 0·87 (d, $J = 5·5$ Hz, 26-H and 27-H), 0·89 (d, $J = 5·5$ Hz, 21-H), 0·98 (s, 19-H), 3·30 (d, $J = 3·5$ Hz, 4α-H), 4·25 (mt, 3β-H). For $C_{28}H_{47}BrO$ (479·6) calculated: 70·12% C, 9·88% H, 16·66% Br; found: 70·16% C, 9·87% H, 16·79% Br.

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 infra red spectra were recorded by Mr P. Formánek under the direction of Dr J. Smolíková. The NMR spectra were recorded and interpreted by Dr M. Buděšínský. Technical assistance was provided by Mrs J. Mašková.

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