ON STEROIDS. CLIV.* B-HOMOSTEROIDS. IX.** THE EPIMERIC 5,7-CYCLO-B-HOMOANDROSTANE DERIVATIVES

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The synthesis of 5,7-cyclo-B-homoandrostane derivatives by Simmons-Smith methylenation of the steroidal 5,6-double bond is described. By standard reactions a series of analogues of androgens has been prepared.

In one of our previous papers[1] we described the synthesis of the epimeric 5,7-cyclo-B-homocholestanes by Simmons–Smith methylenation of the 5,6-double bond in cholesterol and proved also the stereochemistry of these compounds. In the course of our studies of the relationship between structure and physiological activity of steroids with modified skeleton the 5,7-cyclo-B-homoandrostane derivatives – analogues of androgens – were of potential interest. In this paper we describe the synthesis of a series of such compounds.

Compounds with an oxo group at $C_{(17)}$ were synthetised starting from 3β-acetoxy-5-androsten-17-one (*I*). When submitted to the conditions of Simmons–Smith methylenation this olefin afforded the epimeric cyclo derivatives *VII* and *III*, the former in 3% and the latter in 8% yield. The configurations of the cyclopropane ring were assigned on the basis of the NMR spectra and by analogy with the cholestane series[1]. Here again the signal of the 19-protons in the 5β,7β-adduct *VII* is shifted to the lower field (1·13 p.p.m.) when compared with the signal of the 19-protons in the 5α,7α-epimer *III* (0·89 p.p.m.). Alkaline hydrolysis of the acetates *III* and *VII* led to the corresponding alcohols *II* and *VI* which were oxidised by Jones' reagent to the diketones *VIII* and *XI* respectively. The alcohols *II* and *VI* served also as the starting material for the synthesis of the analogues of methyltestosterone and ethinyltestosterone: Reaction with methylmagnesium bromide in ether afforded the diols *IV* and *XII* respectively, which on subsequent oxidation with Jones' reagent gave the desired analogues of testosterone *IX* and *XIV*. On the other hand, addition of acetylene under the presence of potassium tert-butoxide led to the diol *V* and diol

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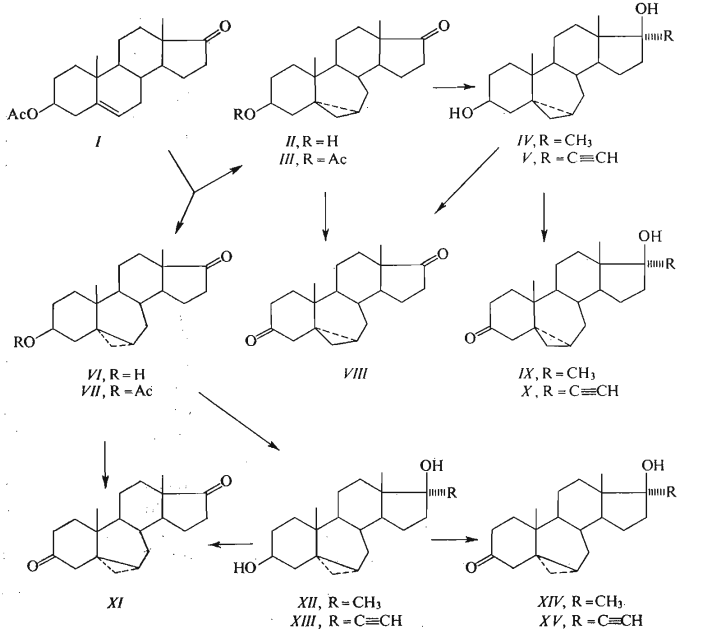
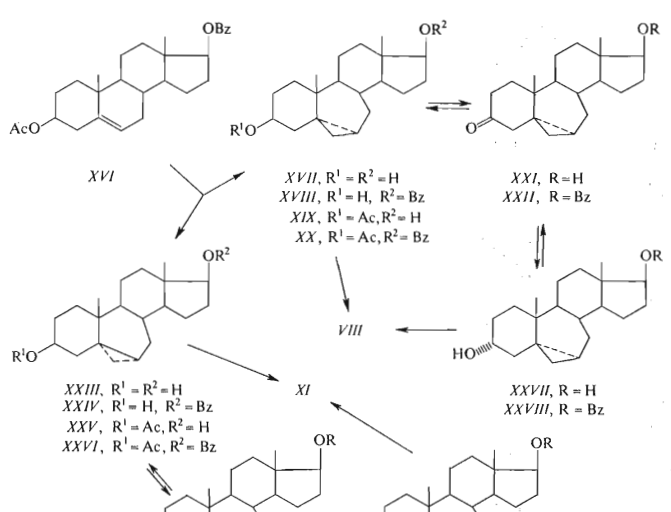
XIII, which on Oppenauer oxidation afforded the desired ketones *X* and *XV* – analogues of the potent gestagen – 17α-ethinyltestosterone.

The analogues with a hydroxyl group at $C_{(17)}$ were prepared from the diester *XVI*. Simmons–Smith methylenation afforded the 5α,7α-cyclo compound *XX* in 16% yield and the epimeric derivative *XXVI* in 4% yield. Partial hydrolysis gave the diol-monobenzoates *XVIII* and *XXIV* which on oxidation with Jones' reagent afforded the ketones *XXII* and *XXX*. Hydrolysis of the 17β-benzoyloxy group led to the keto-alcohols *XXI* and *XXIX* which may be considered as analogues of testosterone. In order to prepare the analogues of the active androstane-3,17-diols, the ketones *XXII* and *XXX* were reduced with lithium tri-tert-butoxyaluminium hydride to yield, after chromatographic separation of the isomers and hydrolysis of the benzoyloxy group, the desired diols *XVII*, *XXVII*, *XXIII* and *XXXI*. All these alcohols afforded on oxidation with Jones' reagent the corresponding diketones *XI* or *VIII* respectively. The physiological properties of the compounds described are under investigation.





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. UV spectra were recorded on the CF 4 spectrometer in ethanol. The mass spectra were recorded on the mass spectrometer AEI MS 902. The NMR spectra were recorded on the Varian HA-100 instrument in deuteriochloroform unless otherwise stated with tetramethylsilane as internal reference. 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% HCl, water, 5% $NaHCO_3$ and water, drying with magnesium sulphate, and evaporation of the solvent.

3β-Hydroxy-5,7α-cyclo-B-homo-5α-androstan-17-one (*II*)

A solution of the acetate *III* (570 mg) and potassium hydroxide (600 mg) in methanol (25 ml) was refluxed for 40 minutes. The solvent was removed under reduced pressure, the product extracted into benzene, the benzene extract was washed with 5% HCl, 5% $NaHCO_3$, water, dried, and evaporated. The oily residue (495 mg) was chromatographed over silica gel (10 g) in ligroin–ether (2 : 1). The corresponding fractions were combined, the solvent was distilled off, and the product

crystallised from ligroin. Yield 350 mg of the alcohol *II*, m.p. 125–127°C, $[\alpha]_D^{20}$ +40·6° (*c* 1·65); IR: 3610, 3060, 1740, 1042 cm^{-1}; CD: $\Delta\varepsilon$ +3·15 (300 nm); NMR: −0·10 to +0·10 (mt, one cyclopropane proton), 0·32 (t, one cyclopropane proton), 0·79 (s, 18-H), 0·88 (s, 19-H), 3·60 to 4·05 (mt, 3α-H). For $C_{20}H_{30}O_2$ (302·4) calculated: 79·42% C, 10·00% H; found: 79·36% C, 10·12% H.

3β-Acetoxy-5,7α-cyclo-B-homo-5α-androstan-17-one (*III*)

a) Elution of the chromatography after isolation of the β-epimer *VII* under *a*) with the same solvent mixture afforded fractions containing the more polar acetate *III*. Combination and evaporation left 1·23 g of the acetate *III* which resisted all attempts at crystallisation; $[\alpha]_D^{20}$ −31·1° (*c* 1·34); IR: 3060, 1738, 1248, 1030 cm^{-1}; NMR: −0·10 to +0·15 (mt, one cyclopropane proton), 0·32 (t, one cyclopropane proton), 0·80 (s, 18-H), 0·89 (s, 19-H), 1·98 (s, acetate), 4·89 (mt, 3α-H). For $C_{22}H_{32}O_3$ (344·5) calculated: 76·70% C, 9·36% H; found: 76·65% C, 9·41% H.

b) The alcohol *II* (40 mg) was acetylated with acetic anhydride (0·6 ml) in pyridine (1 ml) for 18 h at room temperature. The reaction mixture was decomposed with ice, diluted with water, and the product was taken into ether, and worked up. The residue (40 mg) was chromatographed preparatively on one plate of silica gel (20 . 20 cm) in ligroin–ether (2 : 1). The corresponding zone was separated, eluted with ether, and the solvent removed. Yield 32 mg of the oily acetate *III*, $[\alpha]_D^{20}$ +32·5° (*c* 1·26), identical with the sample prepared as under *a*).

c) A solution of the alcohol *XIX* (90 mg) in acetone (5 ml) was treated with excess Jones' reagent and allowed to stand at room temperature for 10 min. The excess reagent was removed with methanol, the reaction mixture was diluted with water, and the product taken into benzene. The benzene extract was washed with 5% $NaHCO_3$, water, dried, and evaporated to leave 90 mg of the oily acetate *III*, $[\alpha]_D^{20}$ +33° (*c* 1·32).

17α-Methyl-5,7α-cyclo-B-homo-5α-androstan-3β,17β-diol (*IV*)

A solution of methylmagnesium bromide prepared from 500 mg of magnesium in ether was added dropwise to a solution of the ketone *II* (500 mg) in ether (100 ml) and refluxed for 1 h. The reaction mixture was decomposed successively with ice, water, and 5% hydrochloric acid, and the product isolated with ether. Working up and evaporation left 500 mg of a product which on crystallisation from methanol gave 295 mg of the diol *IV*, m.p. 184–186°C (subl. at 170°C), $[\alpha]_D^{20}$ −38·2° (*c* 1·20); IR (nujol): 3410, 3065, 1048 cm^{-1}; NMR: −0.07 (q, one cyclopropane proton), 0·31 (t, one cyclopropane proton), 0·79 (s, 18-H), 0·87 (s, 19-H), 1·15 (s, 17α-methyl), 3·76 (mt. 3α-H). For $C_{21}H_{34}O_2$ (318·5) calculated: 79·19% C, 10·76% H; found: 79·49% C, 11·02% H;

17α-Ethinyl-5,7α-cyclo-B-homo-5α-androstan-3β,17β-diol (*V*)

The ketone *II* (800 mg) was dissolved in toluene (30 ml) and acetylene was passed into the solution under stirring. Freshly sublimed potassium tert-butoxide (100 mg) was added and after 10 hours the reaction mixture was decomposed with 30% sulphuric acid (8 ml). The product was extracted with benzene, the organic layer was washed with 5% sodium hydrogen carbonate solution, water, dried, and evaporated. The residue was dissolved in ethyl acetate (80 ml) and treated with lithium tri-tert-butoxyaluminium hydride (800 mg) in order to reduce the unreacted starting material which showed a very close polarity to the ethinyl derivative. After 10 min at room temperature the mixture was decomposed with diluted hydrochloric acid, and the product was isolated with ether. The product after evaporation of the solvent was chromatographed over

silica gel (80 g) in benzene–ether (9 : 1). The corresponding fractions were combined, evaporated, and the residue (610 mg) was crystallised from ether to yield 490 mg of the diol *V*, m.p. 184—185°C $[\alpha]_D^{20}$ −64° (*c* 0·78 in methanol); IR (nujol): 3599, 3300, 3060, 1040, 1019 cm^{-1}; NMR: −0·08 (q, one cyclopropane proton), 0·31 (t, one cyclopropane proton), 0·78 (s, 18-H), 0·88 (s, 19-H), 2·53 (s, acetylenic proton), 3·84 (mt, 3α-H). For $C_{22}H_{32}O_2$ (328·5) calculated: 80·44% C, 9·82% H; found: 80·50% C, 10·06% H.

3β-Hydroxy-5,7β-cyclo-B-homo-5β-androstan-17-one (*VI*)

A solution of the acetate *VII* (105 mg) and potassium hydroxide (200 mg) in methanol (25 ml) was refluxed for 40 min. The solvent was distilled off under reduced pressure, the product taken into ether, the ethereal solution was washed with water, dried, and evaporated. The residue (90 mg) was crystallised from methanol to yield 60 mg of the alcohol *VI*, m.p. 178—179°C, $[\alpha]_D^{20}$ −12·6° (*c* 0·79); IR (nujol): 3600, 3060, 1730, 1060, 1035 cm^{-1}; CD: $\Delta\varepsilon$ +1·47 (301 nm); NMR: 0·10 to 0·45 (mt, two cyclopropane protons), 0·80 (s, 18-H), 1·09 (s, 19-H), 3·73 (mt, 3α-H). For $C_{20}H_{30}O_2$ (302·4) calculated: 79·42% C, 10·00% H; found: 79·65% C, 10·01% H.

3β-Acetoxy-5,7β-cyclo-B-homo-5β-androstan-17-one (*VII*)

a) 0·7% Zn—Cu couple was prepared by adding zinc dust (52 g) into a solution of cupric acetate monohydrate (1·2 g) in acetic acid (50 ml) at 50—60°C and shaking until the solution decolorised. Fresh acetic acid (50 ml) was added and the sedimented zinc was decanted with eight 80 ml portions of ether. The alcohol *I* (15 g) was dissolved in ether, methylene iodide (46 ml) in ether (100 ml) and the couple were added, and the mixture was heated to 100°C in an autoclave for 6 h. After cooling off to room temperature the metal was filtered off, the filtrate was poured into 5% $NaHCO_3$, washed with water, 5% HCl, again with sodium hydrogen carbonate solution, then with 10% sodium thiosulphate solution, water, dried, and evaporated. The residue was chromatographed over silica gel (150 g) in ether–ligroin (1 : 2). Fractions containing the starting olefin and the desired product (identical polarity) were combined and evaporated to yield 9 g of an oily product. The oil was dissolved in ether (500 ml) and treated with a solution of perphthalic acid (9 g) in ether (90 ml) and allowed to stand at room temperature for 18 hours. The excess peracid was extracted into 5% $NaHCO_3$, the ethereal layer was washed with water, dried, and evaporated. The residue (9·5 g) was chromatographed on a silica gel column (200 g) in ether–ligroin (1 : 4). Fractions containing the lipophilic component were combined and evaporated, and the residue (463 mg) was crystallised from ligroin to yield 385 mg of the acetate *VII*, m.p. 217—219°C, $[\alpha]_D^{20}$ −17·1° (*c* 1·27); IR: 3065, 1740, 1248, 1030 cm^{-1}; NMR: 0·20—0·50 (mt, two cyclopropane protons), 0·79 (s, 18-H), 1·11 (s, 19-H), 1·97 (s, 3β-acetate), 4·80 (mt, 3α-H). For $C_{22}H_{32}O_3$ (344·5) calculated: 76·70% C, 9·36% H; found: 76·39% C, 9·30% H.

b) A solution of the alcohol *XXV* (160 mg) in acetone (10 ml) was treated with excess Jones' reagent and allowed to stand at room temperature for 10 min. Methanol was added to remove the excess agent, the mixture was diluted with ether, washed with water, a sodium hydrogen carbonate solution, water, dried, and evaporated. The residue (160 mg) was crystallised from ligroin to yield 135 mg of the ketone *VII*, m.p. 217—219°C, $[\alpha]_D^{20}$ −16·2° (*c* 1·62).

c) The alcohol *VI* (40 mg) in pyridine (1 ml) was acetylated with acetic anhydride (0·6 ml) for 20 h at room temperature. The reaction mixture was decomposed with ice, and the product isolated with ether. Working up and crystallisation from ligroin gave 25 mg of the acetate *VII*, m.p. 216—218°C, $[\alpha]_D^{20}$ −16·7° (*c* 1·19).

5,7α-Cyclo-B-homo-5α-androstan-3,17-dione (*VIII*)

a) The diol *XVII* (1 g) in acetone (150 ml) was treated with excess Jones' reagent and allowed to stand at room temperature for 10 minutes. The excess oxidising agent was destroyed with methanol, ether was added, and the reaction mixture was washed with water, $NaHCO_3$ solution, water, dried, and evaporated. The residue (1·02 g) was crystallised from ethanol–water to yield 740 mg of the dione *VIII*, m.p. 108—109°C, $[\alpha]_D^{20}$ +150°C (*c* 1·32); IR: 3060, 1740, 1723 cm^{-1}; CD: $\Delta\varepsilon$ +5·87 (300 nm), +5·73 (293·5 nm); NMR: 0·10—0·46 (mt, two cyclopropane protons), 0·83 (s, 18-H), 0·97 (s, 19-H), 2·80 (d, J = 15 Hz, 4-H, one proton). For $C_{20}H_{28}O_2$ (300·4) calculated: 79·95% C, 9·39% H; found: 79·99% C, 9·35% H.

b) The alcohol *II* (150 mg) in acetone (20 ml) was oxidised with Jones' reagent as given in the foregoing experiment. Similar working up afforded a residue (150 mg) which was crystallised from ethanol–water to yield 85 mg of the diketone *VIII*, m.p. 106—109°C, $[\alpha]_D^{20}$ +148° (*c* 1·12).

c) The diol *XXVII* (50 mg) was oxidised in acetone (20 ml) with Jones' reagent and worked up as given under *a*). Crystallisation from ethanol–water gave 28 mg of the dione *VIII*, m.p. 108—109°C, $[\alpha]_D^{20}$ +149° (*c* 1·16).

d) The alcohol *XXI* (85 mg) in acetone (30 ml) was oxidised with Jones' reagent as described under *a*). Similar working up and crystallisation from ethanol–water afforded 52 mg of the dione *VIII*, m.p. 107—109°C, $[\alpha]_D^{20}$ +153° (*c* 1·17).

e) The diol *V* (300 mg) in acetone (30 ml) was oxidised with Jones' reagent and the reaction mixture worked up as described previously. The residue (300 mg) was chromatographed on 7 plates (20 . 20 cm) of silica gel in benzene–ether (4 : 1). The corresponding zones were collected, the product eluted with ether, and the eluate was evaporated to yield 196 mg of a residue which on crystallisation from n-heptane afforded 158 mg of the dione *VIII*, m.p. 107—109°C, $[\alpha]_D^{20}$ +156° (*c* 1·00).

17α-Methyl-17β-hydroxy-5,7α-cyclo-B-homo-5α-androstan-3-one (*IX*)

The diol *IV* (400 mg) in acetone (60 ml) was oxidised with Jones' reagent and the reaction mixture was worked up as described in the previous experiments. The residue after evaporation of the solvent (370 mg) was chromatographed over silica gel (30 g) in ligroin–ether (2 : 1). The corresponding fractions were combined and evaporated to yield 265 mg of a product which on crystallisation from ethyl acetate–ether afforded 202 mg of the ketone *IX*, m.p. 165—166°C, $[\alpha]_D^{20}$ +47·4° (*c* 1·27); IR (nujol): 3500, 3065, 1719 cm^{-1}; NMR: 0·15 (q, one cyclopropane proton), 0·36 (t, one cyclopropane proton), 0·80 (s, 18-H), 0·95 (s, 19-H), 1·17 (s, 17α-CH_3), 2·79 (d, 4-H, one proton). For $C_{21}H_{32}O_2$ (316·5) calculated: 76·69% C, 10·19% H; found: 76·75% C, 10·10% H.

17α-Ethinyl-17β-hydroxy-5,7α-cyclo-B-homo-5α-androstan-3-one (*X*)

A solution of the alcohol *V* (750 mg) in toluene (60 ml) was treated with cyclohexanone (11 ml) and 10 ml of the solution were distilled off. The residue was treated with a solution of aluminium isopropoxide (600 mg) in toluene (3 ml) and 15 ml of the distillate were collected by slow distillation. The cooled reaction mixture was poured into dilute hydrochloric acid, ether was added, and the ethereal solution was worked up. The residue after evaporation of the solvent was submitted to steam distillation until the volatile components were removed. The residue was extracted with benzene, the extract was dried, and the solvent distilled off. The residue was chromatographed on a silica gel column (70 g) ligroin–ether (7 : 1). Combination and evaporation of the corresponding fractions left 530 mg of a product which on crystallisation from ethyl acetate–ligroin yielded 350 mg of the ketone *X*, m.p. 188—189°C, $[\alpha]_D^{20}$ +34·7° (*c* 1·24); IR (nujol): 3340, 2280,

3270, 3240, 3060, 1703, 1056 cm^{-1}; NMR: 0·14 (q, one cyclopropane proton), 0·35 (t, one cyclopropane proton), 0·81 (s, 18-H), 0·96 (s, 19-H), 1·88 (s, 17β-OH), 2·54 (s, acetylenic proton), 2·88 (d, one proton, 4-H or 2-H). For $C_{22}H_{30}O_2$ (326·5) calculated: 80·93% C, 9·26% H; found: 80·94% C, 9·39% H.

5,7β-Cyclo-B-homo-5β-androstan-3,17-dione (*XI*)

a) The diol *XXIII* (160 mg) in acetone (15 ml) was oxidised with Jones' reagent as described for the preparation of the epimeric dione *VII*. Similar working up afforded 155 mg of an oil which was chromatographed on four plates of silica gel (20 × 20 cm) in benzene–ether (3 : 1). The corresponding zones were collected, the product eluted with ether, and the solvent was distilled off. The residue (150 mg) was crystallised from ethyl acetate to yield 65 mg of the dione *XI*, m.p. 216–217°C, $[\alpha]_D^{20}$ +36·5° (*c* 1·64); IR: 3060, 1740, 1718 cm^{-1}; CD: $\Delta\varepsilon$ +4·91 (298 nm); NMR: 0·15–0·42 (mt, two cyclopropane protons), 0·82 (s, 18-H), 1·28 (s, 19-H), 3·01 (d, J = = 15 Hz, 4-H, one proton). For $C_{20}H_{28}O_2$ (300·4) calculated: 79·95% C, 9·39% H; found: 80·17% C, 9·48% H.

b) The diol *XXXI* (140 mg) in acetone (30 ml) afforded on oxidation with Jones' reagent as described above and after crystallisation from ethyl acetate 101 mg of the dione *XI*, m.p. 215 to 217°C, $[\alpha]_D^{20}$ +30·9° (*c* 1·16).

c) The alcohol *XXIX* (400 mg) in acetone (400 ml) was oxidised with Jones' reagent as described above. Similar working up and crystallisation from ethyl acetate gave 280 mg of the dione *XI*, m.p. 215–217°C, $[\alpha]_D^{20}$ +31·2° (*c* 1·14).

d) The alcohol *VI* (40 mg) in acetone (10 ml) afforded on oxidation with Jones' reagent as described above and after crystallisation from ethyl acetate 18 mg of the dione *XI*, m.p. 214–216°C, $[\alpha]_D^{20}$ +37·4° (*c* 1·17).

e) The diol *XIII* (200 mg) in acetone (50 ml) was oxidised with Jones' reagent by the standard procedure. The product was isolated with ether to yield after working up and evaporation 200 mg of a product which was chromatographed preparatively on 5 plates of silica gel (20 × 20 cm) in benzene–ether (4 : 1). The corresponding zones were collected, the product eluted with ether, and the solvent was distilled off. The residue (160 mg) was crystallised from methanol to yield 115 mg of the dione *XI*, m.p. 217–218·5°C, $[\alpha]_D^{20}$ +39·4° (*c* 1·06).

17α-Methyl-5,7β-cyclo-B-homo-5β-androstan-3β,17β-diol (*XII*)

A solution of the ketone *VI* (400 mg) in ether (80 ml) was treated dropwise a solution methylmagnesium bromide (prepared from 400 mg of magnesium) in ether (12 ml), and refluxed for 1 h. The reaction mixture was decomposed with water and diluted hydrochloric acid, ether was added, and the ethereal solution was washed with a sodium hydrogen carbonate solution, water, dried, and evaporated. The residue (460 mg) was chromatographed over silica gel (40 g) in ligroin–ether (1 : 1). Fractions containing the diol were combined, evaporated, and the residue (400 mg) was crystallised from ethanol to yield 270 mg of the diol *XII*, m.p. 211–212°C, $[\alpha]_D^{20}$ −72·4° (*c* 1·22); IR (nujol): 3280, 3065, 1158, 1083, 1061, 1045 cm^{-1}; NMR: 0·13 (q, one cyclopropane proton), 0·32 (t, one cyclopropane proton), 0·77 (s, 18-H), 1·08 (s, 19-H), 1·15 (s, 17α-CH_3), 3·68 (mt, 3α-H). For $C_{21}H_{34}O_2$ (318·5) calculated: 79·19% C, 10·76% H; found: 79·55% C, 10·98% H.

17α-Ethinyl-5,7β-cyclo-B-homo-5β-androstan-3β,17β-diol (*XIII*)

The reaction was carried out similarly as given for the 5α-epimer *V*: The ketone *VI* (500 mg) in toluene (25 ml) under the presence of potassium tert-butoxide (300 mg) afforded after similar

working up 470 mg of a product which was dissolved in ethyl acetate (50 ml) and reduced with lithium tri-tert-butoxyaluminium hydride (500 mg). Working up afforded 460 mg of a residue which was chromatographed on a silica gel column (50 g) in benzene–ether (9 : 1). Fractions containing the desired adduct were combined, evaporated, and the residue was crystallised from ethyl acetate to yield 180 mg of the diol *XIII*, m.p. 245—247°C, $[\alpha]_D^{20}$ —113° (*c* 1·19 in methanol). IR (nujol): 3600, 3300, 3060, 1040 cm^{-1}; NMR: 0·00—0·20 (mt, one cyclopropane proton), 0·25—0·35 (mt, one cyclopropane proton), 0·74 (s, 18-H), 1·07 (s, 19-H), 2·55 (s, acetylenic proton), 3·64 (mt, 3α-H). For $C_{22}H_{32}O_2$ (328·5) calculated: 80·44% C, 9·82% H; found: 80·47% C, 9·99% H.

17α-Methyl-17β-hydroxy-5,7β-cyclo-B-homo-5β-androstan-3-one (*XIV*)

The alcohol *XII* (600 mg) in acetone (40 ml) was oxidised with Jones' reagent as described for the 5α-epimer *IV*. Similar working up afforded 600 mg of a product which was chromatographed on 12 plates of silica gel (20 . 20 cm) in ether–chloroform (9 : 1). The corresponding zones were collected, the product eluted with ether, and the residue after evaporation of the solvent was crystallised from chloroform–ether to yield 390 mg of the ketone *XIV*, m.p. 209—211°C, $[\alpha]_D^{20}$ —35·2° (*c* 1·08); IR (nujol): 3460, 3065, 1700, 1150 cm^{-1}; NMR: 0·10—0·45 (mt, two cyclopropane protons), 0·80 (s, 18-H), 1·16 (s, 17α-CH_3), 1·27 (s, 19-H), 2·99 (d, 2-H or 4-H, one proton). For $C_{21}H_{32}O_2$ calculated: 76·69% C, 10·19% H; found: 76·70% C, 10·11% H.

17α-Ethinyl-17β-hydroxy-5,7β-cyclo-B-homo-5β-androstan-3-one (*XV*)

The Oppenauer oxidation was carried out similarly as described for the 5α-epimer *V*: The alcohol *XIII* (600 mg) in toluene (47 ml), and cyclohexanone (9 ml) afforded under the presence of aluminium isopropoxide (450 mg) in toluene (2·5 ml) 600 mg of a crude product which was chromatographed over silica gel (50 g) in ligroin–ether (8 : 1) to yield 550 mg of a purified product. Crystallisation from ethyl acetate gave 440 mg of the ketone *XV*, m.p. 271—273°C, $[\alpha]_D^{20}$ —85° (*c* 0·59); IR (nujol): 3410, 3260, 3060, 1700, 1060 cm^{-1}; NMR: 0·13 (q, one cyclopropane proton), 0·30 (t, one cyclopropane proton), 0·72 (s, 18-H), 1·21 (s, 19-H), 2·45 (s, 17β-OH), 2·56 (s, acetylenic proton), 2·92 (d, 2-H or 4-H, one proton). For $C_{22}H_{30}O_2$ (326·5) calculated: 80·93% C, 9·26% H; found: 81·05% C, 9·26% H.

5,7α-Cyclo-B-homo-5α-androstan-3β,17β-diol (*XVII*)

a) A solution of the benzoate *XVIII* (200 mg) and potassium hydroxide (400 mg) in methanol (50 ml) was refluxed for 2 h. The excess alkali was removed with acetic acid, the organic solvent was removed under reduced pressure, and the product was extracted into benzene. The organic layer was washed with 5% $NaHCO_3$, water, dried, and evaporated. The residue (180 mg) was crystallised from methanol to yield 115 mg of the diol *XVII* m.p. 152—154°C, $[\alpha]_D^{20}$ —26·8° (*c* 1·32); IR (chloroform): 3610, 3065, 1048, 1025 cm^{-1}; NMR: —0·20 to +0·05 (mt, one cyclopropane proton), 0·28 (t, one cyclopropane proton), 0·65 (s, 18-H), 0·84 (s, 19-H), 3·45 (s, 3β-OH and 17β-OH), 3·40—3·70 and 3·70—4·00 (two mt, 3α-H and 17α-H). For $C_{20}H_{32}O_2$ (304·5) calculated: 78·89% C, 10·60% H; found: 78·82% C, 10·63% H.

b) The diester *XX* (1·9 g) was refluxed with a solution of potassium hydroxide (8 g) in methanol (500 ml) for 2 h. The reaction mixture was worked up as described in the foregoing experiment and the residue (1·55 g) after evaporation of the solvent was crystallised from ethyl acetate to yield 1·05 g of the diol *XVII*, m.p. 152—154°C, $[\alpha]_D^{20}$ —29·9° (*c* 1·47).

17β-Benzoyloxy-5,7α-cyclo-B-homo-5α-androstan-3β-ol (*XVIII*)

a) A solution of the diester *XX* (560 mg) in chloroform (3 ml) and methanol (30 ml) was treated with conc. HCl (0·6 ml) and allowed to stand at room temperature for 20 h. The reaction mixture was diluted with water, the product taken into benzene, and the organic layer was washed with 5% $NaHCO_3$, water, dried and evaporated. The residue (500 mg) on crystallisation from methanol afforded 340 mg of the alcohol *XVIII*, m.p. 133–134°C, $[\alpha]_D^{20}$ +15·4° (*c* 1·22); IR: 3610, 3060, 1720, 1278, 1030 cm^{-1}; NMR: −0·20 to +0·10 (mt, one cyclopropane proton), 0·32 (t, one cyclopropane proton), 0·88 (s, 18-H and 19-H), 3·65–4·00 (mt, 3α-H), 4·78 (mt, 17α-H). For $C_{27}H_{36}O_3$ (408·6) calculated: 79·37% C, 8·88% H; found: 79·42% C, 8·90% H.

b) The zones from the preparative thin-layer chromatography after preparation of the 3α-epimer *XXVIII* containing the polar component were collected, eluted with ether, and the solvent was distilled off. The residue was crystallised from methanol to yield 420 mg of the alcohol *XVIII*, m.p. 132–134°C, $[\alpha]_D^{20}$ +16·2° (*c* 1·19).

3β-Acetoxy-5,7α-cyclo-B-homo-5α-androstan-17β-ol (*XIX*)

A solution of the ketone *III* (350 mg) in ethyl acetate (10 ml) was treated with solid lithium tri-tert-butoxyaluminium hydride (700 mg) and allowed to stand at room temperature for 10 min. The excess hydride was decomposed with 2% acetic acid, the product taken into benzene, and the organic layer was washed with water, 5% $NaHCO_3$, water dried, and evaporated. The residual oil (330 mg) was chromatographed on a silica gel column (60 g) in benzene–ether (4 : 1) to yield 305 mg of the alcohol *XIX* which resisted all attempts at crystallisation; $[\alpha]_D^{20}$ −31·0° (*c* 1·87); IR: 3615, 3065, 1732, 1249, 1025 cm^{-1}; NMR: −0·20 to +0·10 (mt, one cyclopropane proton), 0·29 (t, one cyclopropane proton), 0·68 (s, 18-H), 0·88 (s, 19-H), 1·98 (s, 3β-acetate), 3·55 (mt, 17α-H), 4·86 (mt, 3α-H). For $C_{22}H_{34}O_3$ (346·5) calculated: 76·26% C, 9·89% H; found: 75·98% C, 9·99% H.

3β-Acetoxy-17β-benzoyloxy-5,7α-cyclo-B-homo-5α-androstane (*XX*)

a) Elution of the chromatography after isolation of the 5β-epimer *XXVI* with benzene–dichloromethane (1 : 1) afforded fraction with the polar component. Working up afforded 2·4 g of the diester *XX*, $[\alpha]_D^{20}$ +20·5° (*c* 1·86); IR: 3060, 1730, 1720, 1277, 1249, 1030 cm^{-1}; NMR: −0·15 to +0·10 (mt, one cyclopropane proton), 0·31 (t, one cyclopropane proton), 0·87 (s, 18-H and 19-H), 1·97 (s, 3β-acetate), 4·10–5·10 (mt, 3α-H and 17α-H). For $C_{29}H_{38}O_4$ (450·6) calculated: 77·30% C 8·50% H; found: 77·50% C, 8·47% H.

b) The alcohol *XVIII* (100 mg) was acetylated with acetic anhydride (0·6 ml) in pyridine (1 ml) for 16 h at room temperature. The reaction mixture was decomposed with ice, and the product isolated with ether. Working up afforded 102 mg of an oil which was purified by preparative thin-layer chromatography on 2 plates of silica gel (20 . 20 cm) in ligroin–ether (2 : 1). The corresponding zones were collected, eluted with ether, and the solvent distilled off to leave 95 mg of the diester *XX*, $[\alpha]_D^{20}$ +19·8° (*c* 1·14).

17β-Hydroxy-5,7α-cyclo-B-homo-5α-androstan-3-one (*XXI*)

The benzoate *XXII* (440 mg) was refluxed with a solution of potassium hydroxide (1·72 g) in methanol (100 ml) for 2 h. Acetic acid was added to remove the excess alkali, and methanol was distilled off under reduced pressure. The product was taken into benzene, and the organic layer was washed with 5% $NaHCO_3$, water, dried and evaporated. The residue (350 mg) was chromatographed on silica gel (35 g) in benzene–ether (19 : 1) to yield 310 mg of a product

which on crystallisation from ligroin–ethyl acetate afforded 243 mg of the alcohol *XXI*, m.p. 124—126°C (recrystallisation at 110—113°C), $[\alpha]_D^{20}$ +77·0° (*c* 0·88); IR: 3060, 1741, 1721 cm^{-1}; NMR: 0·08—0·30 (mt, one cyclopropane proton), 0·36 (t, one cyclopropane proton), 0·70 (s, 18-H), 0·95 (s, 19-H), 2·80 (d, 2-H or 4-H, one proton), 3·62 (t, 17α-H). For $C_{20}H_{30}O_2$ (302·4) calculated: 79·42% C, 10·00% H; found: 79·70% C, 10·01% H.

17β-Benzoyloxy-5,7α-cyclo-B-homo-5α-androstan-3-one (*XXII*)

a) The alcohol *XVIII* (1·2 g) in acetone (40 ml) was oxidised with Jones' reagent as given for the preparation of the dione *VIII* under *a*). Similar working up afforded 1·2 g of a product which on crystallisation from methanol yielded 920 mg of the ketone *XXII*, m.p. 162—165°C, $[\alpha]_D^{20}$ +105·6° (*c* 0·95); IR: 3060, 1720, 1276 cm^{-1}; NMR: 0·05—0·25 and 0·40—0·45 (two mt, two cyclopropane protons), 0·89 (s, 18-H), 0·96 (s, 19-H), 2·78 (d, J = 16 Hz, 2-H or 4-H, one proton), 4·82 (mt, 17α-H). For $C_{27}H_{43}O$ (406·5) calculated: 79·76% C, 8·43% H; found: 80·01% C, 8·36% H.

b) The alcohol *XXVIII* (200 mg) in acetone (50 ml) afforded on oxidation with Jones' reagent and working up as given for the dione *VIII* under *a*) 153 mg of a product which on crystallisation from methanol afforded 109 mg of the ketone *XXII*, m.p. 162—165°C, $[\alpha]_D^{20}$ +107° (*c* 1·10).

5,7β-Cyclo-B-homo-5β-androstan-3β,17β-diol (*XXIII*)

a) The diester *XXVI* (200 mg) was refluxed with a solution of potassium hydroxide (600 mg) in methanol (50 ml) for 2 h. The reaction mixture was treated with acetic acid to remove the excess alkali, and methanol was distilled off under reduced pressure. The product was taken into ether, the ethereal solution was washed with 5% $NaHCO_3$, water, dried and evaporated. The residue (130 mg) was crystallised from methanol to yield 95 mg of the diol *XXIII*, m.p. 182—183°C $[\alpha]_D^{20}$ −19·8° (*c* 1·27); IR (nujol): 3230, 3055, 1078, 1056 cm^{-1}; NMR: 0·00—0·40 (mt, two cyclopropane protons), 0·66 (18-H), 1·06 (s, 19-H), 3·46 (s, 3β-H and 17β-H), 3·40—3·85 (mt, 3α-H and 17α-H). For $C_{20}H_{32}O_2$ (304·5) calculated: 78·89% C, 10·60% H; found: 79·01% C, 10·61% H.

b) The benzoate *XXIV* (175 mg) was hydrolysed with potassium hydroxide (350 mg) in methanol (50 ml) as given in the foregoing experiment. Similar working up gave 130 mg of a product which was chromatographed preparatively on two plates of silica gel (20 × 20 cm) in benzene–ether (1 : 2). The corresponding zones were collected, product eluted with ether, and the residue after evaporation of the solvent was crystallised from methanol–water to yield 70 mg of the diol *XXIII*, m.p. 181—182°C, $[\alpha]_D^{20}$ −21·6° (*c* 1·43).

17β-Benzoyloxy-5,7β-cyclo-B-homo-5β-androstan-3β-ol (*XXIV*)

a) The diester *XXVI* (240 mg) in chloroform (1·5 ml) and methanol (15 ml) was treated with conc. HCl (0·25 ml) and allowed to stand for 20 h at 30°C. The reaction mixture was treated with benzene and water, the benzene layer was washed with a sodium hydrogen carbonate solution, water, dried and evaporated. The residue (220 mg) was crystallised from methanol to yield 140 mg of the alcohol *XXIV*, m.p. 231·5—233·5°C (recrystallisation at 90—110°C), $[\alpha]_D^{20}$ −21·4° (*c* 1·22); IR (chloroform): 3600, 3065, 1710, 1603, 1585, 1282 cm^{-1}; NMR: 0·00—0·45 (mt, two cyclopropane protons), 0·87 (s, 18-H), 1·10 (s, 19-H), 3·60—3·90 (mt, 3α-H), 4·67—4·95 (mt, 17α-H). For $C_{27}H_{36}O_3$ (408·6) calculated: 79·37% C, 8·88% H; found: 79·60% C, 8·75% H.

b) The zones containing the polar component from the preparative thin-layer chromatography of the 3α-epimer *XXIII* were collected, product eluted with ether, and the solvent was distilled off. The residue (379 mg) was crystallised from methanol to afford 255 mg of the alcohol *XXIV*, m.p. 231–233°C, $[\alpha]_D^{20}$ −21·1° (*c* 1·19).

3β-Acetoxy-5,7β-cyclo-B-homo-5β-androstan-17β-ol (*XXV*)

The ketone *VII* (231 mg) in tetrahydrofuran (25 ml) was treated with solid lithium tri-tert-butoxyaluminium hydride (460 mg) and allowed to stand for 10 minutes at room temperature. The excess hydride was decomposed with 2% acetic acid, water was added, and the product taken into benzene. Working up and crystallisation from methanol–water afforded 165 mg of the alcohol *XXV*, m.p. 150–152°C, $[\alpha]_D^{20}$ −86·1° (*c* 0·88); IR: 3615, 3060, 1730, 1248, 1031 cm^{-1}; NMR: 0·15–0·45 (mt, two cyclopropane protons), 0·68 (s, 18-H), 1·10 (s, 19-H), 1·98 (s, 3β-acetate), 3·59 (mt, 17α-H), 4·83 (3α-H). For $C_{22}H_{34}O_3$ (346·5) calculated: 76·26% C, 9·89% H; found: 76·31% C, 9·71% H.

3β-Acetoxy-17β-benzoyloxy-5,7β-cyclo-B-homo-5β-androstane (*XXVI*)

a) The olefin *XVI* (15 g) was submitted to the conditions of the Simmons–Smith methylenation as described for the preparation of the ketone *VII* under *a*). Similar working up afforded 14 g of a product which was dissolved in ether (500 ml) and treated with a solution of perphthalic acid (28 g) in ether (250 ml). After 20 hours at room temperature the excess peracid was extracted into 5% $NaHCO_3$, the ethereal layer was washed with water, dried and evaporated. The residue (15·5 g) was chromatographed on a silica gel column (200 g) in benzene–dichloromethane (1 : 1). Fractions with the lipophilic component were combined, evaporated, and the product (566 mg) was crystallised from methanol to yield 372 mg of the diester *XXVI*, m.p. 131–133°C, $[\alpha]_D^{20}$ −14·2° (*c* 1·08); IR: 3065, 1730, 1720, 1278, 1248 cm^{-1}; NMR: 0·25–0·50 (mt, two cyclopropane protons), 0·85 (s, 18-H), 1·10 (s, 19-H), 1·97 (s, 3β-acetate), 4·10–5·00 (mt, 3α-H and 17α-H). For $C_{29}H_{38}O_4$ (450·6) calculated: 77·30% C, 8·50% H; found: 77·68% C, 8·32% H.

b) The alcohol *XXIV* (100 mg) in pyridine (1 ml) was acetylated with acetic anhydride (0·6 ml) for 20 h at room temperature. The reaction mixture was decomposed with ice, and the product was isolated with ether. Working up and crystallisation from methanol gave 95 mg of the diester *XXVI*, m.p. 130–132°C, $[\alpha]_D^{20}$ −15·6° (*c* 1·17).

5,7α-Cyclo-B-homo-5α-androstan-3α,17β-diol (*XXVII*)

A solution of the benzoate *XXVIII* (600 mg) and potassium hydroxide (2·4 g) in methanol (60 ml) was refluxed for 2 h. Methanol was distilled off under reduced pressure, the residue was treated with water and benzene, and the benzene layer was washed with 5% HCl, 5% $NaHCO_3$, water, dried, and evaporated. The residue (430 mg) was crystallised from ligroin–ethyl acetate to yield 310 mg of the diol *XXVII*, m.p. 160–161°C, $[\alpha]_D^{20}$ −48·0° (*c* 1·63); IR (chloroform): 3600, 3060, 1725, 1705, 1288, 1250 cm^{-1}; NMR: −0·16 to +0·10 (mt, one cyclopropane proton), 0·18–0·40 (mt, one cyclopropane proton), 0·69 (s, 18-H), 0·83 (s, 19-H), 2·93 (broad s, 3α-OH and 17β-OH), 3·61 (t, 17α-H), 4·05 (mt, 3β-H). For $C_{20}H_{32}O_2$ (304·5) calculated: 78·89% C, 10·60% H; found: 78·95% C, 10·67% H.

17β-Benzoyloxy-5,7α-cyclo-B-homo-5α-androstan-3α-ol (*XXVIII*)

A solution of the ketone *XXII* (2·5 g) in ethyl acetate (250 ml) was treated at room temperature with solid lithium tri-tert-butoxyaluminium hydride (5 g) and allowed to stand at the same

temperature for 10 min. The excess hydride was decomposed with 2% acetic acid, the reaction mixture was treated with water and benzene, and the benzene layer was washed with 5% $NaHCO_3$, water, dried, and evaporated to yield 2·15 g of a product which was chromatographed on 50 plates of silica gel (40×20 cm) in benzene–ether (4 : 1; 3× developed). The zones with the lipophilic component were collected, the product eluted with ether, and the solvent was distilled off to leave 1·49 g of a residue which was crystallised from methanol. Yield 1·18 g of the alcohol *XXVIII*, m.p. 83–87°C, $[\alpha]_D^{20}$ −8·5° (*c* 0·70); IR (chloroform): 3600, 3060, 1708, 1280, 1028 cm^{-1}; NMR: −0·15 to +0·10 (mt, one cyclopropane proton), 0·23 (t, one cyclopropane proton), 4·05 (broad mt, 3β-H), 4·83 (dd, 17α-H). For $C_{27}H_{36}O_3$ (408·6) calculated: 79·37% C, 8·88% H; found: 79·60% C, 8·91% H.

17β-Hydroxy-5,7β-cyclo-B-homo-5β-androstan-3-one (*XXIX*)

A solution of the benzoate *XXX* (120 mg) and potassium hydroxide (480 mg) in methanol (40 ml) was refluxed for 2 h. Methanol was distilled off under reduced pressure, the residue was treated with water and benzene, and the benzene layer was washed with 5% hydrochloric acid, 5% $NaHCO_3$, water, dried, and evaporated. The residue (85 mg) was crystallised from methanol to yield 52 mg of the alcohol *XXIX*, m.p. 183–185°C, $[\alpha]_D^{20}$ −26·8° (*c* 1·42); IR: 3620, 3060, 1710, 1050 cm^{-1}; NMR: 0·10–0·40 (mt, two cyclopropane protons), 0·69 (s, 18-H), 1·26 (s, 19-H), 3·00 (d, J = 16 Hz, 2-H or 4-H, one proton), 3·59 (dd, 17α-H). For $C_{20}H_{30}O_2$ (302·4) calculated: 79·42% C, 10·00% H; found: 79·41% C, 10·28% H.

17β-Benzoyloxy-5,7β-cyclo-B-homo-5β-androstan-3-one (*XXX*)

a) The alcohol *XXIV* (985 mg) in acetone (200 ml) afforded on oxidation with Jones' reagent and after working up as described for the diketone *VIII* under *a*) 960 mg of a product which on crystallisation from methanol gave 615 mg of the ketone *XXX*, m.p. 191–193°C, $[\alpha]_D^{20}$ +20·2° (*c* 1·48); IR: 3060, 1720, 1278 cm^{-1}; NMR: 0·25–0·50 (mt, two cyclopropane protons), 0·89 (s, 18-H), 1·28 (s, 19-H), 3·01 (d, J = 16 Hz, 2-H or 4-H, one proton), 4·81 (mt, 17α-H). For $C_{27}H_{34}O_3$ (406·5) calculated: 79·76% C, 8·43% H; found: 79·45% C, 8·51% H.

b) The alcohol *XXXII* (60 mg) in acetone (20 ml) afforded on oxidation with Jones' reagent and after working up as given for the ketone *VIII* under *a*) 60 mg of a product which on crystallisation from methanol yielded 43 mg of the ketone *XXX*, m.p. 191–192·5°C, $[\alpha]_D^{20}$ +20·3° (*c* 1·12).

5,7β-Cyclo-B-homo-5β-androstan-3α,17β-diol (*XXXI*)

A solution of the benzoate *XXXII* (400 mg) and potassium hydroxide (1·2 g) in methanol (200 ml) was refluxed for 2 hours. Methanol was removed under reduced pressure, the residue was treated with water and benzene, and the organic layer washed with 5% HCl, 5% $NaHCO_3$ water, dried and evaporated. The residue (400 mg) was crystallised from methanol to yield 185 mg of the diol *XXXI*, m.p. 202–203°C (subl. at 180°C), $[\alpha]_D^{20}$ −89·7° (*c* 1·52); IR (chloroform): 3600, 3060 cm^{-1}; NMR: 0·48 (mt, two cyclopropane protons), 0·69 (s, 18-H), 1·05 (s, 19-H), 1·73 (s, 3α-OH and 17β-OH), 3·61 (t, 17α-H), 3·98 (mt, 3β-H). For $C_{20}H_{32}O_2$ (304·5) calculated: 78·89% C, 10·60% H; found: 78·77% C, 10·50% H.

17β-Benzoyloxy-5,7β-cyclo-B-homo-5β-androstan-3α-ol (*XXXII*)

The ketone *XXX* (600 mg) in ethyl acetate (30 ml) was treated with solid lithium tri-tert-butoxyaluminium hydride (1·2 g) and allowed to stand at room temperature for 20 min. The reaction

mixture was decomposed with 1% HCl, water was added, and the product taken into ether. The ethereal solution was worked up and the residue (500 mg) was chromatographed on 10 plates of silica gel (40 . 20 cm) in benzene–ether (3 : 1). The zones with the lipophilic component were collected, the product eluted with ether, and the solvent was distilled off. The residue (186 mg) was crystallised from methanol to yield 135 mg of the alcohol *XXXII*, m.p. 210—211°C, $[\alpha]_D^{20}$ −23·2° (*c* 0·95); IR (chloroform): 3600, 3060, 1710, 1282 cm^{-1}; NMR: 0·51 (mt, two cyclopropane protons), 0·87 (s, 18-H), 1·07 (s, 19-H), 1·62 (s, 3α-OH), 3·98 (mt, 3β-H), 4·82 (mt, 17α-H). For $C_{27}H_{36}O_3$ (408·6) calculated: 79·37% C, 8·88% H; found: 79·29% C, 8·90% H.

The analyses were carried out in the Analytical Laboratories of this Institute by Mr V. Štěrba, Mrs V. Rusová and Mrs E. Sýkorová under the direction of Dr J. Horáček. The IR spectra were recorded by Mrs K. Matoušková and Mr P. Formánek under the direction of Dr J. Smolíková. The NMR spectra were recorded and interpreted by Dr M. Synáčková and Dr M. Buděšínský. Technical assistance was provided by Mrs J. Mašková.

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