6,7-SECOANDROSTANE DERIVATIVES*

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Received July 4th, 1984

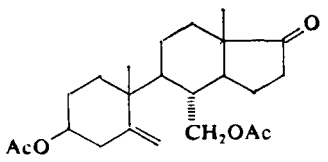
17β-Hydroxy-5-methyl-6-oxa-5β-androstan-3-one (*X*) and 17β-hydroxy-6,7-seco-4-androsten-3--one (*XXV*) were prepared as substances with potential biological activity.

Recently it was found[1] that some A-secoandrostane derivatives display antiandrogenic activity in *in vivo* tests. It is not known whether an intact B ring is indispensable for biological activity. This study describes the preparation of 17β-hydroxy-6,7-seco--4-androsten-3-one (*XXV*) as a substance with potential biological activity in the above-mentioned direction.

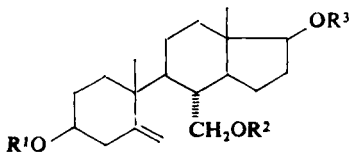
We started from the known[2] 3β,7-diacetoxy-6,7-seco-5-androsten-17-one (*I*) which was reduced with sodium borohydride to 17β-hydroxy derivative *II*, also characterized as acetoxy derivative *IV* and benzoyloxy derivative *III*. Partial alkaline saponification of the 17β-benzoyloxy derivative *III* with potassium hydrogen carbonaze in boiling methanol gave 3β-hydroxy derivative *V* as the main product which was oxidized with Jones's reagent to non-conjugated ketone *VII*. In view of the fact that ketone *VII* is not stable (it very easily undergoes isomerization to conjugated ketone *VIII* even on preparative chromatography), the crude ketone *VII* was converted without previous characterization to ketone *VIII* on reaction with potassium hydrogen carbonate in methanol, at room temperature. In an attempt at partial saponification of the 7-acetoxy group of ketone *VIII* with potassium hydrogen carbonate in boiling methanol it was observed, however, that even under these relatively mild conditions addition of the 7-hydroxy group to the 4,5-double bond takes place under formation of 5β-methyl-6-oxa derivatives *IX* and *X* in an approximately 2 : 1 ratio. In agreement with the proposed structure of the 6-oxa derivative *X* the signals of three methyl groups and of two CH—O protons on the carbon atom $C_{(7)}$ (Table I) are evident in the ^{1}H NMR spectrum of this compound, of which the signal of the $C_{(5)}$-methyl group appears as a doublet. The splitting of the signal of the $C_{(5)}$-methyl group is caused by the long-range coupling between the methyl group protons and the proton on the carbon atom $C_{(4)}$, which was corroborated

* Part CCCXII in the series On Steroids; Part CCCXI: This Journal *50*, 869 (1985).

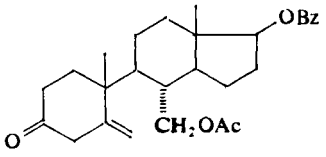
by decoupling experiments. CD spectroscopy was used to determine the configuration of the methyl group at $C_{(5)}$. It is known[3-5] that about 290 nm ($n \rightarrow \pi^*$ transition) the 5β-methyl substituted 3-ketones display a negative Cotton effect, while for the 5α-methyl substituted 3-ketones it is positive. In view of the close valence angles of the oxygen and the carbon atoms it may be assumed that the introduction of the oxygen atom into position 6 of the steroidal skeleton will not affect the conformation of the B ring, so that the distance between the ketonic chromophore and the 5-hetero atom will be so great that it also may be assumed that the Cotton effect will not be



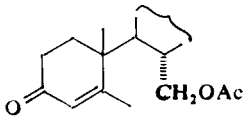
I



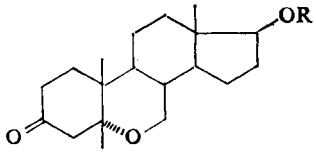
II, $R^1 = R^2 = Ac$, $R^3 = H$
III, $R^1 = R^2 = Ac$, $R^3 = Bz$
IV, $R^1 = R^2 = R^3 = Ac$
V, $R^1 = H$, $R^2 = Ac$, $R^3 = Bz$
VI, $R^1 = R^3 = H$, $R^2 = Ac$



VII

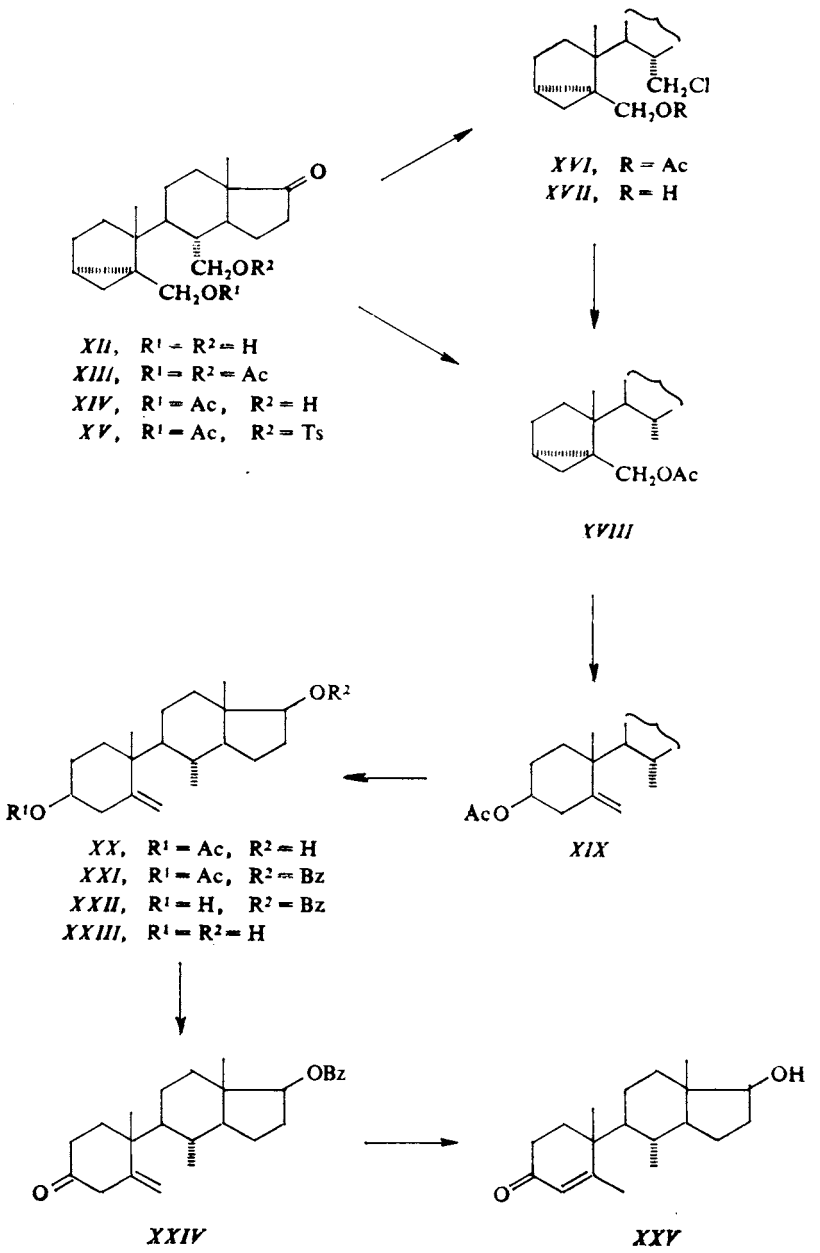


VIII



IX, R = Bz
X, R = H
XI, R = Ac

affected by electronic interactions between the chromophore and the free electron pair of the oxygen atom in position 6 either. So we assume that the above-mentioned dependence of the sign of the Cotton effect of 3-ketones on the configuration of the



methyl group on $C_{(5)}$ might also be used for 6-oxa derivatives. Therefore from the strongly negative Cotton effect ($(\Delta\varepsilon = -1{\cdot}58)$ the following structure may be derived for the compound *X*: 17β-hydroxy-5-methyl-6-oxa-5β-androstan-3-one.

For the preparation of the required 6,7-seco derivative *XXV* an alternative route was selected, starting from the known[2] 6,7-dihydro-3α,5-cyclo-6,7-seco-5α-androstan-17-one (*XII*). Acetylation of diol *XII* with acetic anhydride in triethylamine gave 6-acetoxy derivative *XIV* as the main product which was converted to 7-tosyloxy derivative *XV*. As a by-product 7-chloro derivative *XVI* is also formed during the tosylation of derivative *XIV*, in 37% yield. Both the tosyloxy derivative *XV* and the chloro derivative *XVI* afforded on reaction with sodium iodide and zinc dust in boiling dimethoxyethane 8-methyl derivative *XVIII*, the 3α,5α-cyclopropane ring of which was opened on reaction with boron trifluoride etherate in acetic anhydride under formation of 3β-acetoxy-5,6-unsaturated derivative *XIX*. Reduction with sodium borohydride in ethanol of ketone *XIX* gave 17β-hydroxy derivative *XX* which was converted to 17β-benzoyloxy derivative *XXI*. Partial saponification of derivative *XXI* with potassium hydrogen carbonate in boiling methanol afforded 3β-hydroxy derivative *XXII* which was oxidized with Jones's reagent to the non-conjugated ketone *XXIV*. Alkaline saponification of the 17β-benzoyloxy group of the crude ketone *XXIV* with potassium hydroxide in boiling methanol gave 17β--hydroxy-6,7-seco-4-androsten-3-one (*XXV*) in 97% yield, in the ^{1}H NMR spectrum of which the signals of four methyl groups were found (Table I) in agreement with the proposed structure. Similarly as in 7a,8-secocholestane derivatives[6] the experimentally determined values of the chemical shifts of the angular methyl groups of the 6,7-seco-androstane derivatives *XIX*, *XX*, *XXII* and *XXV* are in good agreement with the calculated values (Table II) which were obtained on the basis of the additivity of the effects of substituents, valid for derivatives with a normal steroid skeleton[7].

TABLE I

Chemical shifts (ppm, δ-scale) and coupling constants (Hz) of compounds *X* and *XXV*

Compound	18-H	19-H	5-CH_3	8-CH_3	$C_{(7)}$-H
X[a]	0·62 (d, $J = 0{\cdot}7$)	0·82 (s)	1·07 (d, $J = 1{\cdot}3$)	—	2·93 (dd, $J_{7,8} = 11{\cdot}3$, $J_{7,7} = 12{\cdot}8$)
XXV[b]	0·74 (s)	1·25 (s)	1·87 (s)	0·90 (d, $J = 5{\cdot}5$)	—

[a] The spectrum was measured on a Varian XL 200 instrument in deuteriobenzene. [b] The spectrum was measured on Tesla B 476 instrument in deuteriochloroform.

EXPERIMENTAL

The melting points were determined on a Kofler block and they are not corrected. Optical rotations were measured in chloroform. The infrared spectra were measured on a Zeiss UR 20 instrument in chloroform unless stated otherwise. The CD spectrum was measured on a Jouan-Roussel Dichrographe II in dioxane. The ^{1}H NMR spectra were measured on a Varian HA 100 (100 MHz) instrument, or also on spectrometers Tesla B 476 (60 MHz) and Varian XL 200 (200 MHz) in deuteriochloroform with tetramethylsilane as internal reference. The chemical shifts are given in δ-scale (ppm). The spectra were interpreted as 1st order spectra. The identity of the samples prepared in various ways was checked by mixture melting points and infrared spectra. The term "conventional work-up" means: washing the solution with 5% hydrochloric acid, 5% aqueous solution of potassium hydrogen carbonate and water, drying over sodium sulfate and evaporating the solvent in a vacuum. Preparative chromatography of the crude products was carried out on silica gel plates (20 × 20 × 0·07 cm) in light petroleum–ether–acetone (8 : 1 : 1), unless stated otherwise. The corresponding zones were combined, extracted with ether and the solvent was evaporated under reduced pressure.

6,7-Seco-5-androstene-3β,7,17β-triol 3,7-Diacetate (*II*)

Sodium borohydride (600 mg) was added to a solution of 3β,7-diacetoxy-6,7-seco-5-androsten-17-one (*I*), ref.[2] (3 g) in ethanol (40 ml) and the mixture was allowed to stand at room temperature for 2 h, then poured into a mixture of ice and 5% hydrochloric acid, and the product was extracted with ether. The ethereal extract was worked up in the conventional manner to give 3 g of a crude product which was chromatographed on a silica gel column (250 g) in light petroleum–ether–acetone (8 : 1 : 1). The required fractions were combined and evaporated to give 2·6 g of oily alcohol *II* which was resistant to all attempts at crystallization, $[\alpha]_D^{20} = +28°$ (*c* 0·5). Infrared spectrum: 3 615 (hydroxyl), 3 090, 1 640, 908 (double bond), 1 732, 1 257 (acetate) cm^{-1}. For $C_{23}H_{36}O_5$ (392·5) calculated: 70·37% C, 9·25% H; found: 70·16% C, 9·03% H.

6,7-Seco-5-androstene-3β,7,17β-triol 3,7-Diacetate 17-Benzoate (*III*)

Benzoyl chloride (4·5 ml) was added to a solution of alcohol *II* (1·4 g) in pyridine (15 ml) and the mixture was allowed to stand overnight. The conventional work-up gave 1,8 g of a crude product which was chromatographed on a silica gel column (150 g) in light petroleum–ether–acetone

TABLE II

Calculated and measured values of the chemical shifts (in ppm) of angular methyl groups of compounds *XIX*, *XX*, *XXII* and *XXV*

Compound	Calculated		Found	
	19-H	18-H	19-H	18-H
XIX	1·06	0·90	1·08	0·85
XX	1·03	0·77	1·06	0·72
XXII	1·03	0·96	1·10	0·93
XXV	1·21	0·80	1·25	0·74

(18 : 1 : 1). The corresponding fractions were combined and worked up to afford 1·15 g of benzoyloxy derivative *III* which was crystallized from aqueous methanol (750 mg), m.p. 123–125°C, $[\alpha]_D^{20} = +61°$ (*c* 0·5). Infrared spectrum (tetrachlormethane): 1 723, 1 277 (benzoate), 1 742, 1 243 (acetate), 3 090, 1 651, 1 640, 906 (double bond) cm^{-1}. For $C_{30}H_{40}O_6$ (496·6) calculated: 72·55% C, 8·12% H; found: 72·34% C, 8·01% H.

6,7-Seco-5-androstene-3β,7,17β-triol 3,7,17-Triacetate (*IV*)

a) Alcohol *II* (170 mg) was acetylated with acetic anhydride (0·8 ml) in pyridine (3 ml) overnight. The conventional work-up gave 165 mg of crude acetate which was chromatographed on 3 preparative thin-layer silica gel plates. The combined zones corresponding to the acetate were worked up to give 153 mg of triacetoxy derivative *IV*, which was crystallized from aqueous methanol (69 mg), m.p. 126–128°C, $[\alpha]_D^{20} = +48°$ (*c* 0·5). Infrared spectrum (tetrachloromethane): 1 741, 1 243 (acetate), 3 090, 1 640, 906 (double bond) cm^{-1}. For $C_{25}H_{38}O_6$ (434·55) calculated: 69·09% C, 8·81% H; found: 68·91% C, 8·74% H.

b) Diol *VI* (100 mg) was acetylated with acetic anhydride (1 ml) in pyridine (5 ml) overnight. The conventional work-up afforded 100 mg of crude acetate which was chromatographed preparatively on 2 silica gel thin-layer plates. The combined zones of the acetate were worked up and 89 mg of triacetoxy derivative *IV* were isolated, which was crystallized from aqueous methanol (58 mg), m.p. 126–128°C, $[\alpha]_D^{20} = +48°$ (*c* 0·5).

6,7-Seco-5-androstene-3β,7,17β-triol 7-Acetate 17-Benzoate (*V*)

An aqueous solution of potassium hydrogen carbonate (1 g, 7 ml) was added to a solution of diacetoxy derivative *III* (1 g) in methanol (50 ml) and the mixture was refluxed for 1 h. After concentration to one third of its original volume in a vacuum the mixture was poured into water and the product extracted with ether. The extract was washed with water, dried over sodium sulfate and the solvent evaporated in a vacuum. The residue (980 mg) was chromatographed on a silica gel column (100 g) in light petroleum–ether–acetone (8 : 1 : 1). The combined fractions of the lipophilic product were worked up to give 550 mg of oily benzoyloxy derivative *V* which would not crystallize, $[\alpha]_D^{20} = +60°$ (*c* 0·5). Infrared spectrum: 3 610 (hydroxyl), 3 090, 1 652, 1 637 (double bond), 1 721, 1 281 (benzoate), 1 731, 1 260 (acetate) cm^{-1}. ^1H NMR spectrum (100 MHz): 0·95 (s, 18-H), 1·08 (s, 19-H), 2·05 (s, acetate), 3·60 (mt, 3α-H), 3·86 (d, 7-H, $J_{7,7} =$ = 12 Hz), 4·45 (dd, 7-H, $J_{7,7} = 12$ Hz, $J_{7,8} = 2$ Hz), 4·78 (s, C=CH_2), 4·92 (t, 17α-H, $J =$ = 8 Hz). For $C_{28}H_{38}O_5$ (454·6) calculated: 73·98% C, 8·43% H; found: 73·74% C, 8·23% H.

6,7-Seco-5-androstene-3β,7,17β-triol 7-Acetate (*VI*)

The combined fractions with the polar product after the separation of benzoyloxy derivative *V* in the preceding experiment were worked up to afford 310 mg of diol *VI* which was crystallized from heptane (268 mg), m.p. 163–165°C, $[\alpha]_D^{20} = +43°$ (*c* 0·5). Infrared spectrum: 3 615 (hydroxyl), 1 730 (acetate), 3 090, 1 652, 1 637 (double bond) cm^{-1}. ^1H NMR spectrum (100 MHz): 0·78 (s, 18-H), 1·08 (s, 19-H), 2·02 (s, acetate), 3·60 (mt, 17α-H + 3α-H), 3·84 (bd, 7-H, $J_{7,7} =$ = 12 Hz), 4·42 (dd, 7-H, $J_{7,7} = 12$ Hz, $J_{7,8} = 2$ Hz), 5·00 (s, C=CH_2). For $C_{21}H_{34}O_4$ (350·0) calculated: 71·96% C, 9·78% H; found: 71·76% C, 9·65% H.

7-Acetoxy-17β-benzoyloxy-6,7-seco-4-androsten-3-one (*VIII*)

Jones's reagent (0·45 ml) was added to a solution of alcohol *V* (300 mg) in acetone (10 ml) and the mixture was allowed to stand at room temperature for 5 min, then poured into water and the product was extracted with ether. The extract was washed with water, 5% potassium hydrogen

carbonate solution and water, dried over sodium sulfate and the solvent was evaporated under reduced pressure. The crude ketone *VII* (290 mg, IR spectrum in tetrachlormethane: 1 742, 1 244 (acetate), 1 723, 1 277 (benzoate), 1 723 (ketone), 3 090, 1 637, 906 (double bond) cm^{-1}) was dissolved in methanol (15 ml), an aqueous potassium carbonate solution was added to it (290 mg), 2 ml) and the mixture was allowed to stand at room temperature for 1 h, then poured into water and the product extracted with ether. The ethereal extract was washed with water, dried over sodium sulfate and the solvent evaporated in a vacuum. The residue (280 mg) was chromatographed on 5 silica gel thin-layer plates to give 250 mg of conjugated ketone *VIII* which would not crystallize, $[\alpha]_D^{20} = +40°$ (*c* 0·5). Infrared spectrum: 1 732, 1 253 (acetate), 1 711, 1 279 (benzoate), 1 664, 1 614 (α,β-unsaturated ketone) cm^{-1}. ^1H NMR spectrum (100 MHz): 0·96 (s, 18-H), 1·33 (s, 19-H), 1·91 (d, $C_{(5)}$—CH_3, $J = 2$ Hz), 2·12 (s, acetate), 4·12 (d, 7-H, $J_{7,7} = 12$ Hz), 4·33 (d, 7-H, $J_{7,7} = 12$ Hz), 4·91 (t, 17α-H, $J = 8$ Hz), 5·78 (d, 4-H, $J = 2$ Hz). For $C_{28}H_{36}O_5$ (452·6) calculated: 74·30% C, 8·02% H; found: 74·11% C, 7·98% H.

17β-Benzoyloxy-5-methyl-6-oxa-5β-androstan-3-one (*IX*)

An aqueous solution of potassium hydrogen carbonate (200 mg, 1 ml) was added to a solution of ketone *VIII* (200 mg) in methanol (15 ml) and the mixture was refluxed for 3 h. After concentration of one third of the original volume in a vacuum the mixture was poured into water and the product extracted with ether. The extract was washed with water, dried over sodium sulfate and the solvent evaporated under reduced pressure. The residue (190 mg) was chromatographed preparatively on 4 silica gel plates and the respective zones with the lipophilic product were worked up to give 120 mg of 6-oxa derivative *IX* which was crystallized from aqueous methanol at 0°C. Yield, 65 mg, m.p. 143—145°C, $[\alpha]_D^{20} = +79°$ (*c* 0·5). Infrared spectrum (tetrachloromethane): 1 722, 1 276 (benzoate + ketone) cm^{-1}. ^1H NMR spectrum (100 MHz): 0·98 (s, 18-H), 1·08 (s, 19-H), 1·16 (d, $C_{(5)}$—CH_3, $J = 2$ Hz), 3·44 (d, 7-H, $J_{7,7} = 12$ Hz), 3·74 (dd, 7-H, $J_{7,7} = 12$ Hz, $J_{7,8} = 5$ Hz), 4·92 (t, 17α-H, $J = 8$ Hz). For $C_{26}H_{34}O_4$ (410·5) calculated: 76·06% C, 8·35% H; found: 75·88% C, 8·16% H.

17β-Hydroxy-5-methyl-6-oxa-5β-androstan-3-one (*X*)

a) The combined zones with the polar product after separation of benzoyloxy derivative *IX* from the preceding experiment afforded after working up 60 mg of alcohol *X* which was crystallized from a mixture of acetone and heptane. Yield, 43 mg, m.p. 178—180°C, $[\alpha]_D^{20} = +27°$ (*c* 0·5). Infrared spectrum: 3 615 (hydroxyl), 1 713 (ketone), 1 281, 1 254, 1 119, 1 082, 1 012 (ether) cm^{-1}. CD spectrum: $\Delta\varepsilon_{292} = -1·58$. ^1H NMR spectrum (200 MHz, C_6D_6): 0·62 (d, 18-H, $J = 0·7$ Hz), 0·82 (s, 19-H), 1·08 (d, $C_{(5)}$—CH_3, $J = 1·3$ Hz), 3·05 (bd, 4-H, $J_{4,4} =$ = 13·7 Hz), 2·93 (dd, 7β-H, $J_{7\beta,8\alpha} = 11·3$ Hz, $J_{7\beta,7\alpha} = 12$ Hz), 3·51 (dd, 7α-H, $J_{7\alpha,8\alpha} = 5·0$ Hz, $J_{7\alpha,7\beta} = 12$ Hz), 3·43 (dd, 17α-H, $J_{17\alpha,16\beta} + J_{17\alpha,16\alpha} = 8·1$ Hz + 8·9 Hz). For $C_{19}H_{30}O_3$ (306·4) calculated: 74·77% C, 9·87% H; found: 74·62% C, 9·73% H.

b) Potassium hydroxide (100 mg) was added to a solution of benzoyloxy derivative *IX* (50 mg) in methanol (5 ml) and the mixture was refluxed for 2 h, poured into water and the product extracted with ether. The extract was washed with water, dried over sodium sulfate and the solvent evaporated in a vacuum. The residue (45 mg) was crystallized from acetone–heptane to give 30 mg of alcohol *X*, m.p. 178—180°C, $[\alpha]_D^{20} = +27°$ (*c* 0·5).

17β-Acetoxy-5-methyl-6-oxa-5β-androstan-3-one (*XI*)

Alcohol *X* (60 mg) was acetylated with acetic anhydride (0·3 ml) in pyridine (1·5 ml) overnight.

The conventional work-up afforded 58 mg of a product which was crystallized from heptane to give 35 mg of acetoxy derivative *XI* with m.p. 131–133°C, $[\alpha]_D^{20} = +16°$ (*c* 0·5). Infrared spectrum (tetrachloromethane): 1 740, 1 247 (acetate), 1 724 (ketone), 1 085, 1 015 (ether) cm^{-1}. ^1H NMR spectrum (100 MHz): 0·86 (s, 18-H), 1·08 (s, 19-H), 1·14 (d, $C_{(5)}$—CH_3, J = 2 Hz), 2·05 (s, acetate), 3·35 (d, 7-H, $J_{7,7}$ = 12 Hz), 3·72 (dd, 7-H, $J_{7,7}$ = 12 Hz, $J_{7,8}$ = 5 Hz), 4·64 (t, 17α-H, J = 8 Hz). For $C_{21}H_{32}O_4$ (348·5) calculated: 72·38% C, 9·26% H; found: 72·96% C, 9·20% H.

6,7-Diacetoxy-3α,5-cyclo-6,7-seco-5α-androstan-17-one (*XIII*)

6,7-Dihydroxy-3α,5-cyclo-6,7-seco-5α-androstan-17-one (*XII*), ref.[2] (980 mg) was acetylated with acetic anhydride (3 ml) in triethylamine (20 ml) for 5h. The conventional work-up gave 980 mg of product which was chromatographed on a silica gel column (100 g) in light petroleum–ether–acetone (8 : 1 : 1). The fractions corresponding to the lipophilic product were combined and worked up to afford 210 mg of diacetoxy derivative *XIII*, which was crystallized from methanol (176 mg), m.p. 141–143°C, $[\alpha]_D^{20} = +76°$ (*c* 0·5). Infrared spectrum: 1 737, 1 727, 1 271 (acetate), 1 737 (ketone), 3 070 (cyclopropane) cm^{-1}. For $C_{23}H_{34}O_5$ (390·5) calculated: 70·74% C, 8·78% H; found: 70·57% C, 8·65% H.

6-Acetoxy-7-hydroxy-3α,5-cyclo-6,7-seco-5α-androstan-17-one (*XIV*)

The corresponding combined fractions of the more polar product after the separation of the diacetoxy derivative *XIII* from the preceding experiment were worked up and 690 mg of acetoxy derivative *XIV* were obtained. It was crystallized from acetone–heptane (547 mg), m.p. 152 to 153·5°C, $[\alpha]_D^{20} = +59°$ (*c* 0·5). Infrared spectrum: 1 737, 1 728, 1 270 (acetate), 1 737 (ketone), 3 070 (cyclopropane), 3 625 (hydroxyl) cm^{-1}. ^1H NMR spectrum (60 MHz): 0·91 (s, 18-H), 1·38 (s, 19-H), 2·04 (s, acetate), 3·70 (d, 7-H, $J_{7,7}$ = 12 Hz), 3·78 (d, 6-H, $J_{6,6}$ = 12 Hz), 3·91 (d, 7-H, $J_{7,7}$ = 12 Hz), 4·53 (d, 6-H, $J_{6,6}$ = 12 Hz). For $C_{21}H_{32}O_4$ (348·5) calculated: 72·38%C, 9·26% H; found: 72·09% C, 9·08% H.

6-Acetoxy-7-*p*-toluenesulfonyloxy-5α,5-cyclo-6,7-seco-5α-androstan-17-one (*XV*)

p-Toluensulfonyl chloride (2 g) was added to a solution of alcohol (*XIV* (2 g) in pyridine (20 ml) and the mixture was allowed to stand at room temperature for 2 days. The conventional work-up gave 2·8 g of a product which was crystallized from ether to give 1·8 g of *XV*, m.p. 140–142°C, $[\alpha]_D^{20} = +61°$ (*c* 0·5). Infrared spectrum: 1 739, 1 264 (acetate), 1 728 (ketone), 1 358, 1 194, 1 181 (tosylate) cm^{-1}. For $C_{28}H_{38}O_6S$ (502·65) calculated: 66·90% C, 7·62% H, 6·38% S; found: 66·58% C, 7·95% H, 6·35% S.

6-Acetoxy-7-chloro-3α,5-cyclo-6,7-seco-5α-androstan-17-one (*XVI*)

Chromatography of the mother liquors after crystallization of the tosyloxy derivative *XV* from the preceding experiment on a silica gel column (100 g) in light petroleum–ether (8 : 2) afforded 750 mg of chloro derivative *XVI* which was crystallized from heptane (595 mg), m.p. 69–70°C, $[\alpha]_D^{20} = +70°$ (*c* 0·5). Infrared spectrum (tetrachloromethane): 1 744 (ketone), 1 744, 1 243, 1 031 (acetate), 3 070 (cyclopropane) cm^{-1}. ^1H NMR spectrum (60 MHz): 0·90 (s, 18-H), 1·31 (s, 19-H), 3·15 (d, 7-H, $J_{7,7}$ = 11 Hz), 3·61 (d, 6-H, $J_{6,6}$ = 12 Hz), 4·075 (d, 6-H, $J_{6,6}$ = 12 Hz), 4·10 (d, 7-H, $J_{7,7}$ = 11 Hz), 0·575 (mt, cyclopropane), 0·30 (dd, cyclopropane, J = 8 + 5 Hz). For $C_{21}H_{31}ClO_3$ (366·9) calculated: 68·74% C, 8·52% H, 9·66% Cl; found: 68·57% C, 8·34% H, 9·42% Cl.

6-Hydroxy-7-chloro-3α,5-cyclo-6,7-seco-5α-androstan-17-one (*XVII*)

An aqueous solution of potassium hydrogen carbonate (60 mg, 1 ml) was added to a solution of acetoxy derivative *XVI* (60 mg) in methanol (6 ml) and the mixture was refluxed for 1 h, poured into water and the product was extracted with ether. The ethereal extract was washed with water, dried over sodium sulfate and the solvent was evaporated in a vacuum. The residue (57 mg) was submitted to preparative chromatography on one silica gel thin-layer plate, giving 48 mg of alcohol *XVII* which was crystallized from acetone–heptane to give 34 mg of product, m.p. 150–152°C, $[\alpha]_D^{20} = +69°$ (*c* 0·5). Infrared spectrum: 3 615, 1 024 (hydroxyl), 1 737 (ketone), 3 065 (cyclopropane) cm^{-1}. For $C_{19}H_{29}ClO_2$ (324·9) calculated: 70·24% C, 9·00% H, 10·91% Cl; found: 69·97% C, 8·81% H, 10·69% Cl.

6-Acetoxy-3α,5-cyclo-6,7-seco-5α-androstan-17-one (*XVIII*)

a) Water (1 ml), sodium iodide (0·15 g) and zinc dust (1·5 g) were added to a solution of tosyloxy derivative *XV* (1·5 g) in 1.2-dimethoxyethane and the mixture was refluxed for 2 h under nitrogen. The mixture was filtered to get rid of inorganic material, the filtrate was poured into water and the product extracted with ether. The extract was washed with water, sodium thiosulfate solution, water, dried over sodium sulfate and the solvent was evaporated in a vacuum. The residue (900 mg) was crystallized from heptane, giving 590 mg of acetoxy derivative *XVIII*, m.p. 121–123°C, $[\alpha]_D^{20} = 70°$ (*c* 0·5). Infrared spectrum: 1 731, 1 262 (acetate), 1 731 (ketone), 3 070 (cyclopropane) cm^{-1}. ^1H NMR spectrum (60 MHz): 0·90 (s, 18-H), 1·06 (d, $C_{(8)}$—CH_3, J = 5·5 Hz), 1·25 (s, 19-H), 2·01 (s, acetate), 3·75 (d, 6-H, $J_{6,6}$ = 12 Hz), 4·41 (dd, 6-H, $J_{6,6}$ = = 12 Hz, $J_{6,4}$ = 1·5 Hz), 0·40 (dd, cyclopropane, J = 8 + 5 Hz), 0·46 (mt, cyclopropane). For $C_{21}H_{32}O_3$ (332·5) calculated: 75·86% C, 9·70% H; found: 75·85% C, 9·62% H.

b) Water (0·1 ml), sodium iodide (160 mg) and zinc dust (160 mg) were added to a solution of chloro derivative *XVI* (120 mg) in 1,2-dimethoxyethane (2 ml) and the mixture was refluxed under nitrogen for 6 h. The same work-up procedure as in the preceding experiment gave 100 mg of acetoxy derivative *XVIII*, which was crystallized from heptane (65 mg), m.p. 121–123°C, $[\alpha]_D^{20} = +70°$ (*c* 0·5).

3β-Acetoxy-6,7-seco-5-androsten-17-one (*XIX*)

An ethereal solution of boron trifluoride (0·2 ml) was added to a solution of 3α,5α-cyclo derivative *XVIII* (560 mg) in acetic anhydride (11 ml) and the mixture was allowed to stand at room temperature for 2 h, then poured into water and the product extracted with ether. The ethereal extract was washed with 5% potassium hydrogen carbonate solution and water, dried over sodium sulfate and the solvent evaporated in a vacuum. The residue (550 mg) was chromatographed on a silica gel column (60 g) with light petroleum–ether–acetone mixture (18 : 1 : 1) to give 450 mg of olefin *XIX* which was crystallized from heptane (382 mg), m.p. 137–138°C, $[\alpha]_D^{20} = +149·5°$ (*c* 0·5). Infrared spectrum: 1 731, 1 255 (acetate), 1 731 (ketone), 3 090, 1 633, 905 (double bond) cm^{-1}. ^1H NMR spectrum (60 MHz): 0·85 (s, 18-H), 0·925 (d, $C_{(8)}$—CH_3, J = 5·5 Hz), 1·075 (s, 19-H), 2·02 (s, acetate), 4·58 (mt, 3α-H), 4·84 (s, C=CH_2). For $C_{21}H_{32}O_3$ (332·5) calculated: 75·86% C, 9·70% H; found: 76·52% C, 9·56% H.

6,7-Seco-5-androstene-3β,17β-diol 3-Acetate (*XX*)

Sodium borohydride (30 mg) was added to a solution of ketone *XIX* (120 mg) in ethanol (3 ml) and the mixture was allowed to stand at room temperature for 1 h. After pouring it to a mixture of ice and 5% hydrochloric acid the product was extracted with ether. The extract was washed

with a 5% potassium hydrogen carbonate solution and water, dried over sodium sulfate and the solvent evaporated under reduced pressure. The residue (110 mg) was submitted to preparative thin-layer chromatography on 2 silica gel plates, affording 100 mg of alcohol *XX* which was crystallized from heptane. Yield 69 mg, m.p. 102–103·5°C, $[\alpha]_D^{20} = +74°$ (*c* 0·5). Infrared spectrum: 3 615 (hydroxyl), 3 090, 1 634, 905 (double bond), 1 729, 1 258 (acetate) cm^{-1}. ^1H NMR spectrum (60 MHz): 0·725 (s, 18-H), 0·82 (d, $C_{(8)}$—CH_3, $J = 5·5$ Hz), 1·06 (s, 19-H), 3·625 (t, 17α-H, $J = 8$ Hz), 4·81 (s, C=CH_2), 4·65 (mt, 3α-H), 2·01 (s, acetate). For $C_{21}H_{34}O_3$ (334·5) calculated: 75·40% C, 10·25% H; found: 75·24% C, 10·11% H.

6,7-Seco-5-androstene-3β,17β-diol 3-Acetate, 17-Benzoate (*XXI*)

Alcohol *XX* (100 mg) was benzoylated with benzoyl chloride (0·3 ml) in pyridine (2 ml) overnight. The conventional work-up gave 100 mg of product which was chromatographed preparatively on 2 silica gel thin-layer plates. The combined required zones were worked up to give 89 mg of benzoyloxy derivative *XXI* which was resistant to all attempts at crystallization, $[\alpha]_D^{20} = +86°$ (*c* 0·5). Infrared spectrum: 3 090, 1 638, 904 (double bond), 1 730, 1 256 (acetate), 1 713, 1 281 (benzoate) cm^{-1}. For $C_{28}H_{38}O_4$ (438·6) calculated: 76·67% C, 8·73% H; found: 76·45% C, 8·53% H.

6,7-Seco-5-androstene-3β,17β-diol 17-Benzoate (*XXII*)

An aqueous solution of potassium hydrogen carbonate (100 g, 1 ml) was added to a solution of acetoxy derivative *XXI* (100 mg) in methanol (5 ml) and the mixture was refluxed for 30 min, then poured into water and the product extracted with ether. The extract was washed with water, dried over sodium sulfate and the solvent evaporated in a vacuum. The residue (97 mg) was chromatographed preparatively on 2 silica gel plates, using triple development. The required zones were combined and worked up to give 78 mg of alcohol *XXII* which was crystallized from acetone–heptane (57 mg), m.p. 115–117°C, $[\alpha]_D^{20} = +67°$ (*c* 0·5). Infrared spectrum: 3 610 (hydroxyl), 3 090, 1 633, 899 (double bond), 1 712, 1 281 (benzoate) cm^{-1}. ^1H NMR spectrum (100 MHz): 0·90 (d, $C_{(8)}$—CH_3, $J = 5·5$ Hz), 0·93 (s, 18-H) 1·10 (s, 19-H), 3·57 (mt, 3α-H), 4·78 (s, C=CH_2), 4·81 (t, 17α-H, $J = 7$ Hz). For $C_{26}H_{36}O_3$ (396·55) calculated: 78·44% C, 9·15% H; found: 78·58% C, 9·06% H.

6,7-Seco-5-androstene-3β,17β-diol (*XXIII*)

The combined zones corresponding to the polar product after the separation of benzoyloxy derivative *XXII* in the preceding experiment were worked up to give 8 mg of diol *XXIII* which was crystallized from a mixture of acetone and heptane. Yield, 5·4 mg, m.p. 196–198°C. Infrared spectrum: 3 615, 1 036 (hydroxyl), 3 090, 1 634, 901 (double bond) cm^{-1}. For $C_{19}H_{32}O_2$ (292·45) calculated: 78·03% C, 11·03% H; found: 77·86% C, 10·98% H.

17β-Hydroxy-6,7-seco-4-androsten-3-one (*XXV*)

Jones's reagent (0·3 ml) was added to a solution of alcohol *XXII* (150 mg) in acetone (6 ml) and the mixture was allowed to stand at room temperature for 5 min. After pouring into water the precipitated product was extracted with ether and the extract washed with 5% potassium hydrogen carbonate solution water and dried over sodium sulfate. After filtration the solvent was distilled off under reduced pressure and the crude unsaturated ketone *XXIV* (150 mg, infrared spectrum (tetrachloromethane): 1 723 (benzoate), 3 090, 1 633, 900 (double bond), 1 711 (ketone), 1 679, 1 616 (α,β-unsaturated ketone) cm^{-1}) was dissolved in methanol (6 ml). Sodium hydroxide

(200 mg) was added to the solution and the mixture was refluxed for 1 h, then poured into water and the product extracted with ether. The extract was washed with water, dried over sodium sulfate and the solvent distilled off under reduced pressure. The residue (145 mg) was chromatographed on 3 silica gel thin-layer plates and 124 mg of alcohol *XXV* were obtained after working up. It was crystallized from acetone–heptane to give 98 mg of product, m.p. 173—174°C, $[\alpha]_D^{20} = +61°$ (*c* 0·5). Infrared spectrum: 1 660, 1 613 (α,β-unsaturated ketone), 3·610 (hydroxyl) cm^{-1}. ^1H NMR spectrum (60 MHz): 0·74 (s, 18-H), 0·90 (d, $C_{(8)}—CH_3$, $J = 5·5$ Hz), 1·25 (s, 19-H), 1·87 (s, $C_{(5)}—CH_3$), 3·61 (mt, 17α-H), 5·75 (bs, 4-H). For $C_{21}H_{30}O_2$ (314·5) calculated: 80·21% C, 9·62% H; found: 80·07% C, 9·56% H.

The analyses were carried out in the analytical laboratory of this Institute under the direction of Dr J. Horáček. We thank Mrs K. Matoušková for the measurement of the infrared spectra and Dr J. Smolíková for their interpretation. We also thank Dr J. Zajíček for the measurement of the ^1H NMR *spectrum on the Varian XL 200 (200 MHz) instrument and for its interpretation. Our thanks are further due to Dr S. Vašíčková for the measurement of the* CD *spectra and Mrs J. Jelínková and Mrs M. Snopková for the measurement of the* ^1H NMR *spectra on the Varian* HA 100 (100 MHz) *and Tesla* B 476 (60 MHz) *instruments.*

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Translated by Ž. Procházka.