EPIMERIC 17-HYDROXY DERIVATIVES OF 14β-ANDROST-5-EN-3β-YL ACETATE*,**

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A new, six-step synthesis of 3β-hydroxy-14β-androst-5-en-17-one (*IX*) starting from 3β-hydroxy-androst-5-en-17-one has been elaborated. Reduction of acetate *X* with sodium borohydride afforded 17α-hydroxy-14β-androst-5-en-3β-yl acetate (*XI*). The corresponding 17β-derivative *XIV* was obtained by epimerization of 17α-O-tosyl derivative *XIII* with sodium nitrite in hexamethylphosphoramide. The ^{13}C and ^{1}H NMR spectra of 14β-androstane derivatives are discussed.

14β-Androstane derivatives represent a group of steroids that has hitherto received only marginal attention, the only exception being the 14β-hydroxy derivatives to which belong the natural cardenolides[1]. It might be pointed out that 14β-androstane with the *cis*-fusion of the rings C and D is thermodynamically more stable than the more common parent compound 14α-androstane[2] (*trans*-annulation of the rings[2]). In order to increase the variety of structural types for cardiotonic activity tests, we elaborated a simple synthetic approach to derivatives of this series. This approach leaves the double bond in position 5 intact enabling thus a comparison of the prepared derivatives with those of the usual androst-5-ene series.

The key reaction in the hitherto published approaches[2-6] to 14β-androstanes consists in hydrogenation of androst-14-en-17-one derivatives (this also holds for the estrane series[7]). Starting compounds in these syntheses are 17-ketones which are protected as acetals, brominated in the position 16, converted into the 15-unsaturated derivatives, and after deblocking isomerized[2,4,6,7]. Other syntheses[3-5] start from the 14-hydroxy derivatives which after protection are subjected to elimination, affording directly the 14-ene derivatives.

Our synthesis started from the unprotected bromo ketone *I* (ref.[8]) which was directly dehydrobrominated with a mixture of lithium bromide and lithium carbonate

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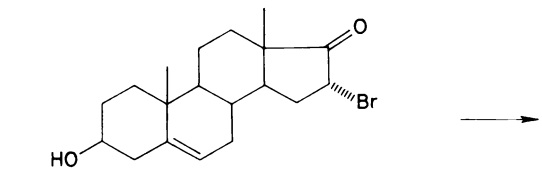
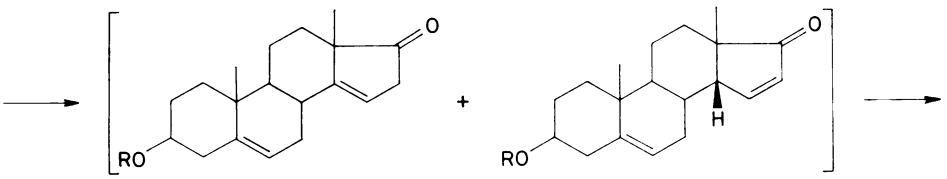
in N,N-dimethylacetamide[8]. The obtained mixture of unseparated ketones *II* and *III* was converted to the corresponding 3,5-cyclo derivatives *VI* and *VII*. Their hydrogenation gave the ketone *VIII*. The double bond in position 5 was then regenerated by cleavage of the 3,5-cyclo-6β-methoxy grouping with aqueous perchloric acid in acetone under formation of ketone *IX*.

We made use of the fact that in other steroid series both the unsaturated ketones arising in the dehydrobromination are hydrogenated to give the same product[4].

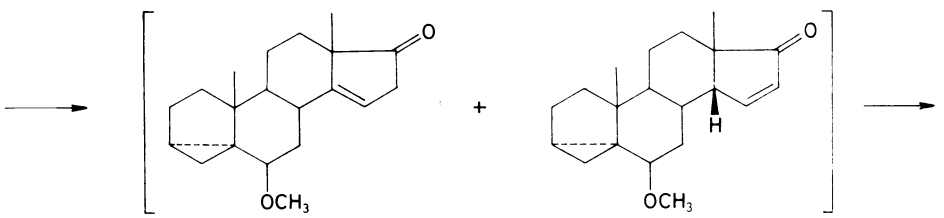


I

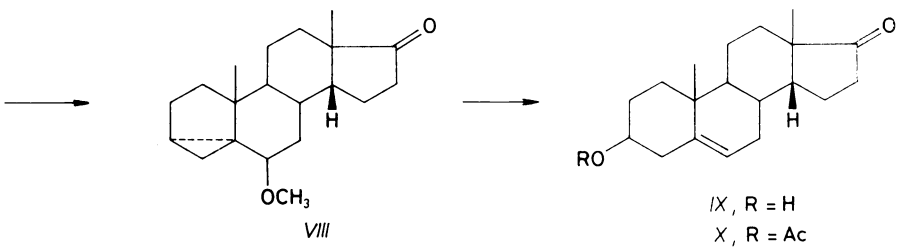


II, R = H
IV, R = Ms

III, R = H
V, R = Ms



VI *VII*



VIII

IX, R = H
X, R = Ac

This enabled us not only to skip the separation of both the unsaturated ketones but also to perform the dehydrobromination with the unprotected bromoketone under conditions of isomerization (undesirable under other circumstances). The pathway[5] starting from 14α-hydroxy derivatives is longer and the starting compounds are less accessible.

The mixture of unsaturated ketones *II* and *III* was studied in more detail. We investigated the possibility of selective hydrogenation of the Δ^{14} or Δ^{15} double bond in the presence of the Δ^5 double bond. After consumption of an equivalent of hydrogen the mixture contained, in addition to ketone *IX*, also the 5α-derivative that was separable only with difficulty. This reaction, which would represent another shortening of the synthesis, is thus preparatively unusable. We were further interested in isomerization of the ketones *II* and *III*. Acid-catalyzed isomerization of androst-15-en-17-one derivatives (refs[2,3]) affords a mixture of the corresponding 14β-androst-15-en-17-one and androst-14-en-17-one compounds (an analogous course of isomerization was observed in the estrane series[7]). In an alkaline medium only the former product was observed[4]. We separated the unsaturated ketones *II* and *III* after the elimination and have proven that both in an alkaline (potassium carbonate in ethanol) and an acidic (hydrochloric acid in ethanol) medium the isomerization takes place already at room temperature, the population of both isomers in the equilibrium mixture being approximately the same (as found by TLC and ^{1}H NMR spectroscopy).

The structure of ketone *IX* was derived predominantly from the spectral data (IR, ^{1}H and ^{13}C NMR spectra) because the agreement of its physical constants with the published data[5] is not very satisfactory (see Experimental). The ^{1}H NMR spectrum (Table I) has shown the presence of 3β-hydroxyl (H-3: δ 3·54 m, W = 30 Hz) and an olefinic hydrogen (H-6: δ 5·43 m). The downfield shift of the H-18 methyl signal (δ 1·11 s) confirms the 14β-configuration and the presence of 17-oxo group (a calculation from the data for 14β-androstane and the effect of 17-oxo group[9] leads to δ 1·075 for H-18). Comparison of the ^{13}C NMR data (Table II) for the ketone *IX* with those published[10] for 3β-hydroxyandrost-5-en-17-one shows marked characteristic differences for some carbon atoms. The upfield shifts of C-7 (−3·2 ppm), C-9 (−7·7 ppm), C-12 (−3·4 ppm) and C-15 (−2·2 ppm) signals are apparently caused by steric γ-gauche interactions of these carbon atoms in the 14β-derivative *IX*. The upfield shift of the C-14 signal (−5·6 ppm) on transition from *trans*- to *cis*-fused system is typical (e.g. for bicyclo[4.3.0]nonane[11] the analogous difference in the shifts at the annulation site amounts to −7·4 ppm). The downfield shift of the methyl carbon atom C-18 (4·7 ppm) in *IX* is evidently due to the absence of the γ-gauche interactions with C-15 and C-16; a contribution of a deshielding effect of the 17-oxo group is also possible (C-18 in *IX* is nearly coplanar with the 17-oxo group).

The hydroxy ketone *IX* was converted into acetyl derivative *X* which was reduced with sodium borohydride to give 17α-hydroxy derivative *XI*. The epimeric 17β--hydroxy derivative *XIV* was prepared by reaction of the tosyl derivative *XIII* with sodium nitrite in hexamethylphosphoramide which proved to be in our case better reaction medium than dimethyl sulfoxide[12]. For characterization, we prepared also the corresponding diacetates *XII* and *XV*. Analogously was synthesized the pair of 17-epimeric compounds *XVII* and *XIX* in the "normal" 14α-series (with *trans*-annulation of the rings C and D). The nucleophilic substitution of the 17β-O--tosyl group in the tosylate *XVIII* is much more difficult than that of the 17α-tosyl group in the 14β-series. Under the same conditions, the reaction required ten times longer reaction time, the yield being approximately the same. The diacetate *XX* and diol *XXI* were prepared for characterization.

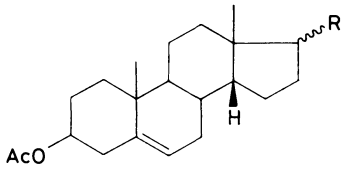
TABLE I

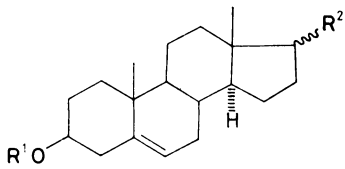
Proton NMR data of androst-5-ene derivatives *VIII*–*XI*, *XIV*, *XVI*, *XIX*, and *XX*

Proton	*VIII*[a]	*IX*	*X*[b]	*XI*	*XI*[c]
H-3 (1 H)	0·41–	3·54 m	4·63 m	4·61 m	4·60 m
H-4 (2 H)	–1·00 m	[d]	2·34 m	2·32 m	2·32 m
H-6 (1 H)	2·84 t (J = 3)	5·43 m	5·43 m	5·37 m	5·39 m
H-17 (1 H)	—	—	—	3·75 t (J = 8·3)	4·84 dd (J = 9·2; 7·2)
H-18 (3 H)	1·13 s	1·11 s	1·10 s	1·04 s	1·10 s
H-19 (3 H)	1·02 s	1·00 s	1·01 s	1·01 s	1·01 s
OAc (3 H)	—	—	2·03 s	2·03 s	2·03 s

	XIV	*XIV*[c]	*XVI*	*XIX*	*XX*
H-3 (1 H)	4·60 m	4·60 m	4·61 m	4·57 m	4·63 m
H-4 (2 H)	2·32 m	2·33 m	2·32 m	2·33 m	2·34 m
H-6 (1 H)	5·39 m	5·38 m	5·39 m	5·41 m	5·42 m
H-17 (1 H)	3·68 dd (J = 6·0; 0·9)	4·88 bd (J = 6)	[d]	3·75 bd (J = 5)	4·84 bd (J = 5)
H-18 (3 H)	1·06 s	1·08 s	1·00 s	0·68 s	0·76 s
H-19 (3 H)	1·01 s	1·01 s	1·01 s	1·04 s	1·04 s
OAc (3 H)	2·03 s	2·03 s	2·03 s	2·03 s	2·04 s (6 H)

[a] OCH_3: 3·37 s; [b] H-16: 2·49 ddd (J = 19·1; 8·3; 1·8), H-16′: 2·12 ddd (J = 19·1; 10·9; 9·0); [c] measured after addition of TAI, NH: *XI* 8·36 s, *XIV* 8·31 s; [d] the signal is overlapped by the steroid envelope.





XI, R = α-OH
XII, R = α-OAc
XIII, R = α-OTs
XIV, R = β-OH
XV, R = β-OAc
XVI, R = H

XVII, R^1 = Ac ; R^2 = β-OH
XVIII, R^1 = Ac ; R^2 = β-OTs
XIX, R^1 = Ac ; R^2 = α-OH
XX, R^1 = Ac ; R^2 = α-OAc
XXI, R^1 = H ; R^2 = α-OH

Ms = methanesulfonyl ; Ts = *p*-toluenesulfonyl ; Ac = acetyl

TABLE II

Carbon-13 chemical shifts of 14β-androst-5-ene derivatives *IX*–*XI*, *XIV*, and *XVI*

Carbon	*IX*	*X*	*XI*	*XI*[a]	*XIV*	*XIV*[a]	*XVI*
C-1	36·95	36·74	36·85	36·74	36·79	36·70	36·81
C-2	31·45	27·62	27·69	27·60	27·69	27·60	27·71
C-3	71·57	73·74	73·89	73·75	73·90	73·75	73·97
C-4	42·16	38·04	38·09	38·00	38·07	37·98	38·07
C-5	140·04	138·98	138·97	138·94	138·87	138·87	138·82
C-6	121·46	122·42	122·77	122·51	122·99	122·71	123·10
C-7	28·90	28·94	29·41	29·36	30·60	30·43	30·82
C-8	29·21	29·24	29·55	29·14	29·33	29·05	29·67
C-9	43·36	43·38	43·33	42·98	43·03	42·65	42·86
C-10	36·62	36·74	36·59	36·51	36·65	36·57	36·64
C-11	20·27	20·26	20·60	20·32	20·72	20·39	20·02
C-12	27·82	27·85	24·93	25·97	30·71	30·03	31·87
C-13	47·99	47·94	42·32	42·17	44·98	44·58	40·25
C-14	46·63	46·68	46·11	45·48	45·22	46·05	49·26
C-15	20·05	20·04	21·07	21·41	23·66	23·55	25·42
C-16	35·67	35·61	29·22	26·08	31·40	28·97	21·46
C-17	222·88	222·46	83·40	87·71	82·57	88·78	41·96
C-18	18·90	18·22	21·80	21·66	17·11	17·60	24·16
C-19	19·44	19·33	19·47	19·40	19·45	19·40	19·44
Ac: CO	—	170·41	170·49	170·46	170·48	170·46	170·50
CH_3	—	21·34	21·40	21·36	21·39	21·35	21·43

[a] Measured after addition of TAI.

As a reference derivative for comparison of the ^{13}C NMR spectra we prepared 14β-androst-5-en-3β-yl acetate (*XVI*) by reaction of the tosylate *XIII* with sodium iodide and zinc in 1,2-dimethoxyethane[13].

Configuration on the C-17 atom in the epimeric 17-hydroxy derivatives *XI* and *XIV* was determined using NMR spectroscopy. In this respect, the ^{13}C NMR data were more convincing. As seen on models, a change of configuration of the 17--hydroxyl affects mostly its spatial relationship to the C-12 and C-18 carbon atoms. The hydroxy group interacts with the C-12 atom only in the 17α-OH derivative whereas with the C-18 atom only in the 17β-OH derivative. The found substitution effects due to introduction of the 17-OH group in both isomers (C-12: −6·94 and −1·16 ppm; C-18: −2·36 and −7·05 ppm for *XI* and *XIV*, respectively; see Table III) are sufficiently different to make possible an unequivocal structural assignment

TABLE III

Substituent effects and TAI-acylation shifts in ^{13}C NMR spectra of 14β-androst-5-ene derivatives *X*, *XI*, and *XIV*

Carbon	Substituent effects[a]			TAI-acylation shifts[b]	
	17α-OH (*XI*−*XVI*)	17β-OH (*XIV*−*XVI*)	17-oxo (*X*−*XVI*)	17α-OH	17β-OH
C-1	0·04	−0·02	−0·07	−0·11	−0·09
C-2	−0·02	−0·02	−0·09	−0·09	−0·09
C-3	−0·08	−0·07	−0·23	−0·14	−0·15
C-4	0·02	0·00	−0·03	−0·09	−0·09
C-5	0·15	0·05	0·16	−0·03	0·00
C-6	−0·33	−0·11	−0·68	−0·26	−0·28
C-7	−1·41	−0·22	−1·88	−0·05	−0·17
C-8	−0·12	−0·34	−0·43	−0·41	−0·28
C-9	0·47	0·17	0·52	−0·35	−0·38
C-10	−0·05	0·01	0·10	−0·08	−0·08
C-11	0·58	0·70	0·24	−0·28	−0·33
C-12	−6·94	−1·16	−4·02	1·04	−0·68
C-13	2·07	4·73	7·69	−0·15	−0·40
C-14	−3·15	−4·04	−2·58	−0·63	0·83
C-15	−4·35	−1·76	−5·38	0·34	−0·11
C-16	7·76	9·94	14·15	−3·14	−2·43
C-17	41·08	40·61	180·50	4·67	6·21
C-18	−2·36	−7·05	−5·94	−0·14	0·49
C-19	0·03	0·01	−0·11	−0·07	−0·05

[a] Substituted and reference compounds are given in parentheses; [b] defined as: δ(R–OCONHCO.CCl_3) − δ(R–OH).

to the 17α-OH and 17β-OH derivatives. Similar values of substitution effects due to the 17-OH group have also been described[10] in the 14α-steroid series (C-12: −7·4 and 2·1 ppm; C-18: −0·4 and −6·4 ppm). Less marked are the differences in chemical shifts in the ^{1}H NMR spectra (H-18: δ 1·04 and 1·06; H-17: δ 3·75 and 3·68 for *XI* and *XIV*, respectively) as well as in the trichloroacetyl isocyanate-induced shifts (TAI-induced shifts, see Table III). The splitting of the H-17 proton signal and the coupling constants J(17, 16α) and J(17, 16β) differ substantially (triplet with J = 8·3 Hz for *XI* as compared with a doublet of doublets, J = 6·0 and 0·9 Hz, for *XIV*); however, without knowledge about the conformation of the five-membered D-ring these data cannot be utilized for an unequivocal determination of configuration at C-17.

The obtained ^{13}C NMR data for compounds *X*, *XI*, *XIV* and *XVI* enabled us to express the substitution effects connected with introduction of a 17α-OH, 17β-OH and 17-oxo group into the skeleton of androst-5-ene with the less common 14β-configuration. These data might be employed for ^{13}C NMR structural analyses or signal assignment in substituted derivatives containing this skeleton. Of similar use may also be the TAI-acylation induced shifts of the 17-OH group, given in Table III.

EXPERIMENTAL

Melting points were determined on a micro melting point apparatus Boetius (G.D.R.). Optical rotations were measured at 25°C on a Perkin–Elmer 141 MC polarimeter. Infrared spectra were recorded on a Perkin–Elmer PE 580 spectrometer (wavenumbers in cm^{-1}). ^{1}H NMR spectra were taken on a Tesla BS-497 (100 MHz) and/or a Varian XL-200 FT-NMR spectrometers (200 MHz) at 23°C in deuteriochloroform with tetramethylsilane as internal standard, unless stated otherwise. Chemical shifts are given in ppm (δ-scale), coupling constants (J) and width of multiplets (W) in Hz (see Table I). All values were obtained by the first order analysis. Proton decoupled ^{13}C NMR spectra (Table II) were measured on a Varian XL-200 instrument (50·3 MHz) with the same solutions and using "attached proton test" pulse sequence for the determination of directly bonded protons. Mass spectra were recorded on a VG Analytical ZAB-EQ spectrometer (energy of ionizing electrons 70 eV, ion source temperature 170–200°C). Flash column chromatography was performed on silica gel (60–120 μm) or neutral alumina. (grade II, Reanal), preparative HPLC on Lichrosorb SI 100 (Merck, 10 μm) using stainless steel column (12·6 × 500 mm), thin-layer chromatography on silica gel G according to Stahl (ICN Biochemicals). Spots were detected by spraying with sulfuric acid followed by heating. Prior to evaporation, solutions in organic solvents were dried over anhydrous sodium sulfate.

3β-Hydroxyandrosta-5,14-dien-17-one (*II*) and 3β-Hydroxy-14β-androsta-5,15-dien-17-one (*III*) and their Isomerization

The bromo ketone *I* (7·00 g, 19·1 mmol) was converted into a crude mixture of unsaturated ketones *II* and *III* as described in ref.[8]. After filtration through an alumina column (150 g, benzene–acetone 10 : 1), the product (5·0 g) could be used for further synthesis.

Separation of this mixture by chromatography on a column of silica gel (300 g) in benzene–ethyl acetate (20 : 1) afforded 2·7 g (49%) of ketone *II*, m.p. 169–171 C (ref.[3] m.p. 280–282°C;

ref.[8] m.p. 167–168°C) and 2·2 g (40%) of ketone *III*, m.p. 221–222°C (reported[8] m.p. 216 to 217°C).

Base-catalyzed isomerization: A mixture of the unsaturated ketone (5 mg), ethanol (1 ml) and potassium carbonate (5 mg) was stirred at room temperature until the equilibrium was achieved (2–3 days, monitoring by TLC). The undissolved carbonate was filtered off, washed with chloroform, the combined filtrates were concentrated and the residue was extracted with chloroform. The extract was filtered and the solvent evaporated. The ratio *II* : *III* was determined from integration of the angular methyl signals in ^{1}H NMR spectrum of the residue (H-18: *II* 1·14 s, *III* 1·10 s; H-19: *II* 1·07 s, *III* 1·00 s).

Acid-catalyzed isomerization: The ketones were isomerized with hydrochloric acid (50 µl) in the same manner as described for the base-catalyzed reaction. The work-up consisted in several coevaporation with ethanol (5 ml) and drying.

6β-Methoxy-3α,5α-cyclo-14β-androstan-17-one (*VIII*)

The mixture of unsaturated ketones *II* and *III* (5·0 g; from 7·0 g (19·1 mmol) of the bromoketone *I*), obtained in the preceding experiment, was dissolved in pyridine (100 ml) and stirred with methanesulfonyl chloride (4·6 ml, 59 mmol) in an ice-bath for 1 h. After pouring onto ice, the mixture was extracted with ether, the ethereal layer was washed successively with 10% hydrochloric acid, saturated sodium chloride and potassium hydrogen carbonate solutions, dried and the solvent was evaporated. The crude mixture of mesyl derivatives *IV* and *V* was dissolved in dioxane (35 ml) and methanol (75 ml), mixed with freshly fused potassium acetate (5·0 g, 51 mmol) and the mixture was refluxed for 2 h. After concentration to a small volume, the mixture was poured into water and extracted with ether. The ethereal solution was washed with saturated potassium hydrogen carbonate solution and water, dried, and the solvent was evaporated. Filtration through a column of alumina (30 g) in benzene–light petroleum (1 : 1) solution, followed by evaporation of the solvents, afforded 5·5 g of an oily mixture of the cyclo derivatives *VI* and *VII*. This mixture was hydrogenated over 10% Pd on active carbon (0·5 g) in 96% ethanol (0·5 l) in the presence of potassium carbonate (0·5 g) for 5 h. The catalyst was filtered off, the solvent evaporated and the residue chromatographed on alumina (150 g) in benzene–light petroleum to give 3·3 g (57% related to bromo ketone *I*) of the ketone *VIII*, which after crystallization from ether–hexane melted at 108–109°C; $[\alpha]_D$ +99° (*c* 0·2, chloroform). IR spectrum (tetrachloromethane): 3 060 (CH, cyclopropane); 2 820 (OCH_3); 1 737 (C=O); 1 094 (C–O). For $C_{20}H_{30}O_2$ (302·5) calculated: 79·42% C, 10·00% H; found: 79·28% C, 9·84% H.

3β-Hydroxy-14β-androst-5-en-17-one (*IX*)

A mixture of the cyclo derivative *VIII* (2·00 g, 6·61 mmol), acetone (40 ml) and 50% perchloric acid (4 ml) was stirred at room temperature for 2 h. The solution was concentrated to a small volume, diluted with a mixture of ether and dichloromethane (1 : 5), washed with a saturated solution of sodium hydrogen carbonate (2×), dried and filtered through a column of alumina (20 g). The solvent was evaporated and the residue (1·98 g) purified by chromatography on silica gel (100 g) in benzene–acetone (25 : 1) and crystallization from acetone; yield 1·30 g (68%) of *IX*, m.p. 179–180°C, $[\alpha]_D$ +60° (*c* 0·2, chloroform). Reported[5] m.p. 160–162°C, $[\alpha]_D$ +72·6° (*c* 0·05, chloroform). IR spectrum (chloroform): 3 610, 3 440 (O–H); 1 730 (C=O); 1 674 (C=C). For $C_{19}H_{28}O_2$ (288·4) calculated: 79·12% C, 9·78% H; found: 79·29% C, 9·82% H.

17-Oxo-14β-androst-5-en-3β-yl Acetate (*X*)

The hydroxy derivative *IX* (800 mg, 2·78 mmol) was acetylated by treatment with a mixture of pyridine (20 ml) and acetic anhydride (2 ml) overnight. The mixture was poured into ice-cold water and extracted with ether. The ethereal layer was washed with 10% hydrochloric acid and water, dried, filtered through a column of alumina (20 g) and the solvent was evaporated. The residue was crystallized from dichloromethane–hexane to give 813 mg (89%) of acetyl derivative *X*, m.p. 172–173°C, $[\alpha]_D$ +42° (*c* 0·2, chloroform). IR spectrum (tetrachloromethane): 1 736 (C=O); 1 675 (C=C); 1 244, 1 034 (C–O). For $C_{21}H_{30}O_3$ (330·5) calculated: 76·33% C, 9·15% H; found: 76·16% C, 9·33% H. The yield of *X* could be increased to 80% (related to the derivative *VIII*) when the crude hydroxy derivative *IX* was used.

17α-Hydroxy-14β-androst-5-en-3β-yl Acetate (*XI*)

The ketone *X* (810 mg, 2·45 mmol) was dissolved in a mixture of methanol (10 ml) and ethyl acetate (5 ml). The solution was cooled in an ice-bath to 10°C and sodium borohydride (115 mg, 3 mmol) was added during 5 min to the stirred solution. After stirring for further 5 min at the same temperature, the excess reagent was destroyed by addition of acetic acid (0·5 ml) and water (1 ml). The reaction mixture was concentrated to a minimum volume, diluted with ethyl acetate and washed successively with saturated solution of sodium chloride, 10% hydrochloric acid and saturated potassium hydrogen carbonate solution. After drying, filtration through an alumina column (20 g) and evaporation of the solvent, the residue was crystallized from a minimum volume of ether to give 742 mg (91%) of hydroxy derivative *XI*, m.p. 119–121°C, $[\alpha]_D$ −12° (*c* 0·3, chloroform). IR spectrum (chloroform): 3 610, 3 480 (O–H); 1 724 (C=O); 1 674 (C=C); 1 256 (C–O). Mass spectrum, *m/z*: 272 ($M^+ - CH_3COOH$); 257 ($M^+ - CH_3$); 254 ($M^+ - CH_3COOH - H_2O$); 239 ($M^+ - CH_3COOH - CH_3 - H_2O$). For $C_{21}H_{32}O_3$ (332·5) calculated: 75·86% C, 9·70% H; found: 75·76% C, 9·73% H.

14β-*Androst*-5-*ene*-3β,17α-*diyl diacetate* (XII), m.p. 171–172°C (ethanol), $[\alpha]_D$ −10° (*c* 0·6, chloroform), was obtained from the hydroxy derivative *XI* by acylation with acetic anhydride in pyridine at room temperature. For $C_{23}H_{34}O_4$ (374·5) calculated: 73·76% C, 9·15% H; found: 73·78% C, 9·20% H.

14β-Androst-5-ene-3β,17α-diyl 3-Acetate 17-*p*-Toluenesulfonate (*XIII*)

The hydroxy derivative *XI* (817 mg, 2·46 mmol) was tosylated with *p*-toluenesulfonyl chloride (2·00 g, 10·5 mmol) in pyridine (20 ml) overnight. The reaction mixture was poured into cold water and set aside for 1 h. The separated product was filtered, dissolved in ethyl acetate and the solution was washed successively with 10% hydrochloric aicd, potassium hydrogen carbonate solution and water. After drying and evaporation, the residue was dissolved in benzene and filtered through an silica gel column (20 g). The solvent was evaporated and the crude product (1·12 g) crystallized from acetone, affording 850 mg (71%) of the tosylate *XIII*, m.p. 179–180°C, $[\alpha]_D$ 0° (*c* 0·3, chloroform). IR spectrum (chloroform): 1 724 (C=O); 1 674 (C=C); 1 599, 1 495 (arom.); 1 365, 1 174 (SO_2); 1 250 (C–O). For $C_{28}H_{38}O_5S$ (486·7) calculated: 69·10% C, 7·87% H, 6·59% S; found: 69·37% C, 8·13% H, 6·59% S.

17β-Hydroxy-14β-androst-5-en-3β-yl Acetate (*XIV*)

A mixture of the tosyl derivative *XIII* (600 mg, 1·23 mmol), hexamethylphosphoramide (10 ml) and sodium nitrite (2·0 g, 32 mmol) was stirred at 90°C for 5 h. The reaction mixture was diluted with ethyl acetate and the solution washed with brine, 10% sulfuric acid, and potassium hydrogen

carbonate solution. After drying and evaporation of the solvent, the residue was coevaporated several times with benzene, dissolved in benzene and passed through a column of silica gel (20 g) which was then washed with benzene–ethyl acetate (10 : 1). The solvent was removed and the residue purified by HPLC in light petroleum–ethyl acetate (25 : 4) and crystallization from ether–light petroleum; yield 250 mg (61%) of hydroxy derivative *XIV*, m.p. 59–60°C, $[\alpha]_D$ 0° (*c* 0·2, chloroform). IR spectrum (chloroform): 3 616, 3 460 (O–H); 1 723 (C=O); 1 258, 1 032 (C–O). Mass spectrum, *m/z*: 272 ($M^+ - CH_3COOH$); 257 ($M^+ - CH_3COOH - CH_3$); 239 ($M^+ - CH_3COOH - CH_3 - H_2O$). For $C_{21}H_{32}O_3$ (332·5) calculated: 75·86% C, 9·70% H; found: 75·78% C, 9·75% H.

14β-*Androst*-5-*ene*-3β,17β-*diyl diacetate* (XV), m.p. 156–158°C (ethanol), $[\alpha]_D$ +8° (*c* 0·2, chloroform), was obtained from derivative *XIV* by acetylation with acetic anhydride in pyridine at room temperature. For $C_{23}H_{34}O_4$ (374·5) calculated: 73·76% C, 9·15% H; found: 73·85% C, 9·19% H.

14β-Androst-5-en-3β-yl Acetate (*XVI*)

A mixture of the tosyl derivative *XIII* (200 mg, 0·41 mmol), 1,2-dimethoxyethane (5 ml), water (5 drops), sodium iodide (300 mg, 2·00 mmol) and zinc powder (300 mg, 4·6 mmol) was stirred at 80°C for 8 h. The solid material was filtered off, the filtrate diluted with ether and washed successively with water, 10% hydrochloric acid and saturated solutions of sodium chloride, potassium hydrogen carbonate and sodium chloride. After drying and evaporation of the solvent, the residue was flash-chromatographed on a column of silica gel (10 g) in benzene–acetone (10 : 1). Subsequent chromatography on a column of silica gel, pretreated with silver nitrate[14], in light petroleum–ether (10 : 1) afforded 75 mg (58%) of deoxy derivative *XVI*, m.p. 98–99°C (ethanol), $[\alpha]_D$ −10° (*c* 0·6, chloroform). IR spectrum (chloroform): 1 725 (C=O); 1 670 (C=C); 1 257, 1 032 (C–O). For $C_{21}H_{32}O_2$ (316·5) calculated: 79·70% C, 10·19% H; found: 79·75% C, 10·21% H.

17α-Hydroxyandrost-5-en-3β-yl Acetate (*XIX*)

Tosyl derivative *XVIII* (ref.[15], 1·20 g, 2·47 mmol) was converted into hydroxy derivative *XIX* as described for compound *XIV*, except that the reaction time was 52 h; yield 410 mg (50%) of *XIX*, m.p. 139–141°C (acetone), $[\alpha]_D$ −81° (*c* 0·2, chloroform). IR spectrum (chloroform): 3 616, 3 460 (O–H); 1 723 (C=O); 1 258, 1 032 (C–O). For $C_{21}H_{32}O_3$ (332·5) calculated: 75·86% C, 9·70% H; found: 75·71% C, 9·75% H.

Androst-5-*ene*-3β,17α-*diyl diacetate* (XX), m.p. 166–167°C (ethanol), $[\alpha]_D$ −74° (*c* 0·2, chloroform), was obtained from the hydroxy derivative *XIX* by acetylation with acetic anhydride in pyridine at room temperature. For $C_{23}H_{34}O_4$ (374·5) calculated: 73·76% C, 9·15% H; found: 73·81% C, 9·21% H.

Androst-5-*ene*-3β,17α-*diol* (XXI), m.p. 195–196°C (subl.), $[\alpha]_D$ −85° (*c* 0·2, chloroform), was obtained by deacetylation of the diacetate *XX* by 5 minutes' boiling with 10% potassium hydroxide in dioxane–methanol. Reported[15] m.p. 197°C, $[\alpha]_D$ −56° (*c* 1, chloroform).

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