SYNTHESIS OF SOME 19-HYDROXYLATED ANDROGEN ANALOGUES WITH THE CYCLOPROPANE RING IN 4,5-POSITION*

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Synthesis of 19-hydroxylated analogues of 17α-methyltestosterone and 17α-methylandrostanediols with the cyclopropane ring in position 4β,5β is described.

In the course of our studies of the relationship between the structural changes in the steroid molecule and biological activity we became interested in 19-hydroxylated analogues of steroid hormones carrying the cyclopropane ring in position 4,5. In this paper we describe synthesis of such analogues of methyltestosterone and of methylandrostanediols with the hydroxyl groups epimeric at $C_{(3)}$.

The ketone *VII* required for subsequent steps was prepared by two unambiguous routes: The first route set out from the bromo derivative[1] *I* which was transformed to the methyl carbinol *II* on reaction with methylmagnesium iodide by standard procedure. Following oxidation and simultaneous dehydrohalogenation gave the unsaturated epoxy-ketone[2] *III* which on cleavage with zinc in acetic acid afforded the 19-hydroxy derivative *VIII*. The second route started with the diol *IV* which on reaction with methylmagnesium iodide gave the methyl carbinol[3] *V*, characterised also as the diacetate *VI*. Mild Oppenauer oxidation afforded the ketone *VII* in good yield. Sodium borohydride reduction of the acetate *VIII* afforded the allylic alcohol *X*, characterised also as the diol *IX* and diacetate *XI*; only traces of the 3α-hydroxy compound were detected by TLC in the reduction mixture.

Simmons–Smith methylenation of the olefin *X* gave the cyclopropano derivative *XIII* in excellent yield. The β-configuration of the cyclopropane ring was assigned by analogy with the cholestane series[4] where the configuration of the allylic hydroxyl determined the stereochemistry of the methylenation, this being always *cis* to the hydroxyl group. Jones' oxidation afforded the ketone *XVI* which was hydrolysed to the diol *XV*, representing the desired analogue of methyltestosterone. Hydride reduction of the oxo-group in the ketone *XVI* yielded the 3α-hydroxy derivative *XVIII* as the main product (about 80%). Hydrolysis of the acetates *XIII* and *XVIII*

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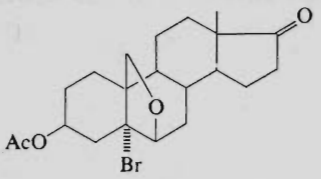

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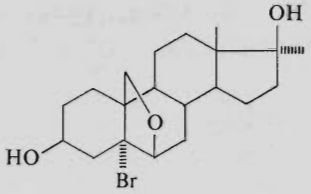

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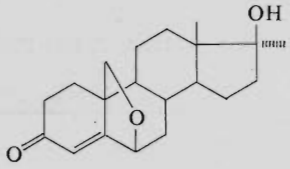

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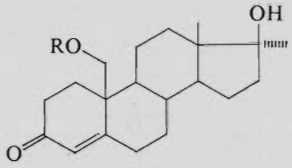

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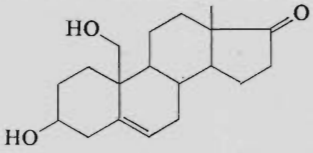
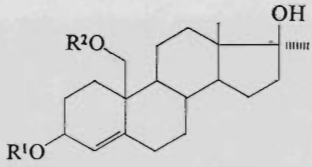
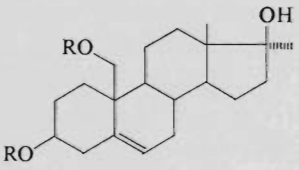
VIII, R = Ac



IV



IX, $R^1 = R^2 = H$
X, $R^1 = H$, $R^2 = Ac$
XI, $R^1 = R^2 = Ac$



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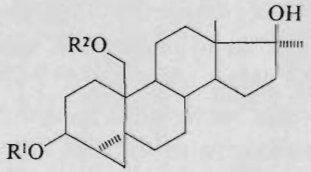
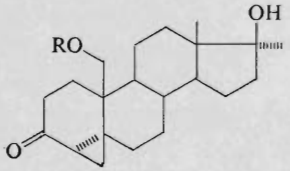
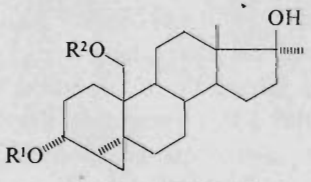
VI, R = Ac



XII, $R^1 = R^2 = H$
XIII, $R^1 = H$, $R^2 = Ac$
XIV, $R^1 = R^2 = Ac$



XV, R = H
XVI, R = Ac



XVII, $R^1 = R^2 = H$
XVIII, $R^1 = H$, $R^2 = Ac$
XIX, $R^1 = R^2 = Ac$

yielded the 19-hydroxylated analogues of methylandrostane diols epimeric at $C_{(3)}$ – *i.e.* compounds *XII* and *XVII*.

EXPERIMENTAL

Melting points were determined on a Kofler block. Optical activity measurements were carried out in chloroform with an error of $\pm 2°$. The infrared spectra were recorded on the Zeiss UR 20 spectrometer in tetrachloromethane. Mass spectra were recorded on the mass spectrometer AEI MS 902. The identity of samples prepared by different routes was checked by mixture melting point determination, by thin-layer chromatography (TLC) and by spectral evidence. Usual working up of a solution implies washing the solution with 5% aqueous hydrochloric acid, water, drying over sodium sulphate, and evaporation of the solvent under reduced pressure. Ligroin refers to the fraction of b.p. 40–60°C.

5-Bromo-17α-methyl-6β,19-oxido-5α-androstan-3β,17β-diol (*II*)

A solution of methylmagnesium iodide was prepared from magnesium (2·4 g) and methyl iodide (6·6 ml) in ether (60 ml) and treated at boiling temperature under stirring with a solution of the acetate *I* (2 g) in ether (150 ml). The mixture was refluxed under stirring for 30 min. Ether was then removed (100 ml) by distillation and replaced simultaneously by the same volume of benzene. The mixture was refluxed for another 4 h and allowed to stand overnight. The excess Grignard reagent was decomposed with a saturated solution of ammonium chloride, the benzene layer was separated, washed with a sodium thiosulphate solution, with sodium hydrogen carbonate, water, dried, and solvents were distilled off. The residue was crystallized from ethyl acetate to yield 1·15 g of the diol *II*, m.p. 204–206°C, $[\alpha]_D^{20}$ −30° (*c* 1·0 in ethanol). For $C_{20}H_{31}BrO_3$ (399·3) calculated: 60·15% C, 7·82% H, 20·01% Br; found: 59·90% C, 7·71% H, 17·70% Br.

17β-Hydroxy-17α-methyl-6β,19-oxidoandrost-4-en-3-one (*III*)

The chromium trioxide–pyridine complex was prepared from chromium trioxide (2·5 g) and pyridine (25 ml) at 0°C. A solution of the diol *II* (1·1 g) in pyridine (5 ml) was added. The mixture was stirred at room temperature for 5 h, left overnight at 20°C, treated with solid sodium hydrogen carbonate (3·5 g) and pyridine was removed by steam distillation. The residue was extracted with ether, the ethereal solution was worked up as usual and the residue after evaporation of the solvent (840 mg) was crystallized from ethyl acetate to yield 620 mg of ketone *III*, m.p. 149 to 151°C $[\alpha]_D^{20}$ −139° (*c* 1·6). For $C_{20}H_{28}O_3$ (316·4) calculated: 75·91% C, 8·92% H; found: 75·72% C, 8·79% H.

17α-Methylandrost-5-en-3β,17β,19-triol (*V*)

To a Grignard reagent prepared from magnesium (36 g) and methyl iodide (99 ml) in ether (700 ml) a solution of the ketone *IV* (15 g) in ether (300 ml) was added dropwise under stirring. The mixture was refluxed for 30 min, ether was distilled off (300 ml) and replaced with benzene (900 ml). The mixture was refluxed under stirring for 7 h and set aside overnight. The excess reagent was removed with a saturated solution of ammonium chloride, and the product was taken into ethyl acetate. The extract was combined with the benzene layer, washed with a sodium thiosulphate solution, a sodium hydrogen carbonate solution, water, dried, and solvents removed. The residue was crystallized from methanol–ethyl acetate to yield 8·5 g of the triol *V*, m.p. 247–248°C, $[\alpha]_D^{20}$ −77° (*c* 1·4 in ethanol). For $C_{20}H_{32}O_3$ (320·5) calculated: 74·95% C, 10·07% H; found: 75·30% C, 10·28% H.

17α-Methylandrost-5-en-3β,17β,19-triol 3,19-Diacetate (*VI*)

The triol *IV* (200 mg) in pyridine (4 ml) was acetylated with acetic anhydride (2 ml) for 20 h at room temperature. The mixture was decomposed with ice, diluted with water, the product was extracted with ether, and the ethereal solution was worked up. The residue was purified by column chromatography over silica gel in benzene–ether (19 : 1). Working up of the corresponding fractions, evaporation of the solvents, and crystallization from methanol gave 130 mg of the diacetate *VI*, m.p. 105—107°C, $[\alpha]_D^{20}$ —105° (*c* 1·2). For $C_{24}H_{36}O_5$ (404·5) calculated: 71·25% C, 8·97% H; found: 71·10% C, 8·87% H.

17β,19-Dihydroxy-17α-methylandrost-4-en-3-one (*VII*)

a) *From* 17α-*methylandrost*-5-*en*-3β,17β,19-*triol* (V): The triol *V* (8·5 g) was dissolved in toluene (400 ml) and cyclohexanone (35 ml) and 80 ml of the solvents were distilled off. The mixture was treated with aluminium isopropylate (2 g) in toluene (30 ml), refluxed for 15 min, cooled of with ice, decomposed with 10% hydrochloric acid and the organic layer was separated and washed with a sodium hydrogen carbonate solution. The solvents were removed by steam distillation and the precipitated product was taken into ethyl acetate. The residue after evaporation of the solvent was chromatographed on a silica gel column (500 g) in ethyl acetate–ether (3 : 7). Fractions with the product were combined, solvents removed, and the residue was crystallized from ethyl acetate to afford 3·04 g of the ketone *VII*, m.p. 196—197°C, [α] +79° (*c* 0·96 in ethanol). IR spectrum: 3 620 (hydroxyl), 1 666, 1 621 cm^{-1} (C=C—C=O). For $C_{20}H_{30}O_3$ (318·4) calculated: 75·43% C, 9·50% H; found: 75·21% C, 9·32% H.

b) *From* 17β-*hydroxy*-17α-*methyl*-6β,19-*oxidoandrost*-4-*en*-3-*one* (III): A solution of the oxide *III* (8·15 g) in acetic acid (500 ml) was treated with zinc dust (30 g) activated by washing twice with 50% acetic acid and five times with glacial acetic acid. The mixture was heated in a water bath 90°C under efficient stirring for 1 h. The zinc dust was filtered off, washed with acetic acid. The acid was distilled off *in vacuo* and the residue was dissolved in ether. The ethereal solution was washed with 5% hydrochloric acid, a sodium hydrogen carbonate solution, water, dried, and ether removed. The residue (7·4 g) was chromatographed on a silica gel column (500 g) in benzene–ethyl acetate (1 : 1). Working up of the corresponding fractions and crystallization from ethyl acetate yielded 3·8 g of the ketone *VII*, m.p. 197—199°C, $[\alpha]_D^{20}$ +84° (*c* 1·0 in ethanol).

19-Acetyloxy-17β-hydroxy-17α-methylandrost-4-en-3-one (*VIII*)

The diol *VII* (1·1 g) in pyridine (4 ml) was acetylated with acetic anhydride (3 ml) at room temperature for 18 h. The mixture was decomposed with ice and water, the product was taken into ether and the ethereal solution was worked up to yield 900 mg of a crude product. Purification over silica gel (65 g) in benzene–ether (1 : 1) and crystallization from ethyl acetate–ether gave 750 mg of the acetate *VIII*, m.p. 122—124°C $[\alpha]_D^{20}$ +126° (*c* 1·2). IR spectrum: 3 625 (hydroxyl), 1 748, 1 233 (acetate), 1 677, 1 625 cm^{-1} (C=C—C=O). For $C_{22}H_{32}O_4$ (360·5) calculated: 73·30% C, 8·95% H; found: 73·04% C, 8·65% H.

17α-Methylandrost-4-en-3β,17β,19-triol (*IX*)

A solution of the acetate *X* (80 mg) in methanol (10 ml) was treated with a solution of potassium hydroxide (40 mg) in methanol (5 ml) and heated in a nitrogen atmosphere to 50°C for 1 h. The excess alkal' was removed with acetic acid, the solvents were distilled off *in vacuo*, and the product was extracted into ethyl acetate. The extract was washed with a sodium hydrogen carbonate

solution, dried, and solvent removed. The residue was crystallized from ethyl acetate to yield 30 mg of the triol *IX*, m.p. 173–175°C, $[\alpha]_D^{20}$ +14° (*c* 1·2 in ethanol). For $C_{20}H_{32}O_3$ (320·5) calculated: 74·95% C, 10·07% H; found: 74·70% C, 9·83% H.

17α-Methylandrost-4-en-3β,17β-19-triol 19-Acetate (*X*)

A solution of the ketone *VIII* (4·1 g) in methanol (120 ml) and ethyl acetate (40 ml) was treated under stirring at room temperature with sodium borohydride (2 g) which was added in the course of 45 min. Stirring was continued for another 2 h, the hydride was then decomposed with acetic acid and the solvents were removed *in vacuo*. The residue was treated with water and the product was taken into ethyl acetate. The solution was washed with a sodium hydrogen carbonate solution, water, dried, and the residue (4 g) was chromatographed over silica gel (200 g) in benzene–ether (1 : 1). Fractions with the desired product were worked up and the product was crystallized from methanol–water to yield 3·8 g of the acetate *X*, m.p. 148–149°C, $[\alpha]_D^{20}$ +85° (*c* 1·4). For $C_{22}H_{34}O_4$ (362·5) calculated: 72·89% C, 9·45% H; found: 72·70% C, 9·20% H.

17α-Methylandrost-4-en-3β,17β,19-triol 3,19-Diacetate (*XI*)

The monoacetate *X* (200 mg) in pyridine (1 ml) was acetylated with acetic anhydride (0·6 ml) for 18 h at room temperature. Usual working up afforded an oily product which was chromatographed on a silica gel column (8 g) in benzene–ether (19 : 1). Working up of the corresponding fractions afforded 60 mg of the diacetate *XI* which resisted all attempts at crystallization, $[\alpha]_D^{20}$ +30° (*c* 1·5). For $C_{24}H_{36}O_5$ (404·5) calculated: 71·25% C, 8·97% H; found: 71·15% C, 8·80% H.

4β,5-Cyclopropano-17α-methyl-5β-androstan-3β,17β,19-triol (*XII*)

The acetate *XIII* (420 mg) in methanol (18 ml) was treated with a solution of potassium hydroxide (200 mg) in methanol (4 ml) and refluxed for 45 min. The excess alkali was removed with acetic acid and the solvents were distilled off *in vacuo*. The residue was diluted with water and the product was taken into ethyl acetate. The extract was washed with a sodium hydrogen carbonate solution, water, dried, and the product after evaporation of the solvent was chromatographed over silica gel (10 g) in ether. Working up of the fraction with the desired product and crystallization from methanol–ligroin gave 135 mg of the triol *XII*, m.p. 112–114°C, $[\alpha]_D^{20}$ −30° (*c* 1·5 in ethanol). For $C_{21}H_{34}O_3$ (338·5) calculated: 75·40% C, 10·25% H; found: 75·20% C, 10·11% H.

4β,5-Cyclopropano-17α-methyl-5β-androstan-3β,17β,19-triol 19-Acetate (*XIII*)

a) *From* 17α-*methylandrost*-4-*en*-3β,17β,19-*triol* 19-*acetate* (X): The Zn–Cu couple (5%) was prepared by adding zinc dust (6·5 g; Baker 60–200 mesh) into a solution of cupric acetate monohydrate (112 mg) in acetic acid (40 ml) at 50–60°C and shaking until the solution decolorized. The solvent was poured off, the metal was washed first with acetic acid (60 ml) and then decanted with eight portions of ether (60 ml each). The metal was covered with ether (70 ml), iodine (30 mg) and diiodomethane (9 ml) and the mixture was refluxed in an argone atmosphere for 3 h under stirring. After cooling off to room temperature a solution of the acetate *X* (2·5 g) in ether (100 ml) was added. The mixture was stirred in the inert atmosphere at room temperature for 2 h, diluted with ether and poured into 5% sodium hydrogen carbonate solution. The ethereal layer was washed with 5% sodium thiosulphate, water, dried, and the solvents were removed under reduced pressure. The residue was chromatographed on a silica gel column (200 g) in benzene–ether (2 : 1). Fractions with the starting material and the adduct (identical R_F) were

combined, solvents distilled off, and the residue (2·38 g) was dissolved in ether and treated with a solution of perphthalic acid (900 mg) in ether (12 ml). After 20 h at room temperature the excess peracid was extracted into 5% sodium carbonate solution, the ethereal solution was washed with water, dried, and ether removed. The residue was chromatographed over silica gel (200 g) in benzene–ether (2 : 1). Fractions with the lipophilic component were combined, solvents removed, and the residue (1·95 g) was crystallized from ethyl acetate to afford 1·6 g of the derivative *XIII*, m.p. 152—154°C, $[\alpha]_D^{20}$ —17° (*c* 1·3). IR spectrum: 3 620 (hydroxyl), 3 080 (cyclopropane), 1 742, 1 240, 1 035 cm^{-1} (acetate). Mass spectrum: $M^{+\cdot}$ 376. For $C_{23}H_{36}O_4$ (376·5) calculated: 73·36% C, 9·64% H; found: 73·21% C, 9·52% H.

b) *From* 19-*acetyloxy*-4β,5-*cyclopropano*-17β-*hydroxy*-17α-*methyl*-5β-*androstan*-3-*one* (XVI): The ketone *XVI* (350 mg) in tetrahydrofuran (10 ml) was treated with lithium tri-tert-butoxyaluminium hydride (700 mg) and allowed to stand at room temperature for 4 h. The mixture was diluted with ether, washed with 3% hydrochloric acid, a sodium hydrogen carbonate solution, water, dried, and solvents removed *in vacuo*. The residue contained two compounds: The main lipophilic component was the 3α-isomer *XVIII* and the minor polar product the 3β-isomer *XIII*. It was chromatographed on a silica gel column (60 g) in benzene–ether (2 : 1). Fractions with the polar product were combined and solvent removed to leave 30 mg of the crude compound. Crystallization from ethyl acetate gave 18 mg of the alcohol *XIII*, m.p. 151—153°C, $[\alpha]_D^{20}$ —19° (*c* 1·0).

4β,5-Cyclopropano-17α-methyl-5β-androstan-3β,17β,19-triol 3,19-Diacetate (*XIV*)

The monoacetate *XIII* (200 mg) in pyridine (0·8 ml) was acetylated with acetic anhydride (0·6 ml) at room temperature for 20 h. Usual working up afforded 190 mg of the diacetate *XIV*, $[\alpha]_D^{20}$ —40° (*c* 1·2) resisting all attempts at crystallization. For $C_{25}H_{38}O_5$ (418·6) calculated: 71·74% C, 9·15% H; found: 71·50% C, 9·02% H.

4β,5-Cyclopropano-17β,19-dihydroxy-17α-methyl-5β-androstan-3-one (*XV*)

A solution of the acetate *XVI* (100 mg) in methanol (10 ml) was refluxed with a solution of potassium hydroxide (100 mg) in methanol (2 ml) for 45 min. The excess alkali was removed with acetic acid, solvents were distilled off *in vacuo* and the residue was diluted with water. The product was taken into ethyl acetate, the extract was washed with a sodium hydrogen carbonate solution, water, dried, and solvent removed. The residue was crystallized from ethyl acetate to yield 45 mg of the diol *XV*, m.p. 191—193°C, $[\alpha]_D^{20}$ +45° (*c* 1·2). For $C_{21}H_{32}O_3$ (332·5) calculated: 75·86% C, 9·70% H; found: 75·71% C, 9·60% H.

19-Acetyloxy-4β,5-cyclopropano-17β-hydroxy-17α-methyl-5β-androstan-3-one (*XVI*)

A solution of the alcohol *XIII* (1·6 g) in acetone (60 ml) was treated with excess Jones' reagent and allowed to stand at room temperature for 10 min. The excess reagent was destroyed with methanol, the mixture was diluted with water and the product was taken into ethyl acetate. The extract was washed with a sodium hydrogen carbonate solution, water, dried, and the product after evaporation of the solvent was crystallized from ethyl acetate to yield 1·25 g of the ketone *XVI*, m.p. 151—153°C, $[\alpha]_D^{20}$ +68° (*c* 1·4). IR spectrum: 3 615 (hydroxyl), 3 090 (cyclopropane), 1 734, 1 249, 1 042 (acetate), 1 679 cm^{-1} (carbonyl). Mass spectrum: $M^{+\cdot}$ 374. For $C_{23}H_{34}O_4$ (374·5) calculated: 73·76% C, 9·15% H; found: 73·51% C, 9·01% H.

3β,5-Cyclopropano-17α-methyl-5β-androstan-3α,17β,19-triol (*XVII*)

A solution of the acetate *XVIII* (280 mg) in methanol (80 ml) was refluxed for 1 h with a solution of potassium hydroxide (200 mg) in methanol (20 ml). The excess alkali was neutralized with acetic acid, solvents were distilled off *in vacuo* and the product was extracted with ethyl acetate. The extract was worked up and the residue was chromatographed over silica gel (60 g) in benzene–ether (1 : 1). Fractions with the desired triol were worked up and the crude product was crystallized from ethyl acetate to afford 130 mg of the triol *XVII*, m.p. 161–163°C, $[\alpha]_D^{20}$ +5° (*c* 1·3. in ethanol). For $C_{21}H_{34}O_3$ (338·5) calculated: 75·40% C, 10·25% H; found: 75·20% C, 10·20% H.

4β,5-Cyclopropano-17α-methyl-5β-androstan-3α,17β,19-triol 19-Acetate (*XVIII*)

Fractions with the lipophilic component from the chromatography of the acetate *XIII* under *a*) afforded after working up, evaporation of the solvents, and crystallization from ethyl acetate 210 mg of the diol *XVIII*, m.p. 174–176°C, $[\alpha]_D^{20}$ +12° (*c* 1·25). IR spectrum: 3 615 (hydroxyl), 3 070 (cyclopropane), 1 729, 1 243 cm^{-1} (acetate). For: $C_{23}H_{36}O_4$ (376·5) calculated: 73·36% C, 9·64% H; found: 73·12% C, 9·43% H.

4β,5-Cyclopropano-17α-methyl-5β-androstan-3α,17β,19-triol 3,19-Diacetate (*XIX*)

The acetate *XVIII* (200 mg) in pyridine (2 ml) was acetylated with acetic anhydride (0·8 ml) at room temperature for 18 h. Working up afforded an oily product which was purified by column chromatography over silica gel (20 g) in benzene–ether (19 : 1). Working up of the fractions with the desired product yielded 140 mg the diacetate *XIX*, $[\alpha]_D^{20}$ +18° (*c* 1·3) which resisted all attempts at crystallization. For $C_{25}H_{38}O_5$ (41·8·6) calculated: 71·74% C, 9·15% H; 71·50% C, 9·00% H.

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