SYNTHESIS OF 3β,4β-CYCLOPROPANO-19-NOR-A-HOMOSTEROIDS*

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Acetolysis of the tosylate *XIII*, afforded the olefin *XIV* as the sole product. Epoxidation of the double bond gave the epoxide *XV* which on metal hydride reduction yielded the alcohol *XVI*. The structures of these products were established by spectral and chemical means and conformation of the A-homo ring in the epoxide *XV* is discussed on the basis of the ^{1}H NMR spectra.

In the course of our studies on steroids with a modified steroid skeleton we became interested in homosteroids carrying a cyclopropane ring in the 7-membered ring A and a hydroxyl function in position 1, 2, or 10 with a well defined conformation of the A ring. Our intention is to study rearrangements of this system. The olefin *XIV* represented a convenient starting material for this purpose. In one of our previous papers[1] we have shown that solvolysis of a 19-tosyloxy-5,6-cyclopropano derivative yields, next to a product of participation of the cyclopropane ring, the bicyclo[4,4,1]undecane system. However, it was shown by Dauben[2], that solvolysis of 19-tosyloxy-5α-steroids leads exclusively to bicyclo[5,4,0]undecane derivatives and thus offers a convenient route to A-homo-19-norsteroids. We should therefore expect that solvolysis of a 19-tosyloxy 2,3-cyclopropano derivative as represented by structure *XIII* would yield the desired olefin *XIV*. Using this approach we describe in this paper syntheses of some 3β,4β-cyclopropano-A-homocholestane derivatives and discuss the conformation of this system on the basis of the ^{1}H NMR spectra.

The starting alcohol[3] *I* was transformed to the benzoate *II* which on partial hydrolysis afforded the monobenzoate *III*. Its tosylate *IV* gave on reaction with *sym*-collidine the olefin *IX* which was hydrolysed to the alcohol *VIII*. This alcohol was also obtained from the diacetate[4] *V* by similar reaction sequence. However, the benzoates gave higher overall yields of the alcohol *VIII*. Subsequent Simmons–Smith methylenation afforded the desired cyclopropano derivative *XI* as the sole product. The structure of this compound and, expecially the β-configuration of the cyclopropane ring, follows from spectral evidence and is in agreement with the well known observations that the steric course of the Simmons–Smith methylenation is directed by the configuration of the hydroxyl group situated sufficiently close

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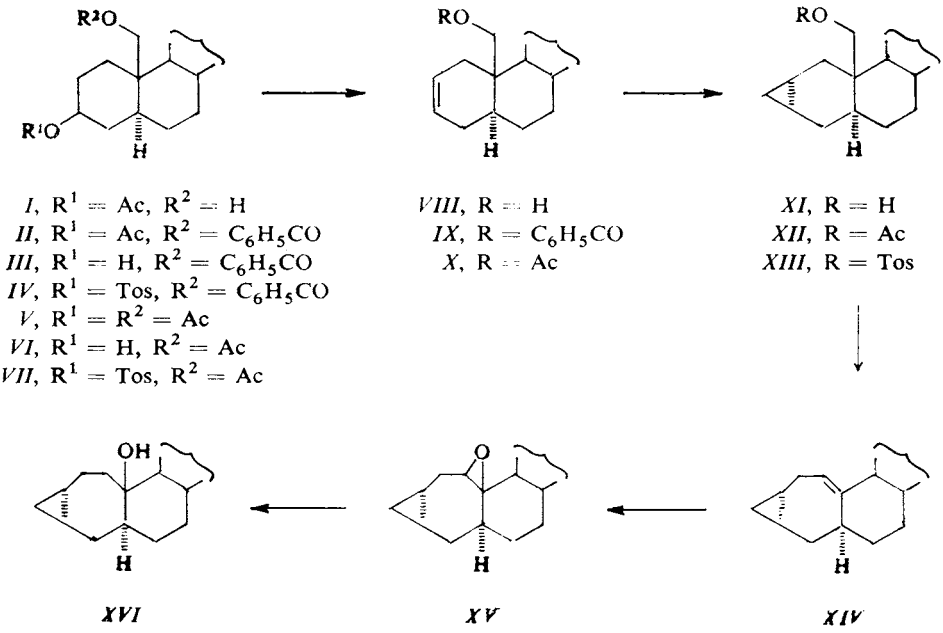
to the reacting center[5]. Acetolysis of the tosylate *XIII*, which was prepared in the usual manner, was carried out in refluxing acetic acid in the presence of acetic anhydride and sodium acetate. The reaction proceeded smoothly and yielded one lipophilic product. Spectral evidence as well as subsequent chemical reactions proved that this product is the expected olefin *XIV*. When treated with peracid in ethereal solution one single epoxide was isolated. Configuration of the oxirane ring and the preferred conformation of the A-homo ring may be deduced from its ^{1}H NMR spectrum.



I, R^1 = Ac, R^2 = H
II, R^1 = Ac, R^2 = C_6H_5CO
III, R^1 = H, R^2 = C_6H_5CO
IV, R^1 = Tos, R^2 = C_6H_5CO
V, R^1 = R^2 = Ac
VI, R^1 = H, R^2 = Ac
VII, R^1 = Tos, R^2 = Ac

VIII, R = H
IX, R = C_6H_5CO
X, R = Ac

XI, R = H
XII, R = Ac
XIII, R = Tos

XVI *XV* *XIV*

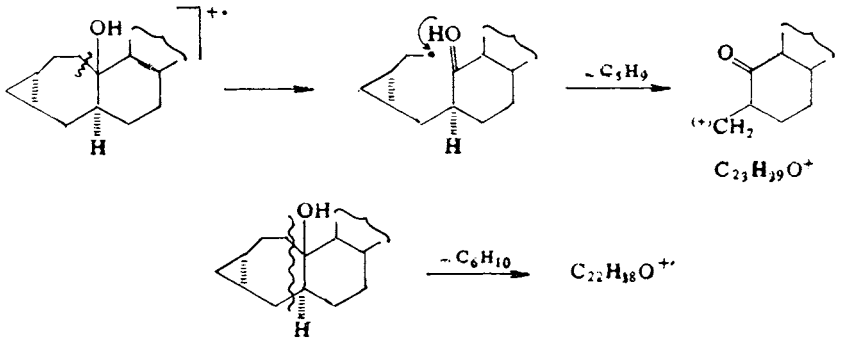
The vicinal coupling constants of the protons at $C_{(1)}$, $C_{(2)}$, and $C_{(3)}$ obtained by the first order analysis are presented in Table I and their values were used for calcula-

TABLE I
Coupling constants for the β-epoxide *XV* and its α-epimer

Compound	$J_{1,2\alpha}$	$J_{1,2\beta}$	$J_{2\alpha,3\alpha}$	$J_{2\beta,3\alpha}$
β-epoxide	7·9 Hz	4·3 Hz	5·7 Hz	11·6 Hz
α-epoxide	4·3 Hz	7·9 Hz	11·6 Hz	5·7 Hz

tions of the dihedral angles $\phi_{1,2}$ and $\phi_{2,3}$ using the Slessor–Tracey method[6]. The method is based on the assumption that the ratio of the coefficients $k_1 : k_2$ in the classical Karplus equation[7] is constant and equal to 0·9 and, further, that $\phi_1 + \phi_2 = \omega$ or $\phi_2 - \phi_1 = \omega$, where ω is the planar projection of the H—C—H angle (value of 120° was used in our case). The calculations were carried out for the 2α and 2β configuration of the oxirane ring and for the all possible assignments of the values of the coupling constants which were in agreement with the multiplicity of the signals of the corresponding protons. Further, we have considered all the possible combinations of the dihedral angle values: four of them with one of the angle larger and others smaller than 90°, next four with two angles larger and two smaller than 90°, and finally one case with all four angles smaller than 90°. From our calculations and from considerations of the Dreiding models follows the β configuration of the oxirane ring and the following approximative values of the dihedral angles: $\phi_{1\alpha,2\alpha} = 14°$, $\phi_{1\alpha,2\beta} = 134°$, $\phi_{2\alpha,3\alpha} = 44°$, and $\phi_{2\beta,3\alpha} = 164°$. The conformation of the A-homo ring corresponding to these findings is shown in Fig. 1.

Metal hydride reduction of the epoxide *XV* yielded an alcohol with a tertiary hydroxyl group resistant to oxidation and esterification; dehydration with thionyl



SCHEME 1

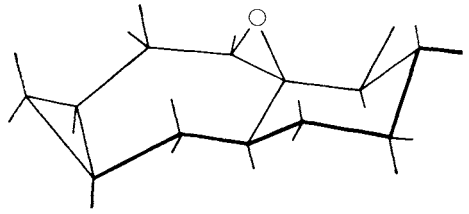


FIG. 1

Conformation of the ring A in the epoxide *XV*

chloride in pyridine gave the olefin *XIV*. We may therefore assign structure *XVI* to this alcohol. The mass spectrum of this alcohol exhibited the expected pattern and Scheme 1 shows the cleavage of the 3β,4β-cyclopropane A-homo ring, this being in agreement with the proposed structure.

EXPERIMENTAL

Melting points were determined on a Kofler block. Optical rotations were carried out in chloroform with an error of ±3°. The infrared spectra were recorded on the Zeiss UR 20 spectrometer in tetrachloromethan.. Mass spectra were recorded on a JEOL JMS D-100 spectrometer. The ^{1}H NMR spectra were recorded at 200 MHz on a Varian XL-200 instrument in deuteriochloroform. Tetramethylsilane was used as internal standard. The chemical shifts are given on δ-scale. The identity of samples was checked by mixture melting point determination, by thin-layer chromatography and by spectral evidence. Usual working up of a solution implies washing the solution with 5% aqueous hydrochloric acid, water, 5% aqueous sodium hydrogen carbonate, water, drying over magnesium sulphate, and evaporation of the solvent under reduced pressure. Ligroin refers to the fraction of b.p. 40–60°C.

5α-Cholestane-3β,19-diol 3-Acetate 19-Benzoate (*II*)

A solution of the alcohol[3] *I* (5 g) in pyridine (50 ml) was treated with benzoyl chloride (7 ml) and set aside for 20 h. The mixture was decomposed with ice and water and the product was isolated with ether. Working up and crystallisation from methanol afforded 6·12 g of the diester *II*, m.p. 127–128°C, $[\alpha]_D^{20}$ +27° (*c* 1·3). For $C_{36}H_{54}O_4$ (550·8) calculated: 78·50% C, 9·88% H; found: 78·43% C, 9·92% H.

5α-Cholestane-3β,19-diol 19-Benzoate (*III*)

The acetate *II* (5 g) was dissolved in chloroform (30 ml) and the solution was treated with 3% methanolic hydrogen chloride (100 ml). The mixture was allowed to stand at room temperature for 48 h. The solution was diluted with chloroform (50 ml) and washed with 5% sodium hydrogen carbonate solution. Working up of the organic layer and crystallisation from methanol yielded 3·8 g of the alcohol *III*, m.p. 152–153°C, $[\alpha]_D^{20}$ +36° (*c* 1·5). For $C_{34}H_{52}O_3$ (508·8) calculated: 80·26% C, 10·30% H; found: 80·14% C, 10·19% H.

5α-Cholestane-3β,19-diol 3-*p*-Toluenesulphonate 19-Benzoate (*IV*)

A solution of the alcohol *III* (6 g) in pyridine (60 ml) was treated with *p*-toluenesulphonyl chloride (7 g) and allowed to stand at room temperature for 24 h. The mixture was decomposed with ice and water and the product was isolated with ether. Usual working up and crystallisation from chloroform–methanol gave 5·8 g of the tosylate *IV*, m.p. 157–159°C, $[\alpha]_D^{20}$ +18° (*c* 1·2). For $C_{41}H_{58}O_5S$ (662·9) calculated: 74·28% C, 8·82% H, 4·84% S; found: 74·15% C, 8·63% H, 4·70% S.

5α-Cholestane-3β,19-diol 19-Acetate (*VI*)

The diacetate *V* (2·6 g) in tetrahydrofuran (20 ml) was treated with a solution of potassium hydroxide (180 mg) in methanol (20 ml) and allowed to stand at 20°C for 2·5 h. The excess alkali was removed with acetic acid, the mixture was diluted with water and the organic solvents

were removed under reduced pressure. The precipitate was taken into ether, the ethereal solution was washed with sodium hydrogen carbonate and worked up. Crystallisation from acetone–water yielded 1·75 g of the monoacetate[3] *VI*, m.p. 114–115°C, $[\alpha]_D^{20}$ +16° (*c* 1·6). For $C_{29}H_{50}O_3$ (446·7) calculated: 77·97% C, 11·28% H; found: 77·83% C, 11·12% H.

5α-Cholestan-3β,19-diol 3-*p*-Toluenesulphonate 19-Acetate (*VII*)

The alcohol *VI* (1·48 g) was esterified with *p*-toluenesulphonyl chloride (1·5 g) in pyridine (15 ml) as described for the tosylate *IV*. Similar working up and crystallisation from ligroin gave 1·6 g of the tosylate *VII*, m.p. 135–137°C, $[\alpha]_D^{20}$ +2° (*c* 1·5). For $C_{36}H_{56}O_5S$ (600·9) calculated: 71·95% C, 9·39% H, 5·33% S; found: 71·79% C, 9·21% H, 5·02% S.

5α-Cholest-2-en-19-ol (*VIII*)

The benzoate *IX* (2·6 g) in tetrahydrofuran (30 ml) was treated with lithium aluminium hydride (500 mg) and the mixture was stirred at room temperature for 15 min. The excess hydride was decomposed with ethyl acetate, and the product was isolated with ether. Usual working up and evaporation of the solvents yielded a crude product (2·4 g) which was purified by column chromatography over silica gel (300 g) in ligroin–ether (10 : 1) to afford, after crystallisation from methanol, 2·1 g of the alcohol *VIII*, m.p. 78–79°C, $[\alpha]_D^{20}$ +57° (*c* 1·8), in accordance with the literature[8]. The acetate *X* (750 mg) afforded under analogous conditions 580 mg of the alcohol *VIII*, m.p. 82–85°C, $[\alpha]_D^{20}$ +64° (*c* 1·6).

5α-Cholest-2-en-19-ol 19-Benzoate (*IX*)

A solution of the tosylate *IV* (4 g) in *sym*-collidine (120 ml) was refluxed for 6 h. Collidine was removed *in vacuo*, the residue was dissolved in ether and water, and the ethereal solution was worked up as usual. The crude product, after evaporation of the solvent was chromatographed on a silica gel column (300 g) in ligroin–ether (20 : 1) to yield after working up of the corresponding fractions 2·6 g of the oily olefin *IX*, $[\alpha]_D^{20}$ +41° (*c* 1·8). For $C_{34}H_{50}O_2$ (490·7) calculated: 83·20% C, 10·27% H; found: 83·01% C, 10·15% H.

5α-Cholest-2-en-19-ol 19-Acetate (*X*)

The tosylate *VII* (7·7 g) when treated under analogous conditions with *sym*-collidine (200 ml) afforded after working up and chromatography 5·4 g of the oily olefin *X*, $[\alpha]_D^{20}$ +38° (*c* 1·3). For $C_{29}H_{48}O_2$ (428·7) calculated: 81·25% C, 11·29% H; found: 81·09% C, 11·11% H.

2β,3β-Cyclopropano-5α-cholestan-19-ol (*XI*)

The Zn–Cu couple (0·5%) was prepared by adding zinc dust (12 g) into a solution of cupric acetate monohydrate (200 mg) in acetic acid (60 ml) at 50–60°C and shaking until the solution decolorised. The solvent was poured off, the metal was washed first with acetic acid (100 ml) and then decanted with eight portions of absolute ether (100 ml each). The metal was covered with ether (100 ml), iodine (30 mg), and diiodomethane (12 ml) were added and the mixture was refluxed in a nitrogen atmosphere under stirring for 3 h. After cooling off to the room temperature a solution of the alcohol *VIII* (3·7 g) in absolute ether (50 ml) was added and the mixture was stirred under nitrogen at room temperature for 3 h. It was then diluted with ether, poured into 5% sodium hydrogen carbonate solution, the ethereal layer was washed with 5% sodium thio-

sulphate, water, dried, and the solvents were removed under reduced pressure. The residue was chromatographed on a silica gel column (400 g) in ligroin–ether (50 : 1). The corresponding fractions were worked up and the product was crystallised from methanol to yield 2·7 g of the cyclopropano derivative *XI*, m.p. 124–126°C, $[\alpha]_D^{20}$ +42° (*c* 1·3). IR spectrum: 3 075, 3 010 (cyclopropane), 3 635, 1 040, 1 022 cm^{-1} (hydroxyl). Mass spectrum: $M^{+\cdot}$ 400. ^1H NMR spectrum: 0·08 and 0·48 (q and dt, two cyclopropane protons), 0·68 (s, 18-H), 1·24 (dd, J_{gem} = = −14·4 Hz, $J_{1\alpha,2\alpha}$ = 5·8 Hz, 1α-H), 2·48 (bd, $J_{1\beta,2\alpha}$ = 0·6 Hz, 1β-H), 3·42 and 3·71 (two bd, J_{gem} = −12·0 Hz, 19-H. For $C_{28}H_{48}O$ (400·7) calculated: 83·93% C, 12·08% H; found: 83·75% C, 11·95% H.

2β,3β-Cyclopropano-5α-cholestan-19-ol 19-Acetate (*XII*)

The alcohol *XI* (150 mg) was acetylated with acetic anhydride (0·5 ml) in pyridine (2 ml) for 20 h at room temperature. Usual working up yielded 160 mg of a crude product which was purified by column chromatography on silica gel (10 g) in ligroin to afford 105 mg of the oily acetate *XII*, $[\alpha]_D^{20}$ +29° (*c* 1·2). For $C_{30}H_{50}O_2$ (442·7) calculated: 81·39% C, 11·38% H; 81·27% C, 11·25% H.

2β,3β-Cyclopropano-5α-cholestan-19-ol 19-*p*-Toluenesulphonate (*XIII*)

The alcohol *XI* (2·2 g) in pyridine (30 ml) was treated with *p*-toluenesulphonyl chloride (2·5 g) and allowed to stand at 30°C for 3 days. The mixture was decomposed with ice and water and the product was isolated with ether. Usual working up afforded 2·6 g of a product which was chromatographed over silica gel (180 g) in ligroin–benzene (4 : 1). Working up of the corresponding fractions and crystallization from acetone yielded 2·1 g of the tosylate *XIII*, m.p. 126–128°C, $[\alpha]_D^{20}$ +6° (*c* 1·4). IR spectrum: 3 075 (cyclopropane), 1 599, 1 372, 1 190, 1 180 cm^{-1} (tosylate). For $C_{35}H_{54}O_3S$ (554·8) calculated: 75·76% C, 9·81% H, 5·78% S; found: 75·55% C, 9·70% H, 5·59% S.

3β,4β-Cyclopropano-5α-A-homocholest-1(10)-ene (*XIV*)

a) The tosylate *XIII* (2 g) in acetic acid (35 ml) was refluxed with acetic anhydride (3·5 ml) and anhydrous sodium acetate (2·5 g) for 8 h. The mixture was diluted with water and the product was taken into ether. The ethereal solution was washed with 5% sodium hydrogen carbonate, water, dried, and ether was distilled off. The residue, consisting predominantly of a lipophilic component was chromatographed on a silica gel column (60 g) in ligroin to yield after crystallization from acetone 920 mg of the olefin *XIV*, m.p. 111–113°C, $[\alpha]_D^{20}$ −4° (*c* 1·2). IR spectrum: 3 060 (cyclopropane), 1 645, 852 cm^{-1} (double bond). Mass spectrum: $M^{+\cdot}$ 382. ^1H NMR spectrum: 0·02 (mt, one cyclopropane proton), 0·50–0·59 (mt, one cyclopropane proton), 0·65 (s, 18-H), 1·86 (mt, 2β-H), 2·29 ddd, J_{gem} = −15·6 Hz, $J_{2\alpha,1}$ = 8·9 Hz, $J_{2\alpha,cycloprop.}$ = 5·9 Hz, 2α-H), 5·44 (d, $J_{1,2\beta}$ = 4·3 Hz, 1-H). For $C_{28}H_{46}$ (382·6) calculated: 87·88% C, 12·12% H; found: 88·02% C, 12·17% H.

b) The alcohol *XVI* (70 mg) in pyridine (6 ml) was treated at 0°C with thionyl chloride (0·8 ml) and allowed to stand at 0°C for 2 h. The mixture was poured on ice containing 10 ml of conc. hydrochloric acid and the product was isolated with ether. Usual working up afforded a mixture of three olefins in which the 1(10)-isomer predominated. It was separated on one silver coated silica gel plate (200 × 200 mm; ligroin–ether 99 : 1). Working up of the corresponding zone and crystallisation from acetone yielded 30 mg of the olefin *XIV*, m.p. 112–114°C, $[\alpha]_D^{20}$ −5° (*c* 1·3), identical with the compound prepared as under *a*).

3β,4β-Cyclopropano-1β,10β-epoxy-5α-A-homocholestane (*XV*)

The olefin *XIV* (800 mg) in ether (50 ml) was treated with an ethereal solution of perphthalic acid (12 ml; 69 mg/1 ml) and allowed to stand at room temperature for 20 h. The excess peracid was extracted with 5% sodium carbonate solution, the ethereal layer was washed with water, dried, and ether was distilled off to yield 820 mg of aproduct which was chromatographed on a silica gel column (100 g) in ligroin. Fractions with the desired product were combined, solvent was removed and the product was crystallized from acetone to afford 700 mg of the epoxide *XV*, m.p. 109 to 110°C. $[\alpha]_D^{20}$ −11° (*c* 1·6). IR spectrum: 3 620, 1 022 (hydroxyl), 3 065 cm^{-1} (cyclopropane). Mass spectrum: $M^{+\cdot}$ 398. ^1H NMR spectrum: −0·12 (mt, $\sum J$ = 12·8 Hz, cyclopropane proton), 0·53 (mt, $\sum J$ = 19·8 Hz, cyclopropane proton), 0·63 (s, 18-H), 1·16 (ddd, $J_{2\beta,3\alpha}$ = 11·6 Hz, 2β-H), 2·54 (J_{gem} = −15·2 Hz, $J_{2\alpha,3\alpha}$ = 5·7 Hz, 2α-H), 3·27 (dd, $J_{1\alpha,2\beta}$ = 4·3 Hz, $J_{1\alpha,2\alpha}$ = = 7·9 Hz, 1α-H). For $C_{28}H_{46}O$ (398·6) calculated: 84·35% C, 11·63% H; found: 84·10% C, 12·80% H.

3β,4β-Cyclopropano-5α-A-homocholestan-10β-ol (*XVI*)

The epoxide *XV* (200 mg) in tetrahydrofuran (10 ml) was added to a solution of lithium aluminium hydride (200 mg) in tetrahydrofuran (10 ml) and refluxed for 2 h. The excess hydride was decomposed with ethyl acetate, the reaction mixture was diluted with ether, washed with 5% hydrochloric acid and the ethereal solution was worked up in the usual way. The residue after evaporation of the solvent was chromatographed on a silica gel column (30 g) in ligroin–ether (30 : 1) to yield after working up and crystallization from methanol 180 mg of the alcohol *XVI*, m.p. 109–110°C, $[\alpha]_D^{20}$ +22° (*c* 1·5). IR spectrum: 3 620, 1 022 (hydroxyl), 3 065 cm^{-1} (cyclopropane). Mass spectrum: $M^{+\cdot}$ 400, $(M-H_2O)^{+\cdot}$ 382, $(M-C_2H_4)^{+\cdot}$ 372, $(M-C_2H_5)^+$ 371, $(M-C_5H_9)^+$ 331, $(M-C_6H_{10})^{+\cdot}$ 318, $(M-C_5H_9-H_2O)^+$ 313. ^1H NMR spectrum: 0·02 (ddd, $\sum J$ = 13·2 Hz, cyclopropane proton, 0·53–0·66 (mt, cyclopropane proton), 0·66 (s, 18-H). For $C_{28}H_{48}O$ (400·7) calculated: 83·93% C, 12·08% H; found: 83·71% C, 11·89% H.

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