SYNTHESIS OF 4,5-CYCLO-A-HOMO-B-NORCHOLESTANE DERIVATIVES*

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Synthesis of isomeric 4,5-cyclo-A-homo-B-norcholestane derivatives is described and structure of the compounds established by chemical and spectral means (IR, NMR and mass spectra).

In the course of our studies of steroids containing the cyclopropane ring we became interested in A-homo-B-norsteroids, especially in such strained systems like the 2,3-epoxides and in the A-ring unsaturated compounds. We intend to study their chemistry and stereochemistry and in this paper we present synthesis of this new type of compounds.

The unsaturated ketone[1] *I* was reduced with sodium borohydride to yield the 3β-alcohol[2] *II* as the main product and about 3% of the 3α-epimer *III*. Both allylic alcohols, *II* and *III*, were submitted to Simmons–Smith methylenation. The reaction proceeded smoothly when carried out at room temperature; higher temperatures caused elimination of the hydroxyl group. Configurations of the cyclopropane rings in the alcohols *V* and *VIII* follow from the NMR as well as from chemical evidence: Their oxidation afforded two different ketones which are evidently the isomers *VII* and *X*. It is well known from the work of Winstein[3,4] and others that the steric course of Simmons–Smith methylenation of cyclic allylic alcohols is critically influenced by the configuration of the hydroxyl group, the addition taking place *cis* to the hydroxyl group. In agreement with these observations also in our case the addition to the alcohols *II* and *III* proceeded from different sides of the molecule and we may therefore assume that the alcohol *II* afforded the 4α,5α-cyclo compound *V* and the 3α-hydroxy derivative *III* gave the isomeric compound *VIII*. NMR evidence is in agreement with this assumption. The data are summarised in Table I. The cyclopropane ring is known[5–8] to produce a long-range shielding effect on the 19-protons when oriented *cis* to the methyl group and a deshielding effect if the mutual sterical relationship is *trans*. In accordance with these observations the chemical shifts of these protons in our 4α,5α-cyclosteroids *V* and *XII* show upfield shifts of −0·03

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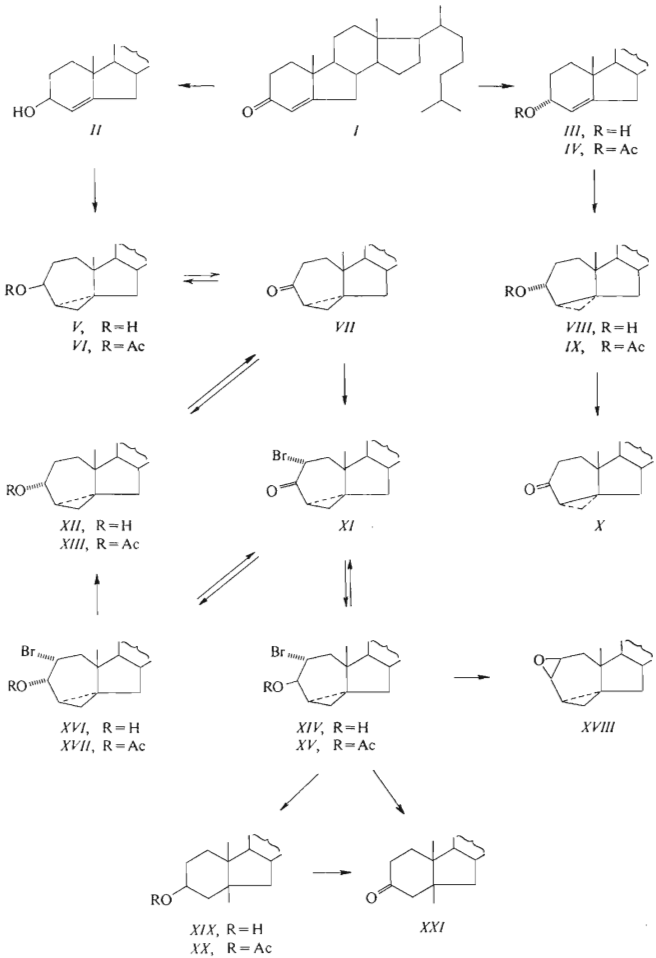
HO
II
O
I
RO
III, R = H
IV, R = Ac
RO
V, R = H
VI, R = Ac
O
VII
RO
VIII, R = H
IX, R = Ac
RO
XII, R = H
XIII, R = Ac
Br
O
XI
O
X
Br
RO
XVI, R = H
XVII, R = Ac
Br
RO
XIV, R = H
XV, R = Ac
O
XVIII
RO
XIX, R = H
XX, R = Ac
O
XXI

TABLE I

Characteristic Parameters of PMR Spectra

PMR spectra were measured in deuteriochloroform with tetramethylsilane as internal reference. Chemical shifts are given in δ-scale (p.p.m.); coupling constants (J) and width of multiplets (W) are given in Hz. For characterisation of the signals following abbreviations are used: b broad, d doublet, m multiplet, s singlet, t triplet, dd doublet of doublets.

Compound	19-H[a]	18-H[a]	21-H[b]	26-H 27-H[b]	3-OR[a]	CH_2[c] (cyclopropane)	3-H	Other protons
II acetate	0·975	0·685	0·92	0·865	2·04	—	5·35 m	5·28 bs (4-H)
IV	0·855	0·695	0·925	0·865	2·01	—	5·22 m	5·33 m (4-H)
V	0·79	0·67	0·925	0·865	1·47	0·41 dd 0·58 t	4·14 m ($W = 22$)	—
VI	0·795	0·665	0·925	0·865	2·03	0·46 dd	5·22 m ($W = 21$)	—
VII	0·97	0·69	0·93	0·87	—	*d*	—	
VIII	0·82	0·665	0·92	0·86	1·16	0·05 t 0·65 dd	4·46 m ($W = 23$)	—
IX	0·865	0·665	0·915	0·865	2·02	*d*	5·46 m ($W = 22$)	—
X[e]	0·825	0·715	1·105	1·04	—	*d*	—	
XII	0·755	0·675	0·925	0·865	1·58	0·19 t 0·46 dd	4·10 m ($W = 9$)	—
XIII	0·755	0·68	0·93	0·865	2·04	0·23 t 0·49 dd	5·11 m ($W = 9$)	—
XV	0·86	0·67	0·925	0·865	2·10	0·49 dd 0·61 t	5·35 dd $J_{3,2} = 9·7$ $J_{3,4} = 5·6$	3·73 m (2-H) $J_{2,1} = 13·1, 3·2$ $J_{2,3} = 9·7$

XVII	0·85	0·67	0·935	0·865	2·14	0·36 t 0·58 dd	5·41 dd $J_{3,2} = 2·8$ $J_{3,4} = 2·8$	3·86 m (2-H) $J_{2,1} = 11·6, 3·8$ $J_{2,3} = 2·8$
XVIII[e]	1·065	0·74	1·115	1·03	—	0·42 dd [d]	3·29 t $J_{3,2} = 3·8$ $J_{3,4} = 3·8$	2·94 bt (2-H) $J_{2,1} = 3·3, 0·9$ $J_{2,3} = 3·8$
XIX	0·76	0·64	0·91	0·865	1·43	—	4·05 m ($W = 19$)	1·06 s (5-CH_3)
XX	0·76	0·64	0·91	0·865	2·01	—	5·01 m ($W = 19$)	1·01 s (5-CH_3)
XXI	0·89	0·66	0·91	0·86	—	—	—	0·97 s (5-CH_3)
XXII[f]	0·66	0·65	0·91	0·86	—	—	[d]	—
XXIII[f]	0·79	0·645	0·91	0·86	—	—	[d]	—
XXIV[f]	0·66	0·645	0·905	0·86	1·43	—	4·10 m ($W = 12$)	—
XXV[f]	0·78	0·64	0·915	0·86	1·59	—	3·69 m ($W = 20$)	—
XXVI[f]	0·92	0·645	0·90	0·86	1·56	—	3·60 m ($W = 30$)	—
XXVII[f]	0·86	0·645	0·915	0·865	1·46	—	4·02 m ($W = 21$)	—

[a] Singlets. [b] Doublets with $J = 6$ Hz. [c] Geminal cyclopropane protons with $J_{gem} = 5$ and $J_{vic} = 5$ resp. 9 for triplet resp. doublet of doublets. [d] Indeterminable value. [e] PMR spectra were measured in C_6H_6. [f] Compounds *XXII*–*XXVII* were measured as models: B-nor-5α-cholestane (*XXII*), B-nor-5β-cholestane (*XXIII*), B-nor-5α-cholestan-3α-ol (*XXIV*), B-nor-5β-cholestan-3α-ol (*XXV*), B-nor-5α-cholestan-3β-ol (*XXVI*), B-nor-5β-cholestan-3β-ol (*XXVII*).

and −0·07 p.p.m. respectively when compared with the model compounds *XXV* and *XXVII*. In the isomeric 4β,5β-cyclosteroids *VIII* and *IX*, on the other hand, the cyclopropane ring produces downfield shifts +0·16 and +0·20 p.p.m. in relation to the model compound *XXIV*. The NMR spectra of the 5β-methyl-B-nor derivatives *XIX*–*XXI* are also significant. The observed upfield shift (−0·10 p.p.m.) of the 19-protons in comparision to the parent unmethylated compound *XXVII* points clearly to the 5β-configuration of the methyl group. Opposite configuration would be expected[9] to cause a downfield shift.

Further reactions have been carried out with the ketone *VII*. Its reduction afforded a mixture of the alcohols *V* and *XII* and they were oxidised back to the ketone *VII*. Bromination with Jacques' reagent in tetrahydrofuran led to the bromo ketone *XI* the structure of which follows from subsequent reactions: Metal hydride reduction afforded two bromohydrins with unchanged configuration of the halogen atom as both bromohydrins gave on oxidation the starting bromo ketone *XI*. Treatement with methanolic potassium hydroxide transformed the lipophilic bromohydrin to the ketone *VII* (*cis* configuration of the substituents) whereas the polar bromohydrin gave under similar conditions the epoxide *XVIII* (*trans* configuration of the substituents). On catalytic dehalogenation the *cis* bromohydrin afforded the 3α-hydroxy derivative *XII*. The configuration of the halogen atom in our brominated compounds is therefore 2α, the lipophilic bromohydrin being the *cis* compound *XVI* and the polar bromohydrin the *trans* isomer *XIV*. In the epoxide *XVIII* the epoxide ring has β-configuration. Catalytic dehalogenation ($Pd/CaCO_3$ in ethanol) of the *trans* bromohydrin *XIV* led to a more complicated mixture: Along with the expected alcohol *V* two additional compounds were isolated none of them containing the cyclopropane ring. Chemical and spectral evidence established their structure as the 5β-methyl-B-nor derivatives *XIX* and *XXI*.

Our next interest was the conformation of ring A in this new type of cyclosteroids. NMR evidence points to a conformation represented by Fig. 1 in which the 3α-bond is axial and 3β equatorial. The widths of the multiplets (21 and 22 Hz) belonging to the 3α-protons in compounds *V* and *VII* are consistent with their axial conformation whereas analogous widths (9 Hz) in the epimeric compounds *XII* and *XIII* are in

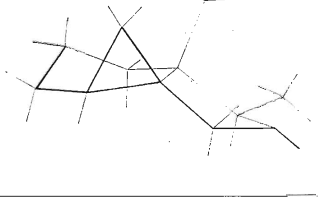

FIG. 1
Conformation of Ring A in 4α,5-Cyclo-A-homo-B-nor-5α-steroids

agreement with equatorial conformation of the 3β-proton. Similarly, in the bromohydrin-acetate *XVII* the 3β-proton is equatorial ($J_{2\beta,3\beta}$ = 2·8 Hz) and in the *trans* compound *XV* the 3α-proton is axial ($J_{2\beta,3\alpha}$ = 9·7 Hz). The vicinal coupling constants in the bromohydrin-acetates *XVII* and *XV* are also in agreement with the suggested conformation of ring A where the 2β-bond is axial ($J_{1\alpha,2\beta}$ = 13·1 and 11·6 Hz).

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 Zeis UR 10 spectrometer in tetrachloromethane unless otherwise stated. The NMR spectra were recorded on the Varian H-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 (TLC), 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, water, drying with magnesium sulphate, and evaporation of the solvent. The mass spectra were recorded on the AEI MS 902 instrument.

B-Nor-4-cholesten-3β-ol (*II*)

A solution of the ketone[1] *I* (3 g) in methanol (70 ml) and ethyl acetate (60 ml) was treated with sodium borohydride (500 mg) and stirred for 8 hours. After 12 hours at room temperature 200 mg of hydride were added and stirred for another 8 hours. The reaction mixture was then poured into 5% acetic acid (600 ml) and the product extracted into ether. The ethereal solution was washed with a sodium hydrogen carbonate solution, water, dried, and the solvent was removed. The residue was crystallised from ether–methanol to yield 2·5 g of the alcohol *II*, m.p. 107—108°C, $[\alpha]_D^{20}$ −30° (*c* 1·09) in accordance with the literature[2].

B-Nor-4-cholesten-3α-ol (*III*)

The mother liquors after crystallisation of the 3β-hydroxy derivative *II* (409 mg) were chromatographed on a silica gel column (150 g) in benzene–ether (19 : 1). The first fractions afforded 180 mg of the starting ketone *I*. Further elution with the same solvent mixture afforded fractions with the 3α-hydroxy compound. Combination and evaporation gave 105 mg of a product which on crystallisation from acetone–water yielded 65 mg of the alcohol *III*, m.p. 95—96°C, $[\alpha]_D^{20}$ +37° (*c* 1·28). IR: 3 600, 1 008 (hydroxyl), 1 670 cm^{-1} (double bond). For $C_{26}H_{44}O$ (372·6) calculated: 83·80% C, 11·90% H; found: 84·02% C, 11·93% H.

3α-Acetoxy-B-nor-4-cholestene (*IV*)

The alcohol *III* (100 mg) in pyridine (0·6 ml) was acetylated with acetic anhydride (0·4 ml) for 18 hours at room temperature. The reaction mixture was decomposed with ice, the product extracted into ether, and the ethereal solution was worked up. The residue after evaporation of the solvent was crystallised from ether–methanol to yield 70 mg of the acetate *IV*, m.p. 91—92°C, $[\alpha]_D^{20}$ +95° (*c* 1·05). For $C_{28}H_{46}O_2$ (414·6) calculated: 81·10% C, 11·18% H; found: 80·82% C, 10·89% H.

4α,5-Cyclo-A-homo-B-nor-5α-cholestan-3β-ol (*V*)

a) *From B-nor-4-cholesten-3β-ol* (II): 0·5% Zn–Cu couple was prepared by adding zinc dust (7·4 g; Baker 60—200 mesh) into a solution of cupric acetate monohydrate (120 mg) in acetic acid (30 ml) at 50—60°C and shaking until the solution decolorised. The solvent was poured off, the zinc was washed first with acetic acid (30 ml) and then decanted with eight portions of absolute ether (20 ml each). The metal was covered with absolute ether (100 ml), iodine (100 mg) and diiodomethane (12 ml) were added and the mixture was refluxed under stirring for 3 hours. After cooling off to the room temperature a solution of the unsaturated alcohol *II* (3 g) in absolute ether (30 ml) was added under stirring and the reaction mixture was stirred at room temperature for 3 hours. The suspension was diluted with ether, poured into 5% sodium hydrogen carbonate, and the ethereal layer was washed with 5% sodium thiosulphate, water, dried, and the solvent was distilled off. The residue was chromatographed on a silica gel column (100 g) in benzene–ether (19 : 1). Fractions with the polar component were combined, the solvent removed, and the residue (1·94 g) was crystallised from methanol to yield 1·7 g of the alcohol *V*, m.p. 124—125°C, $[\alpha]_D^{20}$ −6° (*c* 1·28). IR: 3055 (cyclopropane), 3590, 1029, 1020, 1005 cm^{-1} (hydroxyl). For $C_{27}H_{46}O$ (386·6) calculated: 83·87% C, 11·99% H; found: 83·65% C, 12·18% H.

b) *From* 4α,5-*cyclo-A-homo-B-nor-5α-cholestan-3-one* (VII): The ketone *VII* (1·5 g) in tetrahydrofuran (30 ml) was treated with lithium tri-tert-butoxyaluminium hydride (3·5 g) and allowed to stand at room temperature for 1 hour. The reaction mixture was poured into 2% hydrochloric acid, and the product taken into ether. The ethereal solution was washed with a sodium hydrogen carbonate solution, water, dried, and the solvent removed. The residue was chromatographed over silica gel (100 g) in benzene. Fractions with the polar component were combined, the solvent was distilled off, and the residue was crystallised from methanol to yield 1 g of the alcohol *V*, m.p. 124—125°C, $[\alpha]_D^{20}$ −7° (*c* 1·65).

c) *From* 2α-*bromo*-4α,5-*cyclo-A-homo-B-nor-5α-cholestan*-3β-*ol* (XIV): The bromohydrin *XIV* (200 mg) in ethanol (50 ml) was agitated in a hydrogen atmosphere over 5% $Pd/CaCO_3$ catalyst (350 mg) for 24 hours. Fresh catalyst (100 mg) was then added and agitated for another 24 hours. The reaction mixture was diluted with ether, the catalyst was filtered off, washed with ether and the filtrate was evaporated to dryness under reduced pressure. The residue was dissolved in ether, the ethereal solution was washed with dilute hydrochloric acid, a sodium hydrogen carbonate solution, water, dried and the solvent removed. The residue (180 mg) was chromatographed on a silica gel column (25 g) in benzene–ether (19 : 1). Fractions with the polar component were worked up and the residue was crystallised from methanol to yield 17 mg of the alcohol *V*, m.p. 124—126°C, $[\alpha]_D^{20}$ −8° (*c* 0·98).

3β-Acetoxy-4α,5-cyclo-A-homo-B-nor-5α-cholestane (*VI*)

The alcohol *V* (100 mg) in pyridine (0·6 ml) was acetylated with acetic anhydride (0·4 ml) for 18 hours at room temperature. The reaction mixture was decomposed with ice, the product isolated with ether, and worked up. The residue was crystallised from methanol to yield 65 mg of the acetate *VI*, m.p. 110—111°C, $[\alpha]_D^{20}$ −35° (*c* 1·53). For $C_{29}H_{48}O_2$ (428·7) calculated: 81·25% C, 11·29% H; found: 81·49% C, 11·07% H.

4α,5-Cyclo-A-homo-B-nor-5α-cholestan-3-one (*VII*)

a) *From* 4α,5-*cyclo-A-homo-B-nor-5α-cholestan*-3β-*ol* (V): The alcohol *V* (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, water was added, and the product was taken

into ether. The ethereal solution was washed with water, a sodium hydrogen carbonate solution, water, dried, and evaporated. The residue was crystallised from methanol to yield 4·1 g of the ketone *VII*, m.p. 149–150°C, $[\alpha]_D^{20}$ −18° (*c* 1·67). IR: 3065 (cyclopropane), 1694 (carbonyl next to cyclopropane), 1430 cm^{-1} (CH_2 next to carbonyl). For $C_{27}H_{44}O$ (384·6) calculated: 84·31% C, 11·53% H; found: 84·35% C, 11·45% H.

b) *From 4α,5cyclo-A-homo-B-nor-5α-cholestan-3α-ol* (XII): The alcohol *XII* (100 mg) in acetone (5 ml) was oxidised with Jones' reagent as described in the previous experiment. Similar working up and crystallisation from methanol afforded 72 mg of the ketone *VII*, m.p. 148–149°C, $[\alpha]_D^{20}$ −16° (*c* 1·06).

c) *From 2α-bromo-4α,5cyclo-A-homo-B-nor-5α-cholestan-3α-ol* (XVI): The bromohydrin *XVI* (250 mg) in methanol (25 ml) was refluxed with a solution of potassium hydroxide (250 mg) in methanol (5 ml) for 1 hour. Methanol was removed under reduced pressure, the residue was treated with water, and the product extracted with ether. The ethereal solution was washed with water, dried, and evaporated. The residue was chromatographed on a silica gel column (10 g) in ligroin–benzene (1 : 1). The corresponding fractions were worked up, and the product was crystallised from methanol to yield 191 mg of the ketone *VII*, m.p. 148–149°C, $[\alpha]_D^{20}$ −20° (*c* 1·28).

4β,5Cyclo-A-homo-B-nor-5β-cholestan-3α-ol (*VIII*)

0·5% Zn–Cu couple was prepared from zinc dust (1·2 g) and cupric acetate monohydrate (20 mg) as described for the preparation of the alcohol *V* under *a*). The couple was then refluxed for 3 hours with iodine (25 mg) and diiodomethane (2 ml) in absolute ether (30 ml). The complex was treated with a solution of the alcohol *III* (510 mg) in absolute ether (10 ml) and refluxed for another 3 hours. Similar working up and evaporation of the solvent afforded the crude product which was chromatographed over silica gel (25 g) in benzene. Fractions with the polar component were combined, the solvent removed, and the residue was crystallised from acetone–water to yield 105 mg of the alcohol *VIII*, m.p. 119–120°C, $[\alpha]_D^{20}$ +15° (*c* 1·04). IR: 3060 (cyclopropane), 3600, 1027 cm^{-1} (hydroxyl). For $C_{27}H_{46}O$ (386·6) calculated: 83·87% C, 11·99% H; found: 83·65% C, 11·72% H.

3α-Acetoxy-4β,5-cyclo-A-homo-B-nor-5β-cholestane (*IX*)

The alcohol *VIII* (20 mg) in pyridine (0·5 ml) was acetylated with acetic anhydride (0·3 ml) for 20 hours at room temperature. The reaction mixture was decomposed with ice, the product taken into ether, and the ethereal solution was worked up. The residue after evaporation of the solvent was crystallised from ether–methanol to yield 18 mg of the acetate *IX*, m.p. 91–92°C, $[\alpha]_D^{20}$ +19° (*c* 1·24). For $C_{29}H_{48}O_2$ (428·7) calculated: 81·25% C, 11·29% H; found: 81·12% C, 11·19% H.

4β,5-Cyclo-A-homo-B-nor-5β-cholestan-3-one (*X*)

The alcohol *VIII* (20 mg) in acetone (3 ml) was treated with excess Jones' reagent. After 10 minutes at room temperature the excess oxidising agent was removed with methanol, the reaction mixture was diluted with water, and the product taken into ether. The extract was washed with water, a sodium hydrogen carbonate solution, and water, dried, and the solvent removed. The residue was crystallised from ether–methanol to yield 11 mg of the ketone *X*, m.p. 112–113°C, $[\alpha]_D^{20}$ −7° (*c* 0·89). IR: 3070 (cyclopropane), 1692 cm^{-1} (carbonyl next to cyclopropane). For $C_{27}H_{44}O$ (384·6) calculated: 84·31% C, 11·53% H; found: 84·30% C, 11·70% H.

2α-Bromo-4α,5-cyclo-A-homo-B-nor-5α-cholestan-3-one (*XI*)

a) *From* 4α,5-*cyclo-A-homo-B-nor*-5α-*cholestan*-3-*one* (VII): A solution of the ketone *VII* (6 g) in tetrahydrofuran (70 ml) was treated with Jacques' reagent (6·2 g) and allowed to stand at room temperature for 20 minutes. The reaction mixture was diluted with ether (700 ml) and washed with 5% sodium hydrogen carbonate, and water, the organic layer was dried, and solvent removed. The residue was chromatographed on a silica gel column (250 g) in ligroin–benzene (3 : 2). The corresponding fractions were combined, the solvent was removed, and the residue (3·6 g) was crystallised from ether–methanol to yield 3·1 g of the bromo ketone *XI*, m.p. 161—162°C, $[\alpha]_D^{20}$ —13° (*c* 1·37). IR: 3065 (cyclopropane), 1710 cm^{-1} (carbonyl). For $C_{27}H_{43}BrO$ (463·5) calculated: 69·95% C, 9·35% H, 17·25% Br; found: 70·14% C, 9·36% H, 17·60% Br.

b) *From* 2α-*bromo*-4α,5-*cyclo-A-homo-B-nor*-5α-*cholestan*-3α-*ol* (XVI): The bromohydrin *XVI* (80 mg) in acetone (3 ml) was treated with excess Jones' reagent. After 10 minutes at room temperature methanol was added, the reaction mixture was diluted with water, and the product isolated with ether. The ethereal solution was washed with a sodium hydrogen carbonate solution, water, dried, and evaporated. The residue was chromatographed on a silica gel column (4 g) in ligroin–ether (1 : 1). The corresponding fractions were worked up, and the product was crystallised from methanol to yield 45 mg of the bromo ketone *XI*, m.p. 160—161°C, $[\alpha]_D^{20}$ —14° (*c* 1·35).

c) *From* 2α-*bromo*-4α,5-*cyclo-A-homo-B-nor*-5α-*cholestan*-3β-*ol* (XIV): The bromohydrin *XIV* (80 mg) was oxidised with Jones' reagent in acetone solution as described in the previous experiment. Similar working up afforded a product which was crystallised from methanol to yield 52 mg of the bromo ketone *XI*, m.p. 160—161°C, $[\alpha]_D^{20}$ —13° (*c* 1·42).

4α,5-Cyclo-A-homo-B-nor-5α-cholestan-3α-ol (*XII*)

a) *From* 4α,5-*cyclo-A-homo-B-nor*-5α-*cholestan*-3-*one* (VII): Fractions from the chromatography after isolation of the alcohol *V* under *b*) containing the lipophilic component were combined, the solvent was distilled off, and the residue was crystallised from ether–methanol to yield 310 mg of the alcohol *XII*, m.p. 47—49°C, $[\alpha]_D^{20}$ +32° (*c* 1·08). For $C_{27}H_{46}O$ (386·6) calculated: 83·37% C, 11·99% H; found: 83·69% C, 11·80% H.

b) *From* 2α-*bromo*-4α,5-*cyclo-A-homo-B-nor*-5α-*cholestan*-3α-*ol* (XVI): A solution of the bromohydrin *XVI* (100 mg) in ethanol (25 ml) was agitated in a hydrogen atmosphere over 5% $Pd/CaCO_3$ catalyst (350 mg) for 8 hours. Catalyst was filtered off, washed with ether, the filtrate was washed with 5% hydrochloric acid, a sodium hydrogen carbonate solution, water, dried, and the solvent removed. The residue was chromatographed over silica gel (10 g) in ligroin–benzene (3 : 2). The corresponding fractions were worked up, and the residue was crystallised from ether–methanol to yield 44 mg of the alcohol *XII*, m.p. 46—48°C, $[\alpha]_D^{20}$ +30° (*c* 1·02).

3α-Acetoxy-4α,5-cyclo-A-homo-B-nor-5α-cholestane (*XIII*)

A solution of the alcohol *XII* (200 mg) in pyridine (1·2 ml) was treated with acetic anhydride (0·8 ml) and allowed to stand at room temperature for 20 hours. The reaction mixture was decomposed with ice, the product taken into ether, and the ethereal solution was worked up. The residue was crystallised from ether–methanol to yield 160 mg of the acetate *XIII*, m.p. 122—123°C, $[\alpha]_D^{20}$ +30° (*c* 1·25). For $C_{29}H_{48}O_2$ (428·7) calculated: 81·25% C, 11·29% H; found: 81·43% C, 11·04% H.

2α-Bromo-4α,5-cyclo-A-homo-B-nor-5α-cholestan-3β-ol (*XIV*)

A solution of the bromo ketone *XI* (880 mg) in tetrahydrofuran (10 ml) was treated with lithium-tri-tert-butoxyaluminium hydride (1·9 g). After 1 hour at room temperature the reaction mixture was poured into 5% acetic acid, the product was taken into ether, and the ethereal solution was worked up. The residue after evaporation of the solvent contained according to TLC two compounds in about equal quantities. It was chromatographed on a silica gel column (50 g) in benzene. Fractions with the polar product were combined, the solvent was removed, and the residue was crystallised from methanol to yield 335 mg of the bromohydrin *XIV*, m.p. 144–145°C, $[\alpha]_D^{20}$ −5° (*c* 1·24). IR: 3060 (cyclopropane), 3570, 1040 cm^{-1} (hydroxyl). For $C_{27}H_{45}BrO$ (465·6) calculated: 69·65% C, 9·74% H, 17·17% Br; found: 69·90% C, 9·77 H, 17·41% Br.

3β-Acetoxy-2α-bromo-4α,5-cyclo-A-homo-B-nor-5α-cholestane (*XV*)

The bromohydrin *XIV* (80 mg) was acetylated with acetic anhydride (0·3 ml) in pyridine (0·5 ml) for 18 hours at room temperature. Usual working up and evaporation of the solvent left a product which on crystallisation from ethanol gave 46 mg of the acetate *XV*, m.p. 88–90°C, $[\alpha]_D^{20}$ −65° (*c* 1·28). For $C_{29}H_{47}BrO_2$ (507·6) calculated: 68·62% C, 9·33% H, 15·75% Br; found: 68·81% C, 9·60% H, 15·98% Br.

2α-Bromo-4α,5-cyclo-A-homo-B-nor-5α-cholestan-3α-ol (*XVI*)

Fractions with the lipophilic component from the chromatography after isolation of the bromohydrin *XIV* were worked up, and the residue after evaporation of the solvent was crystallised from methanol to yield 254 mg of the bromohydrin *XVI*, m.p. 109–110°C, $[\alpha]_D^{20}$ +18° (*c* 1·33). IR: 3055 (cyclopropane), 3570, 1028 cm^{-1} (hydroxyl). For $C_{27}H_{45}BrO$ (465·6) calculated: 69·65% C, 9·74% H, 17·17% Br; found: 70·00% C, 9·89% H, 17·57% Br.

3α-Acetoxy-2α-bromo-4α,5-cyclo-A-homo-B-nor-5α-cholestane (*XVII*)

The alcohol *XVI* (80 mg) was acetylated with acetic anhydride (0·3 ml) in pyridine (0·5 ml) for 18 hours at room temperature. Usual working up and crystallisation from ethanol yielded 52 mg of the acetate *XVII*, m.p. 104–106°C, $[\alpha]_D^{20}$ +54° (*c* 1·76). For $C_{29}H_{47}BrO_2$ (507·6) calculated: 68·62% C, 9·33% H, 15·75% Br; found: 67·95% C, 9·20% H, 15·42% Br.

2β,3β-Epoxy-4α,5-cyclo-A-homo-B-nor-5α-cholestane (*XVIII*)

A solution of the bromohydrin *XIV* (1·3 g) in methanol (80 ml) was refluxed with a solution of potassium hydroxide (1·3 g) in methanol (25 ml) for 1 hour. The product was precipitated with water and collected by succion. The crystalls were dissolved in ether, the ethereal solution was washed with water, dried, and ether was distilled off. The residue was crystallised from ether–methanol to yield 1 g of the epoxide *XVIII*, m.p. 102–103°C, $[\alpha]_D^{20}$ +25° (*c* 1·39). IR: 3085 (cyclopropane), 890 cm^{-1} (epoxide). For $C_{27}H_{44}O$ (384·6) calculated: 84·31% C, 11·53% H; found: 84·37% C, 11·48% H.

5-Methyl-B-nor-5β-cholestan-3β-ol (*XIX*)

Fractions from the chromatography of the isolation of the alcohol *V* under *c*) containing the alcohol *XIX* were combined, the solvent was removed, and the residue was crystallised from

methanol to yield 70 mg of the alcohol *XIX*, m.p. 79–80°C, $[\alpha]_D^{20}$ +21° (*c* 1·32). Mass spectrum: M^+ 388· IR: 3630, 1030 cm^{-1} (hydroxyl). For $C_{27}H_{48}O$ (388·7) calculated: 83·43% C, 12·45% H; found: 12·65% C, 83·79% H.

3β-Acetoxy-5-methyl-B-nor-5β-cholestane (*XX*)

The alcohol *XIX* (80 mg) was acetylated with acetic anhydride (0·5 ml) in pyridine (2 ml) for 20 hours at room temperature. Usual working up afforded a product which was chromatographed on a silica gel column (4 g) in ligroin–benzene (1 : 1). Working up of the corresponding fractions and crystallisation from ethanol gave 25 mg of the acetate *XX*, m.p. 63–64°C, $[\alpha]_D^{20}$ +18° (*c* 1·42). For $C_{29}H_{50}O_2$ (430·7) calculated: 80·87% C, 11·70% H; found: 80·73% C, 11·59% H.

5-Methyl-B-nor-5β-cholestan-3-one (*XXI*)

a) *From* 2α-*bromo*-4α,5*cyclo*-*A*-*homo*-*B*-*nor*-5α-*cholestan*-3β-*ol* (XIV): Fractions from the chromatography after isolation of the alcohol *V* under *c*) containing the lipophilic component were worked up, and the residue was crystallised from ether–methanol to yield 17 mg of the ketone *XXI*, m.p. 84–86°C, $[\alpha]_D^{20}$ 0° (*c* 0·98). IR: 1719, 1410 cm^{-1} (carbonyl). For $C_{27}H_{46}O$ (386·6) calculated: 83·87% C, 11·99% H; found: 83·94% C, 12·17% H.

b) *From* 5-*methyl*-*B*-*nor*-5β-*cholestan*-3β-*ol* (XIX): The alcohol *XIX* (40 mg) in acetone (2 ml) was oxidised with excess Jones' reagent and allowed to stand at room temperature 10 minutes. The excess reagent was removed with methanol, the reaction mixture was diluted with water, and the product extracted into ether. The ethereal solution was washed with water, a sodium hydrogen carbonate solution, water, dried, and evaporated. The residue was crystallised from ether–methanol to yield 28 mg of the ketone *XXI*, m.p. 84–86°C, $[\alpha]_D^{20}$ +1° (*c* 1·42).

The analyses were carried out in the Analytical Laboratory of this Institute by Mr V. Štěrba, Mrs V. Rusová and Mrs E. Sykorová 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. Buděšinsky. The mass spectra were recorded and interpreted by Dr L. Dolejš.

REFERENCES

1. Tanabe K., Hayashi R., Takasaki R.: Chem. Pharm. Bull. (Tokyo) *9*, 12 (1961).
2. Fajkoš J., Joska J., Šorm F.: This Journal *30*, 2615 (1965).
3. Winstein S., Sonnenberg J.: J. Am. Chem. Soc. *83*, 3235 (1961).
4. Ginsig R., Cross A. D.: J. Am. Chem. Soc. *87*, 4629 (1965).
5. Tori K., Kitahonoki K.: J. Am. Chem. Soc. 87, 386 (1965).
6. Pierre J. L., Arnaud P.: Bull. Soc. Chim. France *1966*, 1690.
7. Clarke S. C., Frayne K. J., Johnson B. L.: Tetrahedron *25*, 1265 (1969).
8. Kohout L., Fajkoš J.: This Journal *37*, 3490 (1972).
9. Jacquesy J. C., Jacquesy R., Levisalles J., Pete J. P., Ruder H.: Bull. Soc. Chim. France *1964*, 2224.

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