ANTIANDROGENIC A-HOMO-B,19-DINORANDROSTANES FROM 5β-METHYL-19-NORANDROST-9-ENES WITH DIFFERENT SUBSTITUENTS IN POSITIONS 3 AND 17*

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Westphalen-type derivatives *II*, *IV* and *VIII* were converted into derivatives of 4a-methyleno-A-homo-B,19-dinor-5β-androst-9-ene with different substituents in positions 3 and 17 (compounds *XII*, *XIII* and *XV*) which were utilized for the preparation of the antiandrogenic 17β-hydroxy-4aα-methyl-A-homo-B,19-dinor-5β,10α-androstan-3-one (*I*).

In our previous communication[1] we described the preparation of antiandrogenic dihydrotestosterone analogue *I* by a procedure based on elimination with rearrangement of Westphalen-type 6β-chloro derivatives *II*, followed by hydrogenation and partial transformation of the individual hydroxyl groups. Since neither partial oxidation (or acylation) of 4aα-methyl-A-homo-B,19-dinor-5β,10α-androstane-3β, 17β-diol nor partial hydrolysis of its diesters proceeded with sufficient selectivity[1], we performed the same reaction sequence with substrates, containing already suitably protected groups in positions 3 and 17. Because acyl groups were used for the protection, the elimination of hydrogen chloride with rearrangement could not be effected with lithium aluminium hydride in boiling dioxane, as descibed in the previous paper[1]. As the starting compound we used again the known[2] 3β-acetoxy-6β-chloro-5-methyl-19-nor-5β-androst-9-en-17-one (*II*) which was reduced and the obtained 17β-alcohol *III* was benzoylated to give the corresponding diester *IV*. Partial hydrolysis of *IV* afforded quantitatively the 3-alcohol *V* which was oxidized to the 3-ketone *VI* (see Scheme 1).

Treatment of the 3-ketone *VI* with silver acetate in boiling acetic acid under argon did not afford the expected diene *VII* but, instead, a compound containing one more oxygen atom (mass spectrum: 406 *m/z*). To protect the possibly arising diene *VII* from the undesired oxidation, the dehydrohalogenation of compound *VI* was performed under conditions of catalytic hydrogenation over Raney nickel in ethanol

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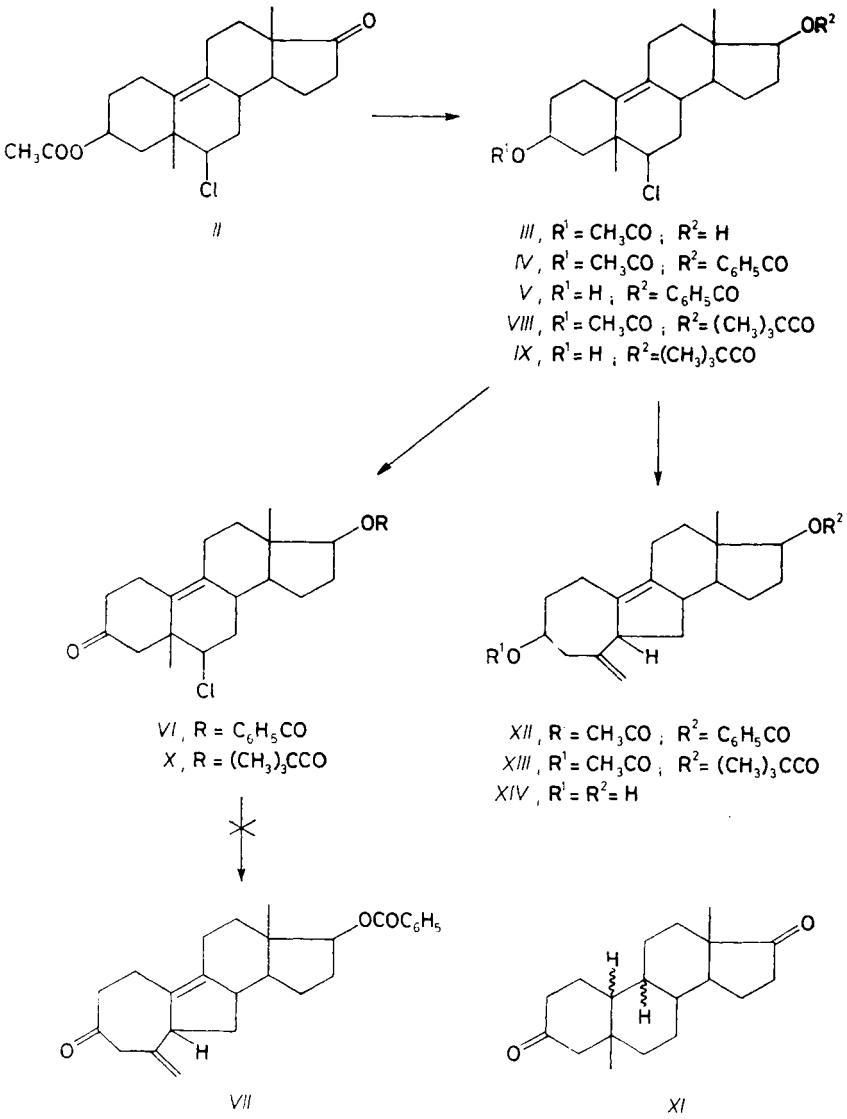
at 100°C and 10 MPa; however, this reaction gave a mixture of dihydroxy derivatives arising by reduction of the 3-keto group and hydrolysis of the 17-benzoyloxy group. In order to suppress this hydrolysis, the 17β-hydroxyl was protected by esterification with pivalic acid: the acetoxy alcohol *III* was acylated to give the 17-pivalate *VIII* which was smoothly partially hydrolyzed and the obtained 3-alcohol *IX* was oxidized to the 3-keto derivative *X*. After treatment of compound *X* with Raney nickel, the



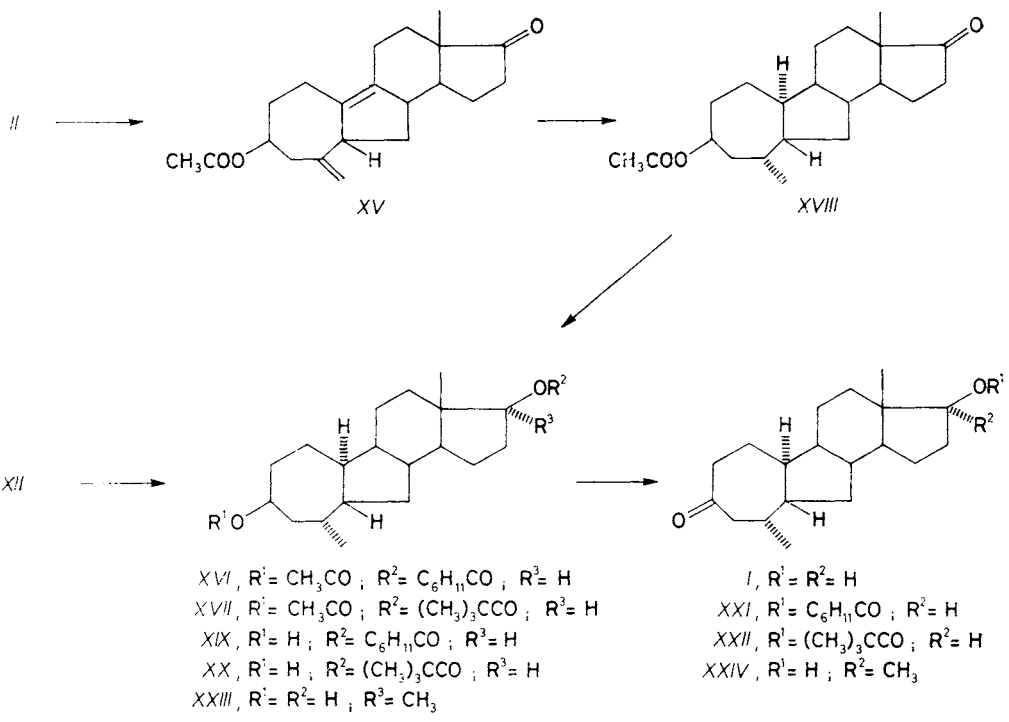
SCHEME 1

product still contained different substituents in positions 3 and 17 (hydroxy and pivaloyloxy groups) but, however, the elimination proceeded predominantly without rearrangement. The principal product of hydrogenolysis, followed by hydrolysis and oxidation (*XI*), exhibited in the ^{1}H NMR spectrum a singlet of 5β-CH_3 which has proven that the loss of 6β-chlorine atom in the chloro derivative *X* had not been accompanied by Wagner–Meerwein rearrangement[3] observed with compounds of this type in reactions with lithium aluminium hydride or silver acetate[4]. We did not determine the configuration in positions 9 and 10 in the compound *XI*; it is however known[5] that catalytic hydrogenation of a Δ^9-double bond is not stereoselective, leading to the 9β,10β-, 9α,10β- and 9β,10α-isomers. Therefore, the idea of transformation of a differently substituted Westphalen-type substrate was applied to the diesters *IV* and *VIII*; the reaction of the 3β-alcohol *V* afforded lower yields because part of the product was acetylated in the acetolysis reaction.

The acetolysis of 6β-chloro derivatives *IV* and *VIII* with silver acetate in boiling acetic acid furnished the dienes *XII* and *XIII* whose structure was proven by conversion into the previously prepared[1] 4a-methyleno-A-homo-B,19-dinor-5β-androst-9-one-3β,17β-diol (*XIV*); because this system was sensitive to oxygen, the acyl groups were removed by reduction with lithium aluminium hydride.

Another type of substrate, differently substituted in positions 3 and 17, is represented by the 3-acetoxy-17-ketone *II*, which under the described conditions afforded the diene *XV*. The infrared spectrum of compound *XV* confirmed the presence of a carbonyl group in a five-membered ring, an acetoxy and an exomethylene group in the molecule. An exomethylene group was also proven by a broad two-proton singlet at δ 4·98 and a triplet of H-5β at δ 3·30 in the ^{1}H NMR spectrum. The structure of compound *XV* was finally confirmed by reduction with lithium aluminium hydride leading to the known[1] unsaturated diol *XIV*.

The dienes *XII*, *XIII* and *XV* were further subjected to catalytic hydrogenation over platinum, which in the case of the 17-ketone was followed by reoxidation of the formed mixture of 17-alcohols. This led to mixture of perhydro derivatives in which the more laevorotatory and more lipophilic components were assigned the structure of 4aα-methyl-A-homo-B,19-dinor-5β,10α-androstane derivatives *XVI* to *XVIII*, in analogy to our previous work[1]. To obtain the desired dihydrotestosterone analogues from the first two products, the easily hydrolyzable acetoxy group was quantitatively removed by acid-catalyzed transesterification with methanol under formation of the 3-alcohols *XIX* and *XX*. In the hydrogenation, the benzoyloxy group was reduced to the cyclohexanecarbonyloxy group which, however, could be differentiated from the acetoxy group in the hydrolysis reaction. Oxidation of these compounds afforded the keto esters *XXI* and *XXII*; the former was directly hydrolyzed to the desired 3-keto-17 alcohol *I*, whereas the latter was heated with lithium aluminium hydride after protection of the 3-oxo group as 1,3-dioxolane (see Scheme 2).



SCHEME 2

The saturated acetoxy ketone *XVIII* could be transformed into the keto alcohol *I* as already described[1]; on the other hand, compound *XVIII* also represented suitable starting material for the preparation of 17α-methyl derivative of compound *I*, which, according to our previous experience, might exhibit still better pharmacodynamic properties. Reaction with methyllithium converted the compound *XVIII* into the 17α-methyl derivative *XXIII* (the configuration at C-17 was assigned by analogy with reactions of standard 17-ketosteroids) which was oxidized to give the desired A-homo-B,19-dinor analogue of 17α-methyldihydrotestosterone *XXIV*.

This procedure, which uses conditions tolerating different substituents in positions 3 and 17, proved to be more advantageous than the previously published one[1].

EXPERIMENTAL

The melting points were determined on a Kofler block and are uncorrected. Optical rotations and IR spectra (Zeiss UR 20) were measured in chloroform solutions, unless stated otherwise (wavenumbers given in cm^{-1}). ^1H NMR spectra were measured in deuteriochloroform with tetramethylsilane as internal standard on a Tesla BS 467 instrument (60 MHz, CW-mode),

chemical shifts are given in ppm (δ-scale), coupling constants (J) and half-height widths (W) in Hz; all parameters were obtained by analysis of the first order. Mass spectra were measured on an AEI MS 902 spectrometer, relative intensities (referenced to the base peak) and assignments are given in parentheses. Identity of compounds, prepared by different procedures, was proven by mixture melting points and comparison of IR spectra. The reaction course was followed, and purity of the samples checked, by thin-layer chromatography (TLC) on silica gel Woelm DC, spots were detected with sulfuric acid and heating. Separation of the compounds was carried out by column flash chromatography[6] on silica gel Silpearl (Kavalier, Votice) or by preparative thin-layer chromatography on silica gel (200 × 200 × 0·7 mm, Woelm DC), detection at 254 nm after spraying with 2% solution of morine in methanol.

6β-Chloro-5-methyl-19-nor-5β-androst-9-ene-3β,17β-diol 3-Acetate (*III*)

Lithium tert-butoxyaluminium hydride (15 g) was added at room temperature to a stirred solution of acetoxy ketone[2] *II* (7·4 g) in tetrahydrofuran (46 ml). After stirring for 1 h, the mixture was poured into dilute hydrochloric acid (5%) and ice, the product was taken up in chloroform, the organic extract was washed with water, dilute solution of potassium hydrogen carbonate and water, and dried over sodium sulfate. Yield 6·9 g (93%), m.p. 130–132°C (toluene), $[\alpha]_D$ +140° (*c* 1·1). IR spectrum: 3 615, 1 034 (OH); 1 725, 1 250, 1 018 (AcO). ^{1}H NMR spectrum: 0·88 s, 3 H (3 × H-18); 1·25 s, 3 H (3 × H-19); 2·06 s, 3 H (CH_3COO); 3·64 t, 1 H (H-17, J = 8); 3·94 dd, 1 H (H-6, J = 4·5, J' = 11·5); 5·08 t, 1 H (H-3, J = 3·5). For $C_{21}H_{31}ClO_3$ (366·9) calculated: 68·74% C, 8·52% H, 9·66% Cl; found: 68·40% C, 8·61% H, 9·28% Cl.

6β-Chloro-5-methyl-19-nor-5β-androst-9-ene-3β,17β-diol 3-Acetate 17-Benzoate (*IV*)

Benzoyl chloride (2 ml) was added to a solution of the 17-alcohol *III* (3 g) in pyridine (10 ml), the mixture was set aside at room temperature for 2 h and decomposed by pouring in water. The separated product was extracted with ethyl acetate, the extract was washed successively with dilute hydrochloric acid (5%), water, potassium carbonate solution and water. After drying over sodium sulfate, the solvent was evaporated in vacuo and the dry residue was crystallized from acetone, affording 3 g (78%) of the title compound, m.p. 163–164°C; $[\alpha]_D$ +188° (*c* 1·5). IR spectrum (CCl_4): 1 738, 1 242, 1 015 (CH_3COO); 1 721, 1 264 (C_6H_5COO). ^{1}H NMR spectrum: 1·05 s, 3 H (3 × H-18); 1·25 s, 3 H (3 × H-19); 2·05 s, 3 H (CH_3COO); 4·00 dd, 1 H (6-H J = 4·5, J' = 11·5); 4·87 t, 1 H (17-H, J = 8); 5·10 m, 1 H (3-H, W = 10); 7·47 m and 8·05 m, 5 H (C_6H_5COO). For $C_{28}H_{35}ClO_4$ (471·0) calculated: 71·39% C, 7·49% H, 7·53% Cl; found: 71·37% C, 7·26% H, 7·29% Cl.

6β-Chloro-5-methyl-19-nor-5β-androst-9-ene-3β,17β-diol 17-Benzoate (*V*)

A solution of concentrated hydrochloric acid (39 ml) in methanol (430 ml) was added to a solution of the diester *IV* (12·8 g) in chloroform (120 ml). After standing at 40°C for 60 h, the mixture was concentrated in vacuo to quarter of the original volume, diluted with water, and the separated product was filtered and washed with water. Yield 10·6 g (91%) of compound *V*, m.p. 176–178°C (chloroform–methanol); $[\alpha]_D$ +211° (*c* 0·8). IR spectrum: 3 615 (OH); 1 711, 1 281 (C_6H_5COO). ^{1}H NMR spectrum: 1·05 s, 3 H (3 × H-18); 1·32 s, 3 H (3 × H-19); 3·97 dd, 1 H (H-6, J = 4·5, J' = 11·5); 4·12 m, 1 H (H-3, W = 10); 4·87 t, 1 H (H-17, J = 8); 7·47 m and 8·05 m, 5 H (C_6H_5COO). For $C_{26}H_{33}ClO_3$ (429·0) calculated: 72·79% C, 7·75% H, 8·27% Cl; found: 72·53% C, 7·82% H, 7·96% Cl.

17β-Hydroxy-6β-chloro-5-methyl-19-nor-5β-androst-9-en-3-one 17-Benzoate (*VI*)

To a solution of hydroxy derivative *V* (2 g) in chloroform (10 ml) was added acetone (10 ml) and then dropwise Jones reagent (in excess) at room temperature. After 10 min the mixture was poured into an aqueous solution of potassium hydrogen carbonate, the product was taken up in chloroform, the extract was washed with water, dried over sodium sulfate, filtered through a column of alumina and the solvent was evaporated in vacuo to dryness; yield 1·7 g (85%) of *VI*, m.p. 159–161°C (ethanol), $[\alpha]_D$ +158° (*c* 1·1). IR spectrum (CCl_4): 1 720, 1 273. ^{1}H NMR spectrum: 1·07 s, 3 H (3 × H-18); 1·17 s, 3 H (3 × H-19); 4·04 dd, 1 H (H-6, $J = 4$, $J' = 10$); 4·88 t, 1 H (H-17, $J = 7·5$); 7·47 m and 8·05 m, 5 H (C_6H_5COO). For $C_{26}H_{31}ClO_3$ (427·0) calculated: 73·13% C, 7·32% H, 8·30% Cl; found: 73·06% C, 7·06% H, 79·93% Cl.

6β-Chloro-5-methyl-19-nor-5β-androst-9-ene-3β,17β-diol 3-Acetate 17-Pivalate (*VIII*)

Hydroxy derivative *III* (7·39 g) was dried by distillation with benzene, dissolved in pyridine (20 ml) and mixed with pivaloyl chloride (12 ml). The mixture was set aside at room temperature for 18 h, poured into an ice-water mixture and the product was taken up in ether. The extract was washed successively with dilute hydrochloric acid (5%), water, potassium hydrogen carbonate and water, and dried over sodium sulfate. The solvent was evaporated in vacuo to dryness to give compound *VIII* (6·6 g, 81%), m.p. 163–165°C (methanol), $[\alpha]_D$ +146° (*c* 1·5). IR spectrum: 1 727, 1 254, 1 024 (CH_3COO); 1 713 shoulder, 1 177 ($(CH_3)_3CCOO$). ^{1}H NMR spectrum: 0·91 s, 3 H (3 × H-18); 1·17 s, 3 H (3 × H-19); 1·23 s, 9 H ($(CH_3)_3CCOO$); 2·03 s, 3 H (CH_3COO); 3·94 dd, 1 H (H-6, $J = 4·5$, and $J' = 12$); 4·58 t, 1 H (H-17, $J = 7·5$); 5·08 m, 1 H (H-3, $W = 10$). For $C_{26}H_{39}ClO_4$ (451·0) calculated: 69·23% C, 8·72% H, 7·86% Cl; found: 69·50% C, 8·92% H, 8·01% Cl.

6β-Chloro-5-methyl-19-nor-5β-androst-9-ene-3β,17β-diol 17-Pivalate (*IX*)

Concentrated hydrochloric acid (3 ml) was added to a solution of acetate *VIII* (1·4 g) in chloroform (5 ml) and methanol (50 ml). After standing at room temperature for 20 h, the mixture was concentrated in vacuo to a quarter of the original volume and then set aside at 0°C for 30 min. The crystalline product *IX* was filtered and washed with cold methanol; yield of compound *IX* was 0·97 g (76%), m.p. 162–164°C (methanol). IR spectrum (CCl_4): 3 620 (OH); 1726, 1 396, 1 360, 1 160 ($(CH_3)_3CCOO$). ^{1}H NMR spectrum: 0·93 s, 3 H (3 × H-18); 1·32 s, 3 H (3 × H-19); 1·18 s, 9 H ($(CH_3)_3CCOO$); 3·95 dd, 1 H (H-6, $J = 4·5$, $J' = 12$); 4·10 m, 1 H (3-H, $W = 10$); 4·58 t, 1 H (H-17, $J = 7·5$). For $C_{24}H_{37}ClO_3$ (40·9·0) calculated: 70·47% C, 9·12% H, 8·67% Cl; found: 70·18% C, 8·98% H, 8·33% Cl.

17β-Hydroxy-6β-chloro-5-methyl-19-nor-5β-androst-9-en-3-one 17-Pivalate (*X*)

To a solution of hydroxy derivative *IX* (40 mg) in acetone (3 ml) was added Jones reagent (in excess) at room temperature. After 10 min the mixture was poured into a solution of potassium hydrogen carbonate and the product was extracted with chloroform. The extract was washed with dilute hydrochloric acid (5%) and water, dried over sodium sulfate and concentrated in vacuo. The dry residue was purified by preparative TLC (one plate) on silica gel in benzene, affording 32 mg (80%) of compound *X*, m.p. 147–149°C (acetone–water); $[\alpha]_D$ +165° (*c* 0·8). IR spectrum (CCl_4): 1 726, 1 285, 1 165. ^{1}H NMR spectrum: 0·96 s, 3 H (3 × H-18); 1·16 s, 3 H (C × H-19); 1·20 s, 9 H ($(CH_3)_3CCOO$); 4·02 dd, 1 H (H-6, $J = 4·5$, $J' = 10$); 4·60 t, 1 H (H-17, $J = 7·5$). For $C_{24}H_{35}ClO_3$ (406·9) calculated: 70·82% C, 8·67% H, 8·71% Cl; found: 70·43% C, 9·01% H, 8·39% Cl.

5-Methyl-19-nor-5β,9ξ,10ξ-androstane-3,17-dione (*XI*)

A solution of ketone *X* (1·5 g) in ethanol (50 ml) was shaken with Raney nickel (5 ml) in an atmosphere of hydrogen at 100°C and 10 MPa. After 6 h the mixture was cooled, and freed of inorganic material by filtration through Celite which was then washed with methanol (100 ml). The filtrate was taken down and the dry residue (1·5 g) was analyzed. Its ^{1}H NMR spectrum showed the absence of C—Cl and C=CH bods and the presence of a pivaloyloxy group. The material was reduced with lithium aluminium hydride and chromatographed on a column of silica gel in acetone–ligroin (1 : 12). A fraction of the same polarity as 4aα-methyl-A-homo-B,19-dinor--5β,10α-androstane-3β,17β-diol[1] (284 mg), m.p. 163—167°C (acetone–heptane) was obtained (however, an authetic sample of the mentioned compound melts at 185—186°C). ^{1}H NMR spectrum: 0·86 s, 6 H (3 × 18-H and 3 × 19-H); 3·92 t, 1 H (H-17, J = 7·5); 4·11 m, 1 H (H-3, W = 10). On oxidation with Jones reagent this product afforded a mixture of diketones. The principal chromatographically isolated component was the diketone *XI*, (210 mg, 20%), m.p. 133—140°C (acetone–heptane). IR spectrum (CCl_4): 1 741 (C=O in five-membered ring), 1 721 (C=O in six-membered ring). Mass spectrum, m/z: 288. ^{1}H NMR spectrum: 0·88 s, 3 H (3 × H-18); 0·98 s' 3 H (3 × H-19).

4a-Methyleno-A-homo-B,19-dinor-5β-androst-9-ene-3β,17β-diol 3-Acetate 17-Benzoate (*XII*)

To a suspension of silver acetate (7 g) in acetic acid (160 ml) was added 6β-chloride *IV* (2 g). After refluxing under argon for 20 h, the mixture was cooled and filtered (under pressure) through Celite. The acetic acid was evaporated to dryness in vacuo, the residue was codistilled with toluene and dissolved in chloroform. The solution was washed with a potassium hydrogen carbonate solution and water, dried over sodium sulfate and concentrated in vacuo to 5 ml. The solution was mixed with silica gel (10 ml), the solvent was evaporated in vacuo and the residue was layered on a column of Silpearl (200 ml) and subjected to flash-chromatography in ethyl acetate–toluene (1 : 50) to give 820 mg (44%) of compound *XII*, m.p. 133—134°C (acetone–-heptane), $[\alpha]_D$ +85° (*c* 0·9). IR spectrum: 1 720, 1 263 (CH_3COO); 1 711 shoulder, 1 289, 1 281 (C_6H_5COO). ^{1}H NMR spectrum: 1·02 s, 3 H (3 × H-18); 2·00 s, 3 H (CH_3COO); 3·38 t, 1 H (5β-H, J = 8); 4·80 m, 2 H (H-3 and H-17, W = 21); 4·93 bd, 2 H (2 × H-4b, W = 4); 7·47 m and 8·05 m, 5 H (C_6H_5COO). For $C_{28}H_{34}O_4$ (434·6) calculated: 77·39% C, 7·89% H; found: 77·43% C, 7·59% H.

4a-Methyleno-A-homo-B,19-dinor-5β-androst-9-ene-3β,17β-diol 3-Acetate 17-Pivalate (*XIII*)

Pivalate *VIII* (1·5 g) was converted into diene *XIII* by treatment with silver acetate as described in the preceding experiment; yield 0·55 g (40%) of *XIII*, m.p. 101—102°C (acetone–heptane), no depression on admixture with the previously prepared sample[4]. ^{1}H NMR spectrum: 0·90 s, 3 H (3 × H-18); 1·19 s 9 H ($(CCH_3)_3CCOO$); 1·99 s, 3 H (CH_3COO); 3·35 t, 1 H (H-5β, J = 8); 4·63 m, 2 H (H-3 and H-17, W = 25); 4·89 bs, 1 H and 4·95 bs, 1 H (2 × H-4b).

4a-Methyleno-A-homo-B,19-dinor-5β-androst-9-ene-3β,17β-diol (*XIV*)

A) From diester *XII*. An excess of lithium aluminium hydride (about 100 mg) was added to a solution of diene *XII* (96 mg) in tetrahydrofuran (5 ml) and the mixture was refluxed in an atmosphere of nitrogen. After 1 h the excess hydride was decomposed with ethyl acetate and several drops of water, the mixture was saturated with solid sodium sulfate and the inorganic material was filtered. The filtrate was concentrated in vacuo and the residue was subjected to TLC (2 plates) in benzene–ether (5 : 1; the ether was distilled from lithium aluminium hydride

immediately before use). The main zone was washed with peroxide-free ether, yielding 38 mg (59%) of diol *XIV*, identical with a previously prepared sample[1].

B) From acetoxy ketone *XV*. Compound *XV* (74 mg) was reduced analogously as described under *A*); yield of *XIV* 32 mg (49%).

C) From diester *XIII*. Compound *XIII* (86 mg) was reduced similarly as described under *A*) affording 34 mg (60%) of *XIV*.

3β-Acetoxy-4a-methyleno-A-homo-B,19-dinor-5β-androst-9-en-17-one (*XV*)

Similarly as described for the preparation of compound *XII*, 6β-chloride *II* (1 g) was treated with silver acetate (3 g) in boiling acetic acid (80 ml) under argon. After 18 h the mixture was worked up and the product was flash-chromatographed on Silpearl in toluene–ethyl acetate (97 : 3) to yield 435 mg (48%) of compound *XV*, m.p. 94–95°C (acetone–heptane), $[\alpha]_D$ +131° (*c* 1·0). IR spectrum: 3 075, 1 642, 903 (C=CH_2); 1 742, 1 405 (–$COCH_2$); 1 742, 1 246, 1 028 (CH_3COO). ^{1}H NMR spectrum: 0·96 s, 3 H (3 × H-18); 2·0 s, 3 H (CH_3COO); 3·37 t, 1 H (H-5β, J = 8); 4·75 m, 1 H (H-3, W' = 19); 4·95 bs and 5·01 bs, 2 × 1 H (2 × H-4b). Mass spectrum, *m/z*: 328 (M^+, 47%); 268 (M^+ – CH_3COOH, 100%); 253 (36%); 211 (29%); 172 (33%). For $C_{21}H_{28}O_3$ (328·4) calculated: 76·69% C, 8·59% H; found: 76·32% C, 8·19% H.

4aα-Methyl-A-homo-B,19-dinor-5β,10α-androstane-
3β,17β-diol 3-Acetate 17-Cyclohexanecarboxylate (*XVI*)

A solution of diene *XII* (3·6 g) in acetic acid (35 ml) was shaken in an atmosphere of hydrogen with platinum oxide (200 mg) at room temperature. After 6 h the catalyst was filtered off, the filtrate was concentrated in vacuo to dryness and the residue was chromatographed on silica gel in toluene to give 1·44 g (42%) of compound *XVI*, $[\alpha]_D$ –34° (*c* 1·0). ^{1}H NMR spectrum: 0·81 s, 3 H (3 × H-18); 0·90 d, 3 H (3 × H-4b, J = 6·5); 4·63 t, 1 H (H-17, J = 7·5); 4·91 m, 1 H (H-3, W = 23). For $C_{28}H_{44}O_4$ (444·6) calculated: 75·63% C, 9·97% H; found: 75·13% C, 10·06% H.

4aα-Methyl-A-homo-5,19-dinor-5β,10α-androstane-
3β,17β-diol 17-Cyclohexanecarboxylate (*XIX*)

A solution of 3β-acetoxy derivative *XVI* (1·2 g) in chloroform (10 ml) was mixed with a solution of concentrated hydrochloric acid (2 ml) in methanol (100 ml). After standing at room temperature for 48 h, the mixture was concentrated in vacuo to a quarter of the original volume, diluted to the original volume with chloroform and again concentrated. The concentrated solution was washed with water, potassium hydrogen carbonate and dried over sodium sulfate. Evaporation of the solvent afforded 930 mg (86%) of *XIX*, m.p. 141–143°C (methanol); $[\alpha]_D$ –48° (*c* 1·2). IR spectrum: 3 610, 1 038 (OH); 1 719, 1 712 shoulder, 1 182 (C=O). ^{1}H NMR spectrum: 0·79 s, 3 H (3 × H-18); 0·90 d, 3 H (3 × H-4b, J = 6·5); 3·92 t, 1 H (H-3, W = 23); 4·62 m, 1 H (H-17, J = 7·5). For $C_{26}H_{42}O_3$ (402·6) calculated: 77·56% C, 10·52% H; found: 77·40% C, 10·39% H.

4aα-Methyl-A-homo-B,19-dinor-5β,10α-androstane-3β,17β-diol
3-Acetate 17-Pivalate (*XVII*)

A solution of diene *XIII* (270 mg) in acetic acid (4 ml) was shaken in an atmosphere of hydrogen with platinum oxide (40 mg) at room temperature. After 6 h the mixture was worked up as described in the preceding experiments and the product was purified by TLC on silica gel (6 plates)

in toluene–ether (33 : 1). Yield of compound *XVII* was 130 mg (48%); m.p. 113–115°C (methanol), $[\alpha]_D$ −36° (*c* 0·9). IR spectrum (CCl_4): 1 738, 1 251 (CH_3COO); 1 738, 1 288, 1 166 ($(CH_3)_3$.CCOO). ^{1}H NMR spectrum: 0·82 s, 3 H (3 × H-4b, J = 6·5); 1·19 s, 9 H ($(CH_3)_3CCOO$); 2·0 s, 3 H (CH_3COO); 4·57 t, 1 H (H-17, J = 7·5); 5·04 m, 1 H (H-3, W = 22). 0·89 d, 3 H (3 × × H-4b, J = 6·5). For $C_{26}H_{42}O_4$ (418·6) calculated: 74·60% C, 10·11% H; found: 74·39% C, 10·12% H.

4aα-Methyl-A-homo-B,19-dinor-5β,10α-androstane-3β,17β-diol 17-Pivalate (*XX*)

A solution of potassium hydroxide (200 mg) in water (0·2 ml) was poured into a solution of acetate *XVII* (340 mg) in methanol (35 ml). After standing at room temperature for 20 h, the mixture was acidified with several drops of acetic acid and concentrated in vacuo to a fifth of the original volume. The separated solid was filtered and washed with water to give 250 mg (82%) of hydroxy derivative *XX*, m.p. 149–151°C (acetone–heptane) $[\alpha]_D$ −31° (*c* 1·1). Mass spectrum, *m/z*: 358 (38, $M^+ - H_2O$), 256 (100). IR spectrum: 3 615, 1 036 (OH); 1 718, 1 293, 1 228, 1 179 ($(CH_3)_3CCOO$). ^{1}H NMR spectrum: 0·79 s, 3 H (3 × H-18); 0·89 d, 3 H (3 × H-4b, J = 6·5); 1·18 s, 9 H ($(CH_3)_3CCOO$); 3·90 m, 1 H (H-3, W = 23); 4·57 t, 1 H (H-17, J = 7·5). For $C_{24}H_{40}O_3$ (376·6) calculated: 76·55% C, 10·71% H; found: 76·60% C, 10·58% H.

17β-Hydroxy-4aα-methyl-A-homo-B,19-dinor-5β,10α-
-androstan-3-one 17-Cyclohexanecarboxylate (*XXI*)

Jones reagent (in excess) was added dropwise at room temperature to a stirred solution of 3β-hydroxy derivative *XIX* (802 mg) in acetone (20 ml). After 5 min the mixture was worked up in the usual manner, affording 765 mg of product *XXI*, m.p. 104–105°C (acetone–heptane), $[\alpha]_D$ +51° (*c* 1·1). IR spectrum (CCl_4): 1 727, 1 176 (COOR); 1 707 (C=O). ^{1}H NMR spectrum: 0·78 s, 3 H (3 × H-18); 0·94 d, 3 H (3 × H-4b, J = 6·5); 4·65 t, 1 H (H-17, J = 7·5). Mass spectrum, *m/z*: 400 (H^+), 382 ($M^+ - H_2O$), 340, 317, 289, 272, 254. For $C_{26}H_{40}O_3$ (400·6) calculated: 77·95% C, 10·07% H; found: 78·02% C, 10·11% H.

17β-Hydroxy-4aα-methyl-A-homo-B,19-dinor-5β,10α-androstan-3-one 17β-Pivalate (*XXII*)

Jones solution (in excess) was added dropwise to a solution of 3β-hydroxy derivative *XX* (40 mg) in acetone (5 ml) at room temperature. After 5 min the mixture was worked up in the usual manner, yielding 40 mg (100%) of the 3-ketone *XXII*, m.p. 145–147°C (chloroform–heptane), $[\alpha]_D$ +33° (*c* 0·9). Mass spectrum, *m/z*: 374 (32%, M^+); 356 (11%, $M^+ - H_2O$); 272 (100%, $M^+ - (CH_3)_3CCOOH$); 254 (53%, 272 − H_2O). IR spectrum (CCl_4): 1 728, 1 288, 1 167 (COOR); 1 708 (C=O). ^{1}H NMR spectrum: 0·79 s, 3 H (3 × H-18); 0·94 d, 3 H (3 × H-4 b, J = 6·5); 1·20 s, 9 H ($(CH_3)_3CCOO$); 4·63 t, 1 H (H-17, J = 7·5). For $C_{24}H_{38}O_3$ (374·5) calculated: 76·96% C, 10·23% H; found: 76·68% C, 10·07% H.

17β-Hydroxy-4aα-methyl-A-homo-B,19-dinor-5β,10α-androstan-3-one (*I*)

A) By hydrolysis of cyclohexanecarboxylate *XXI*. A mixture of compound *XXI* (525 mg), ethanol (20 ml) and potassium hydroxide (300 mg) was refluxed under argon for 24 h. Acetic acid (0·3 ml) was added and the mixture was concentrated to one tenth of the original volume. The concentrate was diluted with saturated aqueous solution of sodium chloride and the separated product was continuously extracted with ether. The extract was purified by TLC (6 plates) on silica gel in benzene–ether (1 : 1) which afforded 350 mg (92%) of compound *I*, m.p. 111–112°C, no depression with a sample prepared previously[1].

B) From pivalate *XXII*. *p*-Toluenesulfonic acid monohydrate (15 mg) was added to a mixture of benzene (100 ml), ethylene glycol (5 ml) and compound *XXII* (230 mg) and the mixture was refluxed for 6 h, using a Dean–Stark apparatus. After cooling, the mixture was washed with aqueous potassium hydroxide (1%) and water, dried over sodium sulfate and the solvent was evaporated to dryness. The residue was dissolved in tetrahydrofuran (10 ml), lithium aluminium hydride (100 mg) was added and the mixture was refluxed for 30 min. The excess hydride was destroyed with a few drops of water, the inorganic material was removed by filtration through sodium sulfate, the filtrate was taken down in vacuo and the dry residue was dissolved in a solution of *p*-toluenesulfonic acid monohydrate (100 mg) in acetone (5 ml). After standing for 18 h the mixture was concentrated to a quarter of the original volume, diluted with saturated sodium chloride solution and the product was taken up in chloroform. The extract was washed with a solution of potassium hydrogen carbonate and water, dried and the solvent was evaporated to give 112 mg (63%) of compound *I*.

4aα,17-Dimethyl-A-homo-B,19-dinor-5β,10α-androstane-3β,17β-diol (*XXIII*)

A 1·4M solution of methyllithium in ether (3 ml) was added to a solution of acetoxy ketone *XVIII* (300 mg) in tetrahydrofuran (2 ml). After standing for 18 h at room temperature, the mixture was decomposed by pouring into dilute hydrochloric acid and the product was extracted with chloroform. The extract was washed with an aqueous solution of potassium hydrogen carbonate and water, concentrated and purified by TLC (7 plates) in benzene–ether (1 : 1, double developing). Elution of the main zone afforded 144 mg (52%) of compound *XXIII*, m.p. 171–173°C (acetone–heptane). $[\alpha]_D$ −73° (*c* 1·3). IR spectrum: 3 610, 1 092, 1 036. ^{1}H NMR spectrum: 0·85 s, 3 H (3 × H-18); 0·90 d, 3 H (3 × H-4b, J = 6·5); 1·22 s, 3 H (17-CH_3); 3·90 m, 1 H (H-3, W = 23). For $C_{20}H_{34}O_2$ (306·5) calculated: 78·38% C, 11·18% H; found: 78·10% C, 11·26% H.

17β-Hydroxy-4aα,17-dimethyl-A-homo-B,19-dinor-5β,10α-androstan-3-one (*XXIV*)

Jones reagent (in excess) was added dropwise to a stirred solution of dihydroxy derivative *XXIII* (110 mg) in acetone (5 ml), the mixture was set aside at room temperature for 10 min and then poured into aqueous potassium hydrogen carbonate solution. The product was taken up in chloroform, and the extract was washed with water and dried. Evaporation of the solvent gave 90 mg (82%) of ketone *XXIV* which on crystallization from acetone–heptane melted at 142 to 144°C. $[\alpha]_D$ +42° (*c* 1·3). IR spectrum: 3 615, 1 092 (OH); 1 697 (C=O). ^{1}H NMR spectrum: 0·84 s, 3 H (3 × H-18); 0·94 d, 3 H (3 × H-4b, J = 6·5); 1·24 s, 3 H (17-CH_3). For $C_{20}H_{32}O_2$ (304·5) calculated: 78·89% C, 10·60% H; found 79·01% C, 10·71% H.

Dehydrochlorination of Chloro Derivative *VI*

A mixture of chloro derivative *VI* (50 mg), acetic acid (5 ml) and silver acetate (180 mg) was refluxed under argon for 18 h. The mixture was worked up in a usual manner and the product was purified by TLC (1 plate) on silica gel in benzene–ether (10 : 1). Elution of the zone of R_F 0·30 afforded the oily main product (20 mg; 42% for $C_{26}H_{30}O_4$). IR spectrum (CCl_4): 1 726, 1 276 (C_6H_5COO); 1 710 (C=O); 1 656 (C=C); 1 248. Mass spectrum, *m/z*: 406. ^{1}H NMR spectrum: 1·06 s, 3 H (3 × H-18); 1·77 s, 3 H (4a-CH_3); 3·35 m, 1 H (H-4, W = 4); 4·84 t, 1 H (H-17, J = 7·5).

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