2,3-DISUBSTITUTED DERIVATIVES OF THE 6β,7aβ-CYCLO-B-HOMO-5α-CHOLESTANE SERIES*

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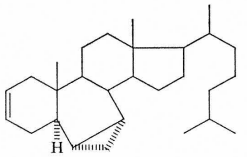
Syntheses of 2,3-disubstituted derivatives of the 6β,7aβ-cyclo-B-homo-5α-cholestane series are described and structures of the compounds are established on the basis of chemical and spectral evidence.

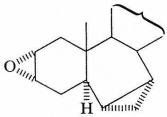
In our previous[1] paper we have dealt with derivatives of the 5,7β-cyclo-B-homo--5β-cholestane bearing substituents in positions 2 and 3. It was of interest to compare the results thus obtained with the behaviour of similar compounds of a closely related system. The present paper represents an extension of our work on steroids with modified skeleton in the desired direction.

Convenient starting material for synthesis of the 2,3-disubstituted derivatives of the 6β,7aβ-cyclo-B-homo-5α-cholestane was the already described[2] olefin *I*. Its epoxidation afforded one single epoxide *II* the structure of which follows from subsequent reactions and from spectral evidence as well. Cleavage with hydrobromic acid yielded a bromohydrin which on alkali treatment afforded the starting epoxide and in which, on the basis of the ^{1}H-NMR evidence, both substituents were axial. This bromohydrin has therefore structure *III* and the epoxide has 2α,3α-configuration. Oxidation of the bromohydrin *III* was accompanied by inversion of configuration of the bromine atom as expected[1,3-5] and afforded the bromo ketone *IV*. This structure follows again from spectral and chemical evidence: In ^{1}H-NMR spectrum the signal of the proton on $C_{(2)}$ shows a broad doublet of doublets and the bromine atom is therefore equatorial. Hydride reduction afforded two bromohydrins none of them being identical with the bromohydrin *III*. On alkali treatment yielded the lower melting bromohydrin the new β-epoxide *IX* whereas the higher melting bromohydrin afforded the ketone *V* which was also obtained on catalytic dehalogenation of the bromo ketone *IV*. On similar treatment, this bromohydrin gave the known[2] 3α-hydroxy derivative *VIII*. The higher melting bromohydrin is therefore the *cis*-compound *VI* and the lower melting bromohydrin is *trans*-derivative *VII*.

* Part CCII in the series On Steroids; Part CCI: This Journal *43*, 638 (1978). Part XVII in the series B-Homosteroids; Part XVI: This Journal *43*, 638 (1978).



I



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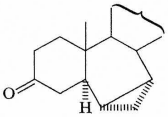

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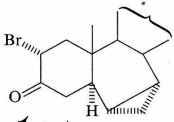

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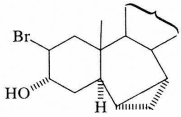
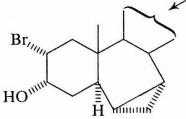
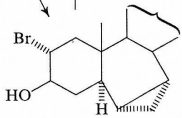


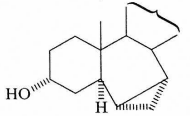
III



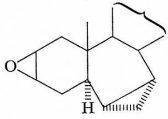
VI



VII

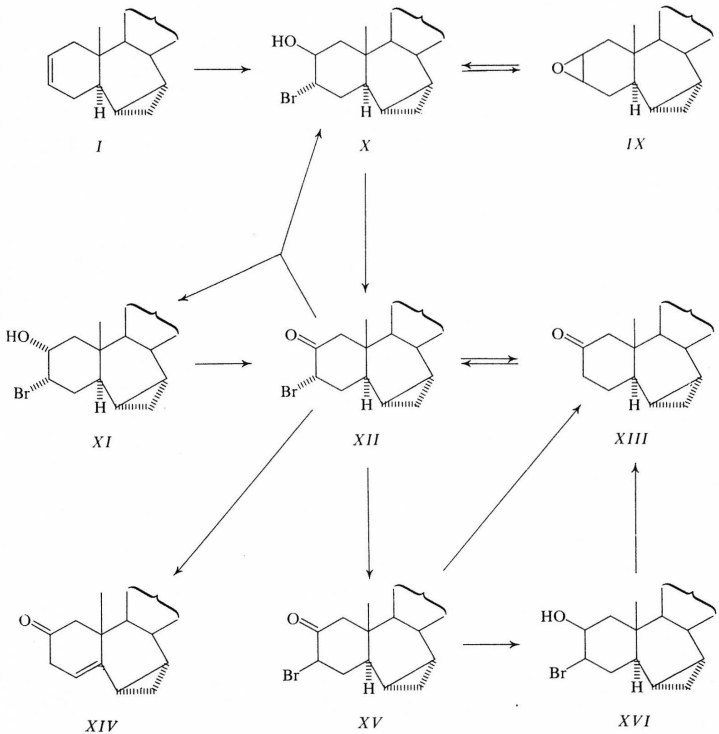


VIII



IX

Addition of hypobromous acid to the olefin *I* proceeded also stereospecifically and yielded one sole product – a bromohydrin which on alkali treatment afforded the β-epoxide *IX*; this bromohydrin is not identical with the bromohydrin *VII* and has therefore the structure *X*. The β-epoxide *IX* afforded on cleavage with hydrobromic acid again the bromohydrin *X*. Oxidation of this bromohydrin gave the bromo ketone *XII* which was also obtained on bromination of the ketone *XIII* with bromine in acetic acid. The bromo ketone *XII* afforded on hydride reduction back the bromohydrin *X* and a new bromohydrin which on oxidation yielded the starting bromo ketone *XII*; it is therefore the *cis*-derivative *XI*.



I *X* *IX*

XI *XII* *XIII*

XIV *XV* *XVI*

In the next experiments we studied the dehydrohalogenation of the bromo ketones *XII* and *XV*. When treated with lithium bromide in N,N-dimethylformamide under the presence of lithium carbonate the bromo ketone *XII* afforded the unsaturated ketone *XIV* in which the double bond rearranged to 4,5-position, conjugated to the cyclopropane ring. Reflux with *sym*-collidine for 8 hours led to the ketone *XIII* which is a product of reductive dehalogenation[1,6]. When the time of reflux was reduced to 30 minutes only partial inversion of the bromine atom took place and some of the 2β-bromo derivative *XV* was isolated next to the starting material. This epimerisation may also be effected by alkali (potassium carbonate) or acid (hydrobromic acid). The bromo ketone *XV* gave on reflux with *sym*-collidine for 8 hours also only the product of reductive debromination, the saturated ketone *XIII*. This reaction was observed in similar derivatives by others[6] and by us as well[1]. In the last experiment the bromo ketone *XV* was reduced with lithium tri-tert-butoxyaluminium hydride to the bromohydrin *XVI* which on alkali treatment yielded the the ketone *XIII*.

EXPERIMENTAL

Melting points were determined on a Kofler block. Optical measurements were carried out in chloroform with an error of ±3°. The infrared spectra were recorded on the Zeiss UR 20 spectrometer in tetrachloromethane unless otherwise stated. The ^{1}H-NMR spectra were recorded on the Tesla 60-MHz instrument in deuteriochloroform and corrected to tetramethylsilane (7·25 ppm), unless otherwise stated. The chemical shift is given in ppm. The identity of samples prepared by different routes was checked by mixture melting point determination, by thin layer chromatography (TLC), and by infrared and ^{1}H-NMR spectra. Ligroin of b.p. 40–60°C was used as a solvent. Usual working up of an ethereal solution means extraction with 5% hydrochloric acid, water, 5% potassium hydrogen carbonate, water, drying with sodium sulphate, and evaporation of the solvent.

2α,3α-Epoxy-6β,7aβ-cyclo-B-homo-5α-cholestane (*II*)

a) *From* 6β,7aβ-*cyclo*-B-*homo*-5α-*cholest*-2-*ene* (I): The olefin *I* (250 mg) in dichloromethane (5 ml) was treated with *m*-chloroperbenzoic acid (250 mg) and allowed to stand at room temperature for 18 h. The mixture was poured into water, the product extracted with ether, and the excess peracid was removed by extraction with 5% sodium carbonate. The organic layer was washed with water, dried, and ether distilled off. The residue (260 mg) was chromatographed on a silica gel column (20 g) in light petroleum–ether (19 : 1). The product (235 mg) was crystallized from methanol to yield 195 mg of the epoxide *II*, m.p. 93–95°C, $[\alpha]_D^{20}$ −47° (*c* 2·40). IR spectrum (CS_2): 3065 (cyclopropane), 805 cm^{-1} (epoxide). ^{1}H-NMR spectrum (Tesla 80 MHz instrument): −0·08 and +0·36 (2 mt, two cyclopropane protons), 0·68 (s, 18-H), 0·73 (s, 19-H), 0·83 (d, J = 6 Hz, 26-H and 27-H), 0·87 (d, J = 5·5 Hz, 21-H), 3·10 (mt, $W_{1/2}$ = 16 Hz, 2β-H and 3β-H). For $C_{28}H_{46}O$ (398·6) calculated: 84·35% C, 11·65% H; found: 84·15% C, 11·45% H.

b) *From* 2β-*bromo*-6β,7aβ-*cyclo*-B-*homo*-5α-*cholestan*-3α-*ol* (III): The bromohydrin *III* (100 mg) was refluxed for 30 min with a solution of potassium hydroxide (100 mg) in methanol (10 ml). Methanol was distilled off *in vacuo*, the residue was treated with water, and the product taken

into ethyl acetate. The organic layer was washed with water, dried, and solvent removed. The residue (90 mg) was purified by preparative TLC on silica gel in light petroleum–ether (9 : 1) to yield after crystallization from methanol 76 mg of the epoxide *II*, m.p. 95–96°C, $[\alpha]_D^{20}$ −47° (*c* 1·59).

2β-Bromo-6β,7aβ-cyclo-B-homo-5α-cholestan-3α-ol (*III*)

A solution of the epoxide *II* (160 mg) in chloroform (5 ml) was treated with 48% hydrobromic acid (0·7 ml) and agitated for 30 min at room temperature. The mixture was diluted with water, the product taken into ethyl acetate, and the organic layer was washed with a potassium hydrogen carbonate solution, water, dried, and solvent removed. The residue (185 mg) was chromatographed on silica gel (10 g) in light petroleum–ether (33 : 1). The corresponding fractions were worked up and the product crystallized from methanol to yield 145 mg of the bromohydrin *III*, m.p. 70°C (decomp.), $[\alpha]_D^0$ +58° (*c* 1·23). IR spectrum: 3624, 3560, 1037, 1021 (hydroxyl), 3050 cm^{-1} (cyclopropane). ^{1}H-NMR spectrum (Varian 100 MHz instrument): −0·15 to +0·10, (mt, one cyclopropane proton), 0·25–0·60 (mt, two cyclopropane protons), 0·69 (s, 18-H), 0·84 (d, J = 6 Hz, 26-H and 27-H), 0·87 (d, J = 5·5 Hz, 21-H), 1·09 (s, 19-H), 3·45 (s, OH), 4·21 (mt, $W_{1/2}$ = 10 Hz, 2α-H and 3β-H). For $C_{28}H_{47}BrO$ (479·6) calculated: 70·12% C, 9·88% H, 16·66% Br; found: 70·01% C, 9·89% H, 16·29% Br.

2α-Bromo-6β,7aβ-cyclo-B-homo-5α-cholestan-3-one (*IV*)

a) *From* 2β-*bromo*-6β,7aβ-*cyclo*-B-*homo*-5α-*cholestan*-3α-*ol* (III): The bromohydrin *III* (160 mg) in acetone (15 ml) was oxidized with excess Jones' reagent. After 5 min at room temperature the excess agent was removed with methanol, and the mixture was diluted with water. The product was extracted with ethyl acetate, the organic layer was washed with potassium hydrogen carbonate, water, dried, and solvent was distilled off. The residue (160 mg) was purified by preparative TLC on silica gel in light petroleum–ether (9 : 1). Working up of the corresponding zones afforded 120 mg of a product which on crystallization from methanol gave 73 mg of the bromo ketone *IV*, m.p. 137–138°C, $[\alpha]_D^{20}$ −6° (*c* 1·24). IR spectrum: 3070 (cyclopropane), 1732 cm^{-1} (carbonyl). ^{1}H-NMR spectrum: −0·10 to +0·60 (2 mt, cyclopropane protons), 0·70 (s, 18-H), 0·83 (d, J = 6 Hz, 26-H and 27-H), 0·86 (d, J = 6 Hz, 21-H), 1·14 (s, 19-H), 4·75 (dd, J = 7 Hz, J' = 13 Hz, 2-H). For $C_{28}H_{45}BrO$ (477·6) calculated: 70·41% C, 9·50% H, 16·73% Br; found: 70·52% C, 9·53% H, 17·54% Br.

b) *From* 3α-*bromo*-6β,7aβ-*cyclo*-B-*homo*-5α-*cholestan*-3β-*ol* (VII): The bromohydrin *VII* (70 mg) in acetone (5 ml) was oxidized with Jones' reagent as described in the foregoing experiment. Similar working up afforded 68 mg of a crude product which was purified by preparative TLC in the same solvent system to yield 50 mg of a purified product. Crystallization from methanol afforded 29 mg of the bromo ketone *IV*, m.p. 133–134°C, $[\alpha]_D^{20}$ −5° (*c* 1·19).

c) *From* 3α-*bromo*-6β,7aβ-*cyclo*-B-*homo*-5α-*cholestan*-3α-*ol* (VI): The bromohydrin *VI* (25 mg) in acetone (5 ml) afforded on oxidation with Jones' reagent and working up as described above 25 mg of a crude product which on crystallization from methanol gave 12 mg of the bromo ketone *IV*, m.p. 135–137°C, $[\alpha]_D^{20}$ −4° (*c* 1·14).

d) *From* 6β,7aβ-*cyclo*-B-*homo*-5α-*cholestan*-3-*one* (V): The ketone *V* (35 mg) in tetrahydrofuran (10 ml) was treated with Jacques' reagent (70 mg) and allowed to stand at room temperature for 20 min. The mixture was poured in water, the product taken into ethyl acetate, and the organic layer was washed with saturated potassium hydrogen carbonate solution, water, dried, and the

solvent distilled off *in vacuo*. The residue (38 mg) was crystallized from methanol to yield 23 mg of the bromo ketone *IV*, m.p. 134—136°C, $[\alpha]_D^{20}$ −6° (*c* 1·16).

6β,7aβ-Cyclo-B-homo-5α-cholestan-3-one (*V*)

a) *From* 2α-*bromo*-6β,7aβ-*cyclo*-B-*homo*-5α-*cholestan*-2-*one* (V): The bromo ketone *V* (50 mg) in ethyl acetate (5 ml) and ethanol (2 ml) was hydrogenated over 5% $Pd/CaCO_3$ catalyst (50 mg) at room temperature for 2 h. The catalyst was filtered off, washed with ether, and the residue after removal of the solvent was purifed by preparative TLC on silica gel in light petroleum–ether (9 : 1). Working up of the corresponding zones afforded 41 mg of a product which was crystallized from methanol–water to yield 28 mg of the ketone *V*, m.p. 104—107°C, $[\alpha]_D^{20}$ +5° (*c* 1·19) in accordance with the literature[2].

b) *From* 2α-*bromo*-6β,7aβ-*cyclo*-B-*homo*-5α-*cholestan*-3α-ol (*VI*): The bromohydrin *V* (25 mg) in methanol (5 ml) was refluxed with potassium hydroxide (50 mg) for 5 min. The mixture was diluted with water, the product isolated with ethyl acetate. The extract was washed with water, dried, and solvent removed. The residue (20 mg) was crystallized from methanol to yield 6·5 mg of the ketone *V*, m.p. 103—107°C, $[\alpha]_D^{20}$ +4° (*c* 1·15).

2α-Bromo-6β,7aβ-cyclo-B-homo-5α-cholestan-3α-ol (*VI*)

a) *With sodium borohydride*: The bromo ketone *IV* (250 mg) was dissolved in ethanol (100 ml) at boiling temperature, and the solution was cooled off to toom temperature. Sodium borohydride (500 mg) was added and the mixture allowed to stand for 1 h at room temperature. The excess hydride was decomposed with 1% acetic acid, most of the solvents were removed *in vacuo*, and the residue was diluted with water. The precipitate was taken into ethyl acetate, the extract was washed with 5% potassium hydrogen carbonate, water, dried, and solvents distilled off. The residue was chromatographed on a silica gel column (30 g) in light petroleum–ether (49 : 1). Fractions with the lipophilic bromohydrin afforded after working up 90 mg of a product which on crystallization from methanol yielded 35 mg of the bromohydrin *VI*, m.p. 126—128°C, $[\alpha]_D^{20}$ −22° (*c* 1·18). IR spectrum: 3615, 3580, 1026 (hydroxyl), 3065 cm^{-1} (cyclopropane). ^{1}H-NMR spectrum (Varian 100 MHz instrument): 0·68 (s, 18-H), 0·80 (s, 19-H), 0·84 (d, J = = 6 Hz, 26-H and 27-H), 0·87 (d, J = 6 Hz, 21-H), 2·03 (s, OH), 4·05 (mt, $W_{1/2}$ = 7 Hz, 3β-H), 4·52 (ddd, J = 2·5 Hz, J' = 8·5 Hz, J'' = 11·5 Hz, 2β-H). For $C_{28}H_{47}BrO$ (479·6) calculated: 70·12% C, 9·88% H, 16·66% Br; found: 70·16% C, 10·21% H, 16·92% Br.

b) *With lithium tri-tert-butoxyaluminium hydride*: The bromo ketone *IV* (150 mg) in tetrahydrofuran (10 ml) was treated with lithium tri-tert-butoxyaluminium hydride (300 mg) and allowed to stand at room temperature for 2 h. The mixture was diluted with water, the excess hydride was destroyed with 2% acetic acid, and the product was taken into ethyl acetate. The extract was washed with potassium hydrogen carbonate, water, dried, and solvent removed. The residue was purified by preparative TLC on silica gel in light petroleum–ether (24 : 1). The zones with the lipophilic bromohydrin were worked up to yield 35 mg of a product which gave on crystallization from methanol 12 mg of the bromohydrin *VI*, m.p. 127—128°C, $[\alpha]_D^{20}$ −21° (*c* 1·36).

2α-Bromo-6β,7aβ-cyclo-B-homo-5α-cholestan-3βol (*VII*)

a) Elution of the chromatography after isolation of the bromohydrin *VI* under *a*) with the same solvent mixture afforded fractions with the polar component. Working up and crystallization of the crude product (131 mg) from methanol gave 65 mg of the bromohydrin *VII*, m.p.

114—116°C, $[\alpha]_D^{20}$ −38° (*c* 0·66). IR spectrum: 3585, 1068, 1025 (hydroxyl), 3070 cm^{-1} (cyclopropane), ^{1}H-NMR spectrum (Varian 100 MHz instrument): 0·68 (s, 18-H), 0·82 (s, 19-H), 0·84, (d, J = 6 Hz, 26-H and 27-H), 0·87 (d, J = 6 Hz, 21-H), 2·13 (s, OH), 3·63 (ddd, J = 5 Hz, J' = 10 Hz, J'' = 10 Hz, 3α-H), 4·19 (ddd, J = 5 Hz, J' = 10 Hz, J'' = 12 Hz, 2β-H). For $C_{28}H_{47}BrO$ (477·6) calculated: 70·12% C, 9·88% H, 16·66% Br; found: 70·14% C, 9·67% H, 16·88% Br.

b) Working up of the zones with the polar component after preparative TLC of the bromohydrin *VI* under *b*) afforded 102 mg of a product which on crystallization from methanol yielded 41 mg of the bromohydrin *VII*, m.p. 115—116°C, $[\alpha]_D^{20}$ −35° (*c* 1·42).

6β,7aβ-Cyclo-B-homo-5α-cholestan-3α-ol (*VIII*)

The bromohydrin *VI* (40 mg) in ethanol (5 ml) and ethyl acetate (25 ml) was hydrogenated over 5% $Pd/CaCO_3$ catalyst (40 mg) for 2 h. The catalyst was filtered off, washed with ether, and solvents removed. The residue was purified by preparative TLC on silica gel in light petroleum–ether (9 : 1) to yield 28 mg of a product which was crystallized from acetone to yield 11 mg of the alcohol *VIII*, m.p. 87—90°C, $[\alpha]_D^{20}$ −39° (*c* 1·10) in accordance with the literature[2].

2β,3β-Epoxy-6β,7aβ-cyclo-B-homo-5α-cholestane (*IX*)

a) *From* 2α-*bromo*-6β,7aβ-*cyclo*-B-*homo*-5α-*cholestan*-3β-*ol* (VII): The bromohydrin *VII* (50 mg) was dissolved in a solution of potassium hydroxide (100 mg) in methanol (10 ml) and set aside for 2 h. Methanol was distilled off *in vacuo*, the residue was treated with water, and the product taken into ethyl acetate. The extract washed with water, dried, and solvent removed. The product (41 mg) was purified by preparative TLC on silica gel in light petroleum–ether (9 : 1) to yield after crystallization from ethanol 29 mg of the epoxide *IX*, m.p. 73—76°C, $[\alpha]_D^{20}$ −12° (*c* 2·40). IR spectrum: 3065 cm^{-1} (cyclopropane). ^{1}H-NMR spectrum (Varian 100 MHz instrument): −0·20 to +0·50 (cyclopropane protons), 0·69 (s, 18-H), 0·82 (s, 19-H), 0·86 (d, J = = 6·5 Hz, 26-H and 27-H), 0·88 (d, J = 5·5 Hz, 21-H). For $C_{28}H_{46}O$ (398·6) calculated: 84·35% C 11·65% H; found: 84·60% C, 11·52% H.

b) *From* 3α-*bromo*-6β,7aβ-*cyclo*-B-*homo*-5α-*cholestan*-2β-*ol* (XII): The bromohydrin *XII* (1·15 g) was refluxed with a solution of potassium hydroxide (2·3 g) in ethanol (230 ml) for 4 h. The solvent was partly removed by distillation, the residue was diluted with water, and the product taken into ethyl acetate. The solution was washed with water, dried, and solvent removed. The residue (1 g) was chromatographed over silica gel (100 g) in light petroleum–ether (49 : 1). Working up of the corresponding fractions yielded 800 mg of a solid which was crystallized from ethanol to afford 570 mg of the epoxide *IX*, m.p. 74—77°C, $[\alpha]_D^{20}$ −14° (*c* 7·61).

3α-Bromo-6β,7aβ-cyclo-B-homo-5α-cholestan-2β-ol (*X*)

a) *From* 6β,7aβ-*cyclo*-B-*homo*-5α-*cholest*-2-*ene* (I): A solution of the olefin *I* (400 mg) in dioxan (50 ml) was treated with water (2 ml), 9% perchloric acid (0·9 ml), and N-bromoacetamide (150 mg) and set aside for 2 h. The mixture was poured into water, the product extracted with ethyl acetate, and the extract was washed with 5% potassium hydrogen carbonate, water, dried, and the solvent removed. The residue (400 mg) was chromatographed on a silica gel column (60 g) in light petroleum–ether (9 : 1) to yield 370 mg of a purified product. Crystallization from methanol afforded 290 mg of the bromohydrin *X*, m.p. 152—155°C, $[\alpha]_D^{20}$ +7° (*c* 1·36). IR spectrum: 3625, 1016, 999 (hydroxyl), 3065 cm^{-1} (cyclopropane). ^{1}H-NMR spectrum (Tesla 80 MHz

instrument): −0·02 and +0·45 (2 mt, cyclopropane protons), 0·69 (s, 18-H), 0·85 (d, $J = 6$ Hz, 26-H and 27-H), 0·88 (d, $J = 6$ Hz, 21-H), 1·02 (s, 19-H), 3·93 (mt, $W_{1/2} = 8$ Hz, 2α-H), 4·07 (mt, $W_{1/2} = 9$ Hz, 3β-H). For $C_{28}H_{47}BrO$ (479·6) calculated: 70·12% C, 9·85% H, 16·66% Br; found: 70·50% C, 9·85% H, 16·19% Br.

b) *From* 2β,3β-*epoxy*-6β,7aβ-*cyclo*-B-*homo*-5α-*cholestane* (IX): A solution of the epoxide *IX* (70 mg) in chloroform (3·5 ml) was treated with 48% hydrobromic acid (0·3 ml) and agitated for 45 min. The mixture was poured into water the product extracted with ether, and the ethereal solution was washed with a potassium hydrogen carbonate solution, water, dried, and ether removed. The residue (78 mg) was purified by preparative TLC on silica gel in light petroleum–ether (33 : 1) to yield after crystallization from methanol 41 mg of the bromohydrin *X*, m.p. 154–156°C, $[\alpha]_D^{20}$ +7° (*c* 2·60).

c) *From* 3α-*bromo*-6β,7aβ-*cyclo*-B-*homo*-5α-*cholestan*-2-*one* (XII): A solution of the bromo ketone *XII* (200 mg) in tetrahydrofuran (10 ml) was treated at room temperature with lithium tri-tert-butoxyaluminiumhydride (400 mg) and set aside for 3 1/2 h. The mixture was diluted with water, the hydride decomposed with 1% hydrochloric acid, and the product taken into ethyl acetate. The extract was worked up, and the residue (210 mg) was purified by preparative TLC on silica gel in light petroleum–ether (33 : 1). The zones with the lipophilic component were worked up to yield 71 mg of a product which on crystallization from methanol gave 42 mg of the bromohydrin *X*, m.p. 151–155°C, $[\alpha]_D^{20}$ +7 (*c* 1·18).

3α-Bromo-6β,7aβ-cyclo-B-homo-5α-cholestan-2α-ol (*XI*)

Zones with the polar product from the foregoing experiment afforded after working up 69 mg of a residue which on crystallization from methanol gave 43 mg of the bromohydrin *XI*, m.p. 148–151°C, $[\alpha]_D^{20}$ −5° (*c* 1·32). IR spectrum: 3580, 1072, 1059 (hydroxyl), 3070 cm^{-1} (cyclopropane). ^{1}H-NMR spectrum (Varian 100 MHz instrument): −0·12 to +0·58 (cyclopropane protons), 0·69 (s, 18-H), 0·82 (s, 19-H), 0·85 (d, $J = 6$ Hz, 26-H and 27-H), 0·88 (d, $J = 6$ Hz 21-H), 1·85 (s, OH), 3·58 (mt, $W_{1/2} = 10$ Hz, 2β-H), 4·71 (mt, $W_{1/2} = 7·5$ Hz, 3β-H). For $C_{28}H_{47}BrO$ (479·6) calculated: 70·12% C, 9·88% H, 16·66% Br; found: 69·81% C, 9·86% H, 17·13% Br.

3α-Bromo-6β,7aβ-cyclo-B-homo-5α-cholestan-2-one (*XII*)

a) *From* 3α-*bromo*-6β,7aβ-*cyclo*-B-*homo*-5α-*cholestan*-2β-*ol* (X): The bromohydrin *X* (120 mg) in acetone (5 ml) was oxidized with excess Jones' reagent. After 10 min the agent was removed with methanol, the mixture was diluted with water, and the product extracted with ethyl acetate. Working up and crystallization of the residue (120 mg) from methanol gave 87 mg of the bromo ketone *XII*, m.p. 117–119°, $[\alpha]_D^{20}$ +67° (*c* 0·72). IR spectrum: 3070 (cyclopropane), 1713 cm^{-1} (carbonyl). ^{1}H-NMR spectrum (Tesla 80 MHz instrument): 0·09 and 0·52 (two mt, cyclopropane protons), 0·68 and 0·69 (two s, 18-H and 19-H), 0·83 (d, $J = 6$ Hz, 26-H and 27-H), 0·86 (d, $J = 6$ Hz, 21-H), 4·29 (mt, $W_{1/2} = 8$ Hz, 3β-H). For $C_{28}H_{45}BrO$ (477·6) calculated: 70·41% C, 9·50% H; found: 70·60% C, 9·27% H.

b) *From* 6β,7aβ-*cyclo*-B-*homo*-5α-*cholestan*-2-*one* (XIII): The ketone *XIII* (100 mg) in acetic acid (2 ml) was treated with bromine (44 mg) in acetic acid (0·25 ml). After 2 min at room temperature the mixture decolorised. It was poured in water and the product was taken into ethyl acetate. The organic layer was washed with water, a potassium hydrogen carbonate solution, water, dried, and solvent distilled off under reduced pressure. The residue (110 mg) was purified by preparative TLC on silica gel in light petroleum–ether (9 : 1). Zones with the lipophilic component

were extracted with ether, and solvent removed. The residue (62 mg) was crystallized from methanol to afford 35 mg of the bromo ketone *XII*, m.p. 117–118°C, $[\alpha]_D^{20}$ + 69° (*c* 1·17).

c) *From* 3α-*bromo*-6β,7aβ-*cyclo*-B-*homo*-5α-*cholestan*-2α-*ol* (XI): Oxidation of the bromohydrin *XI* (24 mg) in acetone (5 ml) as described under *a*) and similar working up afforded a product which was purified by preparative TLC on silica gel in light petroleum–ether (9 : 1). Working up of the corresponding zones yielded 18·5 mg of a product which was crystallized from methanol to yield 6 mg of the bromo ketone *XII*, m.p. 115–118°C, $[\alpha]_D^{20}$ + 60° (*c* 1·11).

6β,7aβ-Cyclo-B-homo-5α-cholestan-2-one (*XIII*)

a) *From* 3α-*bromo*-6β,7aβ-*cyclo*-B-*homo*-5α-*cholestan*-2-*one* (XII) *on hydrogenation*: The bromo ketone *XII* (70 mg) in ethanol (2 ml) and ethyl acetate (5 ml) was hydrogenated over 5% $Pd/CaCO_3$ catalyst (30 mg) for 2 h. The catalyst was filtered off, washed with ether, and the filtrate was evaporated to dryness *in vacuo*. The residue was purified by preparative TLC on silica gel in light petroleum–ether (9 : 1) to yield 68 mg of a solid which on crystallization from methanol afforded 35 mg of the ketone *XIII*, m.p. 115–118°C, $[\alpha]_D^{20}$ −24° (*c* 0·59). IR spectrum: 3065 (cyclopropane) 1713 (carbonyl), 1424 cm^{-1} (CH_2–CO). ^{1}H-NMR spectrum (Varian 100 MHz instrument): 0·01 and 0·58 (two mt, cyclopropane protons), 0·68 and 0·72 (two s, 18-H and 19-H), 0·84 (d, J = 6 Hz, 26-H and 27-H), 0·88 (d, J = 6 Hz, 21-H), 2·80 (mt, two α-protons to carbonyl). For $C_{28}H_{46}O$ (398·6) calculated 84·35% C, 11·63% H; found: 84·51% C, 11·89% H.

b) *From* 3α-*bromo*-6β,7aβ-*cyclo*-B-*homo*-5α-*cholestan*-2-*one* (XII) *with* sym-*collidine*: The bromo ketone *XII* (160 mg) in *sym*-collidine (5 ml) was refluxed for 8 h. Collidine was distilled off under reduced pressure, the residue was dissolved in ethyl acetate, and the rest of the base was removed by extraction with 5% hydrochloric acid. The organic layer was washed with water, saturated potassium hydrogen carbonate solution, water, dried, and solvent removed. The residue was purified by preparative TLC on silica gel in light petroleum–ether (9 : 1) to yield after crystallization from ethanol 91 mg of the ketone *XIII*, m.p. 112–116°C, $[\alpha]_D^{20}$ −25° (*c* 1·18).

c) *From* 3β-*bromo*-6β,7aβ-*cyclo*-B-*homo*-5α-*cholestan*-2-*one* (XV): The bromo ketone *XV* (30 mg) was refluxed in *sym*-collidine (5 ml) as described in the foregoing experiment. Similar working up gave 22 mg of a product which on crystallization from methanol afforded 9 mg of the ketone *XIII*, m.p. 113–116°C, $[\alpha]_D^{20}$ −22° (*c* 1·17).

d) *From* 3β-*bromo*-6β,7aβ-*cyclo*-B-*homo*-5α-*cholestan*-2β-*ol* (XVI): The bromohydrin *XVI* (18 mg) was refluxed with a solution of potassium hydroxide (50 mg) in methanol (5 ml) for 10 min. Methanol was removed *in vacuo*, the residue was treated with water, and the product taken into ethyl acetate. The residue (14 mg) after evaporation of the solvent was crystallized from methanol to yield 5·5 mg of the ketone *XIII*, m.p. 112–117°C, $[\alpha]_D^{20}$ −21° (*c* 1·12).

6β,7aβ-*Cyclo*-B-*homocholest*-4-*en*-2-*one* (*XIV*)

A solution of the bromo ketone *XII* (310 mg) in N,N-dimethylformamide (15 ml) was heated to 130°C with lithium bromide (310 mg) and lithium carbonate (310 mg) for 6 h. The mixture was diluted with water, and the product extracted with ethyl acetate. The organic layer was worked up and the residue was chromatographed on a silica gel column (60 g) in light petroleum–ether (9 : 1) to yield 182 mg of pure olefin *XIV*. Crystallization from methanol gave 45 mg of the olefin *XVI*, m.p. 82–83°C, $[\alpha]_D^{20}$ + 59° (*c* 1·93). IR spectrum: 3080, 1693, 1683, 1645 (C=C-cyclopropane), 1722 cm^{-1} (carbonyl). ^{1}H-NMR spectrum (Varian 100 MHz instrument): 0·13 to 0·63 (cyclopropane protons), 0·69 (s, 18-H), 0·84 (d, J = 6·5 Hz, 26-H and 27-H), 0·88 (d, J =

= 6 Hz, 21-H), 0·89 (s, 19-H), 2·08 and 2·38 (two d, J = 14 Hz, 1-H), 2·38 (mt, $W_{1/2}$ = 7 Hz, two 3-H), 5·89 (t, J = 4 Hz, 4-H). For $C_{28}H_{44}O$ (396·6) calculated: 84·77% C, 11·18% H; found: 84·00% C, 11·17% H.

3β-Bromo-6β,7aβ-cyclo-B-homo-5α-cholestan-2-one (*XV*)

a) *With* sym-*collidine*: The bromo ketone *XII* (150 mg) in *sym*-collidine (5 ml) was refluxed for 30 min. Collidine was distilled off *in vacuo*, the residue was dissolved in ethyl acetate and the solution was worked up. The residue was purified by preparative TLC on silica gel in light petroleum–ether (9 : 1). Working up of the corresponding zones afforded 68 mg of the starting material and 35 mg of the epimeric bromo ketone *XV*, m.p. 159 to 161°C (methanol), $[\alpha]_D^{20}$ −7° (*c* 1·86). IR spectrum: 3065 (cyclopropane), 1730 (carbonyl), 1428 cm^{-1} (CH_2—CO). ^{1}H-NMR spectrum (Varian 100 MHz instrument): −0·05 to +0·67 (cyclopropane protons), 0·69 (s, 18-H), 0·75 (s, 19-H), 0·85 (d, J = 6·5 Hz, 26-H and 27-H), 0·88 (d, J = 6 Hz, 21-H), 2·17 and 2·49 (two d, J = 13·5 Hz, 1-H), 4·58 (dd, J = 7 Hz, J' = 12 Hz, 3α-H). For $C_{28}H_{45}BrO$ (477·6) calculated: 70·41% C, 9·50% H, 16·73% Br; found: 70·77% C, 9·84% H, 17·16% Br.

b) *With potassium carbonate*: The bromo ketone *XII* (30 mg) in ethanol (9 ml) was treated with a solution of potassium carbonate (10 mg) in water (0·5 ml) and ethanol (4 ml) and set aside for 4 h. The mixture was poured into water, the product taken into ethyl acetate, and the solution was washed with water, and dried. The residue was purified by preparative TLC on silica gel in light petroleum–ether (9 : 1) to yield 12·5 mg of the starting material and 11 mg a of new product. Crystallization from methanol gave 4 mg of the bromo ketone *XV*, m.p. 155—159°C.

c) *With hydrobromic acid*: The bromo ketone *XII* (34 mg) in acetic acid (20 ml) was treated with 48% hydrobromic acid (0·3 ml) and set aside for 24 h. The product was precipitated with water, extracted into ethyl acetate, and the organic layer was washed with 5% potassium hydrogen carbonate, water, dried and solvent removed. The mixture was separated as described above to afford 9·5 mg of the starting material and 12·5 mg of the inverted product. Crystallization from methanol gave 3 mg of the bromo ketone *XV*, m.p. 157—159°C.

3β-Bromo-6β,7aβ-cyclo-B-homo-5α-cholestan-2β-ol (*XVI*)

A solution of the bromo ketone *XV* (200 mg) in tetrahydrofuran (10 ml) was treated with lithium tri-tert-butoxyaluminiumhydride (400 mg) and allowed to stand at room temperature for 6 h. The mixture was diluted with water, the excess hydride was destroyed with 2% hydrochloric acid, and the product extracted with ethyl acetate. The organic layer was worked up and the residue was chromatographed on a silica gel column (40 g) in light petroleum–ether (9 : 1). The crude product (160 mg) was crystallized from methanol to yield 112 mg of the bromohydrine *XVI*, m.p. 127—128°C, $[\alpha]_D^{20}$ 0° (*c* 0·84). IR spectrum: 3575, 1031 (hydroxyl) 3060 cm^{-1} (cyclopropane). ^{1}H-NMR spectrum (Varian 100 MHz instrument): −0·04 to +0·60 (cyclopropane protons), 0·70 (s, 18-H), 0·86 (d, J = 6·5 Hz, 26-H and 27-H), 0·885 (d, J = 6 Hz, 21-H), 1·10 (s, 19-H), 4·06 (mt, $W_{1/2}$ = 8 Hz, 2α-H), 4·17 to 4·40 (mt, $W_{1/2}$ = 18 Hz, 3α-H). For $C_{28}H_{47}BrO$ (479·6) calculated: 70·12% C, 9·88% H, 16·66% Br; found: 69·70% C, 9·72% H, 16·95% Br.

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