A-HOMO-B,19-DINORANDROSTANES FROM 6β-METHANESULFONYLOXY-5-METHYL-19-NOR-5β-ANDROST-9-ENE DERIVATIVES*

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Dedicated to the memory of Professor František Šorm.

6β-Methanesulfonyloxy derivatives of 5-methyl-19-nor-5β-androst-9-enes with different oxygen functionalities in positions 3β and 17 (compounds *IX* and *XVII*) were converted to 4a-methyleno--A-homo-B,19-dinor-5β-androst-9-ene derivatives (compounds *X*, *XX* and *XXI*) which were hydrogenated to give derivatives of 4aα-methyl-A-homo-5,19-dinor-5β,10α-androstane (*XXII*, *XXIII*) and 4aα-methyl-A-homo-B,19-dinor-5α,9β-androstane (*XXIV*, *XXV*). The structure of the latter compounds has been confirmed by X-ray diffraction of diketone *XXVII* which has been shown, in accordance with calculations by the MM2 method, to exist in a boat conformation of the ring C. The 17β-hydroxy-3-ketone *XXX* exhibits in vivo antiandrogenic activity.

In our previous communications[1-3] we described the elimination of hydrogen chloride from compounds of the type *VI* under conditions of solvolysis or hydrogenolysis in which rearrangement of the steroid skeleton takes place leading to dienes of the type *X* or *XI*. From the very beginning, total yields of these methods were lowered because in the preparation of the starting 6β-chloro derivatives (type *VI*) one could utilize only one of the isomeric epoxides formed by oxidation of the Δ^5--double bond. We prepared now the required substrates of the type *IX* using a more economical procedure: both the 5,6-epoxides were converted into the single 5α,6β--dihydroxy derivative *IV* which on Westphalen rearrangement and further transformations (partial hydrolysis of the 6β-acetate *VII*, mesylation of the 6β-alcohol *VIII*) afforded product with the nucleofuge in position 6β (see Scheme 1).

Heating of the mesylate *IX* with silver acetate in pyridine afforded 4a-methyleno--B,19-dinor-5β-androst-9-ene-3β,17β-diol 3,17-dibenzoate (*X*); this compound was also formed in the solvolysis of 6β-chloride *VI* with silver acetate. As a side product we isolated the isomeric unsaturated dibenzoate *XII* ($C_{33}H_{36}O_4$ according to the

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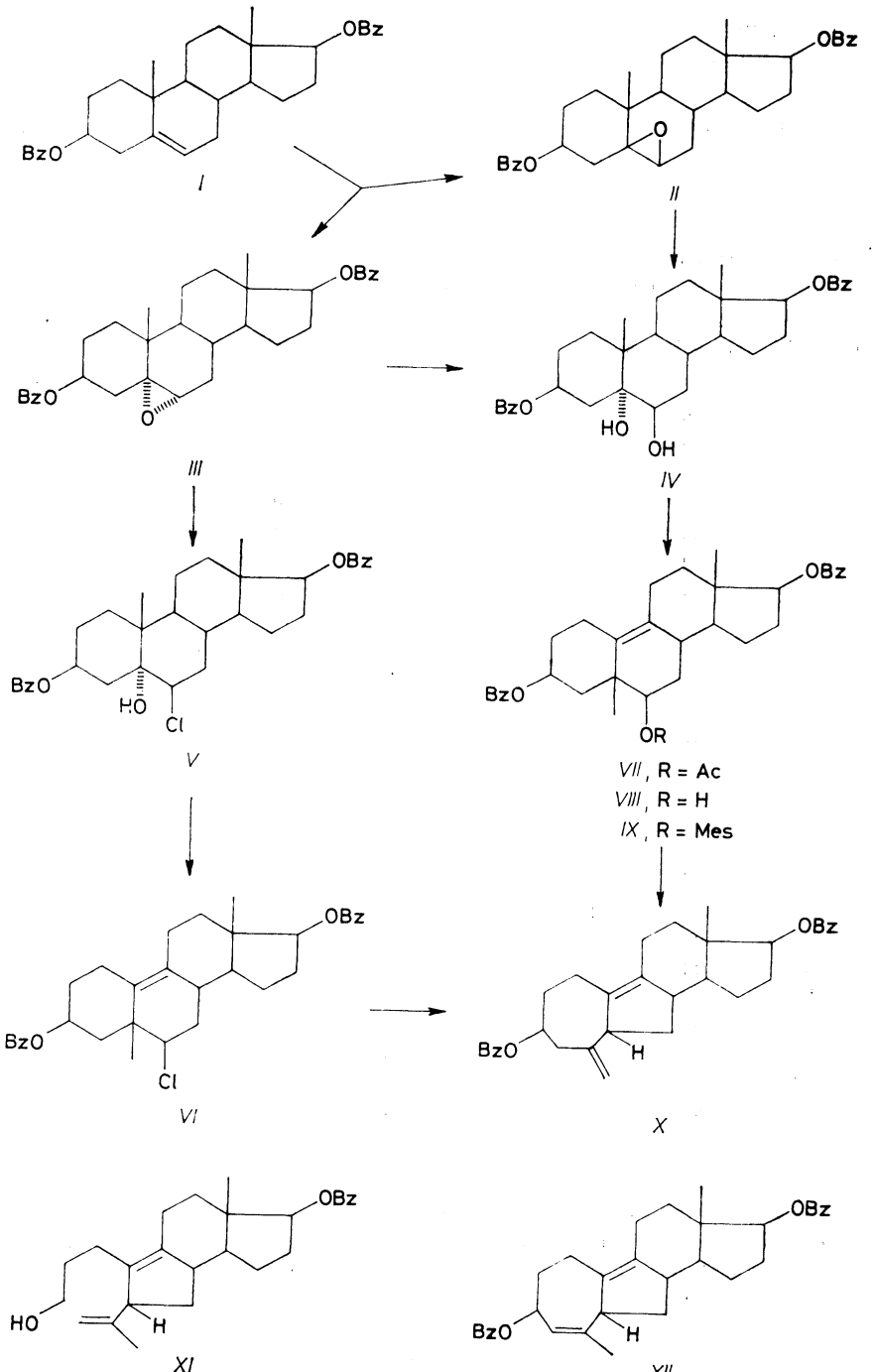

OBz
BzO
I
II
O
III
HO
OH
IV
Cl
V
OR
VII, R = Ac
VIII, R = H
IX, R = Mes
VI
X
H
XI
XII

SCHEME 1

mass spectrum). In contrast to compound *X*, the ^{1}H NMR spectrum of *XII* contained no signals due to the exomethylene group; on the other hand, it exhibited a signal of methyl at a C=C double bond (see Table I). The signal at δ 3·3 of a proton (H-5) in an allylic position to two double bonds had other multiplicity than in the

TABLE I

Characteristics parameters of 100 MHz ^{1}H NMR spectra of androstane derivatives, in deuteriochloroform; for other conditions see Experimental

Comp.[a]	H-18[b]	4a-CH	5-CH_3[b]	H-3	H-6	H-17[c]	Other signals[d]
III	0·90	—	—	5·22[e]	2·95[f]	4·82	1·19[g]
IV	0·97	—	—	5·42[e]	3·61[i]	4·86	1·29[g]
V	0·98	—	—	5·36[e]	3·90[h]	4·87	1·35[g]
VI	1·10	—	1·39	5·40[j]	4·09[k]	4·91	—
VII	1·08	—	1·34	5·37[j]	4·86[k]	4·82	2·04[l]
VIII	1·09	—	1·27	5·38[j]	4·88[k]	3·57	—
IX	1·08	—	1·35	5·40[j]	4·80[m]	4·88	3·00[n]
X	1·05	4·98[o]	—	4·90[m]	—	4·83	3·42[p]
XI	1·01	1·60[q]	—	3·58[r]	—	4·92	4·68[s], 3·23[t]
XII	1·01	1·83[q]	—	5·73[u]	—	4·83	3·43[v], 5·50[w]
XIV	0·89	—	—	5·42[e]	3·63[i]	—	1·27[g]
XV	1·01	—	1·35	5·36[j]	4·76[k]	—	2·05[l]
XVI	1·02	—	1·28	5·36[j]	3·59[k]	—	—
XVII	1·01	—	1·35	5·38[j]	4·63[k]	—	2·99[n]
XVIII	0·99	—	1·26	5·38[j]	3·60[k]	—	3·87[x]
XIX	1·00	—	1·35	5·40[j]	4·64[k]	—	3·00[n], 3·87[v]
XX	0·98	4·99[o]	—	4·99[m]	—	—	3·44[p]
XXI	0·96	4·98[o]	—	4·75[e]	—	—	2·00[l], 3·37[p]
XXII	0·89	0·92[y]	—	5·00[e]	—	—	2·00[l]
XXIII	0·88	0·90[y]	—	5·01[e]	—	—	—
XXIV	0·90	0·99[y]	—	4·89[e]	—	—	2·00[l]
XXV	0·90	0·98[y]	—	4·96[e]	—	—	—
XXVI	0·90	0·99[y]	—	3·88[e]	—	—	—
XXVII	0·94	1·02[y]	—	—	—	—	—
XXVIII	0·86	0·99[y]	—	3·88[e]	—	—	1·20[b]
XXX	0·92	0·99[y]	—	—	—	—	1·22[b]

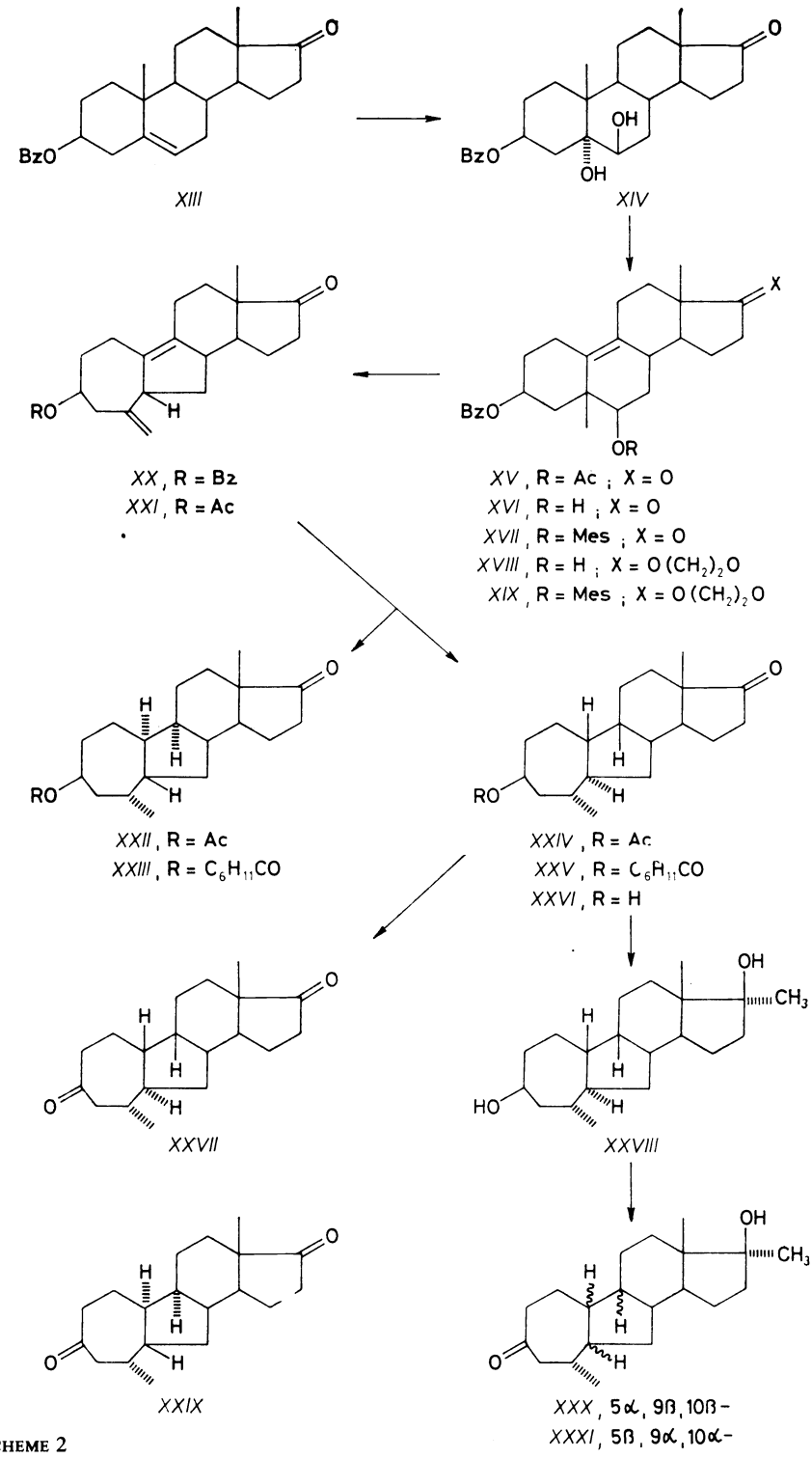
[a] The 200 MHz spectral data are given in Experimental; [b] s, 3 H; [c] t, J = 8; [d] benzoyloxy groups, when present, exhibit two multiplets of aromatic protons at 7·46 and 8·06; [e] m, $W_{1/2}$ = 23; [f] d, J = 4; [g] s, 3 H, H-19; [h] d, J = 2; [i] bs, $W_{1/2}$ = 2·5; [j] p, J = 3; [k] dd, J = 11·5 and 4·8; [l] s, CH_3COO; [m] signal partially overlapped with a neighbouring one; [n] s, CH_3SO_3; [o] d, 2 H, J = 3, [p] t, J = 7·5, H-5; [q] d, 3 H, J = 1; [r] t, 2 H, J = 6·5; [s] s, 2 H, H-4; [t] d, J = 8; [u] m, $W_{1/2}$ = 18; [v] d, J = 9, H-5; [w] m, 1 H, $W_{1/2}$ = 10, H-4; [x] m, 4 H, $W_{1/2}$ = 5, dioxolane grouping; [y] d, 3 H, J = 6·5.

spectrum of isomeric diene *X*. The presence of these two double bonds was moreover confirmed by the corresponding signals in the ^{13}C NMR spectrum (see Experimental). This side product was therefore assigned the structure *XII*.

In our previous paper[3] we noted that the same rearrangement can also be achieved by decomposition of the corresponding 6β-mesyloxy derivative with lithium aluminium hydride. The use of a less reactive complex hydride that would tolerate the ester groups present was not successful; thus, e.g. lithium tri-tert-butoxyaluminium hydride did not react with *IX* at temperatures below 55°C whereas at higher temperatures (65°C and 75°C) the desired diene *X* was accompanied with high proportions (up to 60%) of the undesired fragmentation product[4] *XI*. Therefore in our further experiments we prepared the required dienes of the type *XX* using lithium aluminium hydride but in the substrate we introduced such protecting group that guaranteed the preservation of different substitution in positions 3 and 17. Thus, 3β-hydroxy-5--androsten-17-one benzoate (*XIII*) (see Scheme 2) was converted by treatment with peroxyacetic acid into a mixture of epoxides which were then hydrated to give the uniform diol *XIV*. The Westphalen rearrangement of this compound afforded acetate *XV* in which the 6-ester group was easily preferentially saponified under formation of alcohol *XVI*. For the mentioned elimination with rearrangement to A-homo-B,19--dinorandrostadiene derivatives we used either the solvolysis of mesylate *XVII* leading directly to compound *XX* or the reduction of mesylate *XIX* after which, however, the liberated 3β-hydroxy group had to be again acylated to give acetate *XXI*.

Hydrogenation of keto esters *XX* and *XXI* over platinum catalyst in acetic acid afforded mixtures of saturated hydroxy esters which were reoxidized and chromatographed. The lipophilic components were identified as the known 9α,10α-dihydroxy derivatives *XXII* and *XXIII* whose conversion into the A-homo-B,19-dinor analogues of dihydrotestosterone (e.g. *XXXI*) was already described by us[1,2] (see Table II). The more polar hydrogenation products (perhydro derivatives *XXIV* and *XXV*) could result by a β-attack by hydrogen of the double bonds, nevertheless an automatic assumption of *cis*-addition of hydrogen to the C=C double bond was not quite justified because in hydrogenation of Δ^9-unsaturated compounds of the type *VI* Snatzke[5] isolated 9,10-*trans*-dihydro derivatives whose formation he explained by pre-isomerization of the double bond on the platinum catalyst, followed by the hydrogenation proper. Since a rigorous conformation of structure of these isomers by chemical means was difficult, we prepared in the 9β,10β-series (*XXIV*, *XXV*) a well-crystalizable compound (diketone *XXVII*) which was then studied by the X-ray diffraction method.

The final atomic coordinates are given in Table III and bond lengths and angles in Table IV. Figure 1 depicts a perspective view of the molecule with atom numbering and crystal packing is obvious from Fig. 2. The structure consists of discrete molecules arranged at typical van der Waals C–C distances of 3·9 Å or longer, except


BzO
O
XIII
OH
OH
XIV
X
OR
XV , R = Ac ; X = O
XVI , R = H ; X = O
XVII , R = Mes ; X = O
XVIII , R = H ; X = O(CH2)2O
XIX , R = Mes ; X = O(CH2)2O
RO
H
XX , R = Bz
XXI , R = Ac
XXII , R = Ac
XXIII , R = C6H11CO
XXIV , R = Ac
XXV , R = C6H11CO
XXVI , R = H
CH3
HO
XXVII
XXVIII
XXIX
XXX , 5α, 9β, 10β-
XXXI , 5β, 9α, 10α-

SCHEME 2

of two contacts, C12...C15 $(1 + x, y, z)$ 3·624 Å and C1...C18 $(1/2 + x, 1/2 - y, 1 - z)$ 3·733 Å which, however, do not influence the environment of these atoms in any detectable manner. Geometrical parameters of the molecule strongly indicate an essentially strain-free conformation. Only five C—C distances fall outside the 1σ limit of the mean C—C bond length value of 1·536(11) Å: three of them (C2—C3, C3—C4, C16—C17) are shortened, as usual, by the α-keto group and the C8—C9, C9—C10 distances are lengthened, probably as a result of the strain imposed by the uncommon ring junction (see below). Similarly, bond and torsion angles are also normal for this type of molecule. The ring junction is *trans*, *cis*, *trans* for A/B, B/C, C/D, respectively; the corresponding arrangement of H atoms on the key B-ring is depicted on Fig. 3. The conformation of individual rings needs also some comments. The otherwise strongly flexible seven-membered A-ring is, similarly as in the majority of analogous steroid ketones[6], fixed in the generally energetically favourable[7,8] distorted twist chair conformation with the C_2-axis passing through the atom adjacent to the sp^2-hybridized keto-carbon. ΔC_2(C2) = 12·5° (see refs[7,9]); the mean value of ΔC_2 for eight analogous structures[6] is 14 (2)°. The B-ring adopts a nearly ideal half-chair conformation with[10] ΔC_2(C8) = 1·2°, Φ_m = 42·4°. In contrast, the C ring is unusual in that it can be best described as a strongly distorted boat[9],ΔC_2. .(C9, C11) = 28·0° (see Table V). The only known steroid structure[11] with analogous arrangement of the B, C, D rings has, however, the C ring in a nearly ideal chair: idealized geometry calculations show that a chair conformation of the C ring in the present structure should be unfavourable because of a nonbonding contact of less than 1 Å between H11α and H1β. Finally, the D ring is, as usual, a nearly ideal envelope[10] with ΔC_s(C14) = 1·9°, Φ_m = 42·4°.

TABLE II

CD data of some 3- and 17-ketoandrostane derivatives (in methanol, measured on Jobin–Yvon Mark V instrument)

Compound	Position of the CO group	Configuration in position			$\Delta\varepsilon(\lambda)$
		5	9	10	
XXXI[a]	3	β	α	α	+3·55 (288)
XXX	3	α	β	β	−1·25 (288)
XXII	17	β	α	α	+3·59 (296)
XXIV	17	α	β	β	+2·78 (297)
XXIX[b]	3, 17	β	α	α	+6·58 (295)
XXVII	3, 17	α	β	β	+2·56 (303), −0·36 (267)

[a] Ref.[3]; [b] ref.[1].

This finding agreed with the observed values of the Cotton effect (see Table II): for cycloheptanone derivatives predictions using the octant rule are often difficult due to a considerable flexibility of the seven-membered ring; however, using conformations optimized by the MM2 method (ref.[12]), we were able to derive a negative Cotton effect of the 3-carbonyl group in the 5α-derivatives considered. This result was surprising in the light of the structure[1,2] of the lipophilic hydrogenation products (5β,9α,10α-derivatives of the type *XXII*) and the hydrogenation can thus be interpreted so that, besides the expected normal addition of hydrogen to both the double bonds, in dienes of the type *XX* an addition to the pre-isomerized double bond takes place[5]: a part of the starting Δ^9-olefin forms a complex with the catalyst from the β-side, the first hydrogen atom is attached to position 9β, the 5β-hydrogen is shifted into position 10β, and finally the second external hydrogen atom is bonded in the position 5. Configuration in the position 5 is probably determined by the

TABLE III

Atomic coordinates (.10^4) of non-H atoms in diketone *XXVII* (estimated standard deviations are given in parentheses) $U_{eq} = 1/3 \sum_i \sum_j a_i a_j a_i^* a_j^* U_{ij}$

Atom	*x/a*	*y/b*	*z/c*	U_{eq}(.10^3), Å^2
C1	−674(5)	4435(4)	6525(1)	48(1)
C2	−840(5)	6064(4)	6675(2)	62(1)
C3	687(6)	6687(4)	7013(2)	60(1)
C4	1749(5)	5720(4)	7397(1)	56(1)
C4a	3300(5)	4922(3)	7092(1)	49(1)
C4b	4680(6)	4360(5)	7525(2)	73(1)
C5	2659(4)	3669(3)	6720(1)	39(1)
C6	4182(4)	3040(4)	6359(1)	47(1)
C8	3247(4)	2218(3)	5877(1)	38(1)
C9	1213(4)	2812(3)	5885(1)	39(1)
C10	1202(4)	4041(3)	6284(1)	40(1)
C11	−64(4)	1476(3)	6064(1)	49(1)
C12	70(5)	113(4)	5692(1)	52(1)
C13	2052(4)	−204(3)	5530(1)	43(1)
C14	3354(4)	559(3)	5929(1)	38(1)
C15	5189(4)	−196(4)	5838(2)	54(1)
C16	4618(6)	−1806(4)	5785(2)	68(1)
C17	2676(6)	−1785(4)	5583(1)	53(1)
C18	2407(6)	178(4)	4911(1)	59(1)
O1	1071(5)	7966(3)	6969(1)	90(1)
O2	1774(4)	−2852(3)	5483(1)	75(1)

thermodynamic stability of the product; in the case of the 9β,10β-dihydro derivative the 5α-product is formed.

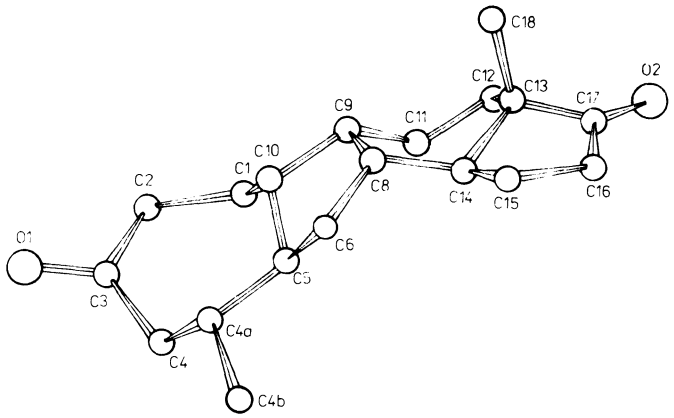


FIG. 1

Perspective view of the molecule with atom numbering. Hydrogen atoms (omitted for clarity) are given the numbers of their bonding partners

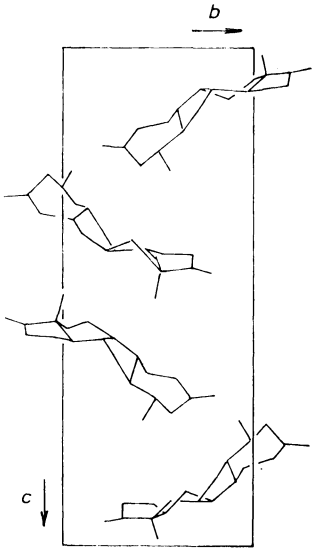


FIG. 2

Unit cell projected onto the *bc* plane

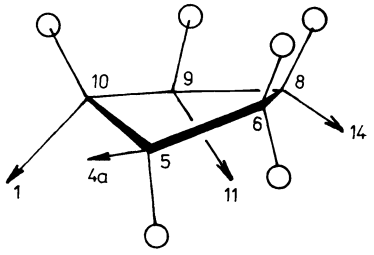


FIG. 3

Configuration of hydrogens on the B ring

TABLE IV

Bond lengths (Å) and angles (°) on diketone *XXVII* (estimated standard deviations are given in parentheses)

Atoms	Bond length	Atoms	Bond angle
C1—C2	1·541(5)	C2—C1—C10	112·7(3)
C1—C10	1·541(5)		
C2—C3	1·499(6)	C1—C2—C3	115·8(3)
C3—C4	1·498(5)	C2—C3—C4	119·8(3)
C3—O1	1·211(5)	C2—C3—O1	119·8(3)
		C4—C3—O1	120·3(3)
C4—C4a	1·541(5)	C3—C4—C4a	112·2(3)
C4a—C4b	1·541(6)	C4—C4a—C4b	109·2(2)
C4a—C5	1·529(4)	C4—C4a—C5	113·8(2)
		C4b—C4a—C5	110·1(3)
C5—C6	1·529(4)	C4a—C5—C6	112·7(2)
C5—C10	1·535(4)	C4a—C5—C10	116·4(2)
		C6—C5—C10	102·3(2)
C6—C8	1·541(4)	C5—C6—C8	106·2(2)
C8—C9	1·566(4)	C6—C8—C9	106·1(2)
C8—C14	1·529(4)	C6—C8—C14	113·8(2)
		C9—C8—C14	109·7(2)
C9—C10	1·549(4)	C8—C9—C10	103·9(2)
C9—C11	1·534(4)	C8—C9—C11	112·1(2)
		C10—C9—C11	114·0(2)
		C1—C10—C5	115·1(2)
		C1—C10—C9	114·9(2)
		C5—C10—C9	103·9(2)
C11—C12	1·538(4)	C9—C11—C12	113·5(2)
C12—C13	1·538(5)	C11—C12—C13	111·1(2)
C13—C14	1·524(4)	C12—C13—C14	110·6(2)
C13—C17	1·526(5)	C12—C13—C17	116·4(3)
C13—C18	1·545(4)	C12—C13—C18	111·1(2)
		C14—C13—C17	101·2(2)
		C14—C13—C18	113·0(2)
		C17—C13—C18	104·1(2)
C14—C15	1·534(4)	C8—C14—C13	111·9(2)
		C8—C14—C15	118·9(2)
		C13—C14—C15	105·0(2)
C15—C16	1·541(5)	C14—C15—C16	101·8(3)
C16—C17	1·510(6)	C15—C16—C17	105·8(3)
C17—O2	1·207(5)	C13—C17—C16	108·9(3)
		C13—C17—O2	126·0(3)
		C16—C17—O2	125·1(3)

After assignment of configuration in positions 9 and 10 we subjected the keto esters *XXIV* and *XXV* to the reaction with methyllithium and the obtained 17α-methyl-3, 17-diol *XXVIII* was oxidized to give the 17-methyldihydrotestosterone analogue *XXX*. The in vivo antiandrogenic activity of this compound was the same as that of cyproteron acetate and the 9α,10α-analogue[3] *XXXI* (the corresponding results will be published elsewhere).

EXPERIMENTAL

The melting points were determined on a Koffer block and are uncorrected; the optical rotation values and IR spectra were measured in chloroform (unless stated otherwise); wavenumbers are given in cm^{-1}. Mass spectra were taken on a VG-ZAB EQ instrument, NMR spectra on a Tesla BS 497 (100 MHz, FT mode, for ^1H) or on a Varian XL-200 (200 MHz for ^1H, and 50 MHz for ^{13}C) spectrometer in deuteriochloroform with tetramethylsilane as internal standard; chemical shifts are given in ppm (δ-scale), coupling constants (J) and half-widths ($W_{1/2}$) in Hz, Column chromatography was performed on silica gel according to Pitra (60—120 μm), thin-layer chromatography (TLC) on 200 × 200 × 0·3 mm plates prepared from silica gel (IGCN Biochemicals). The identity of samples prepared by different routes was checked by comparison of their IR and ^1H NMR spectra, TLC and by mixture melting points. Calculations by the MM2 method were executed on an SM 52/12 computer.

X-Ray crystallography: To obtain X-ray quality crystals, a nearly saturated solution of *XXVII* in acetone/heptane (1 : 3) was slowly evaporated through a narrow-bore capillary at room temperature. The crystals exhibited severe twinning but, using oscillation and Weissenberg photographs, an 0·23 × 0·28 × 0·33 mm single crystal was eventually selected for the measurement on an Enraf Nonius CAD-4 diffractometer. The cell parameters as determined from a least-squares refinement of 23 reflections in the 5—18°, Θ-range are: orthorhombic, $P2_12_12_1$, $a = 7{\cdot}367(1)$,

TABLE V

Selected torsion angles in the molecule of diketone *XXVII*

Torsion angle	Torsion angle (in °) obtained by	
	X-ray[a]	MM2[b]
8—9—11—12	−57·7(6)	−60·2
9—11—12—13	39·8(5)	33·2
11—12—13—14	19·5 (5)	27·6
12—13—14—8	−66·3(8)	−67·1
13—14—8—9	47·7(5)	40·1
14—8—9—11	12·0(5)	21·6

[a] The found standard deviations given in parentheses; [b] the optimum conformation of compound *XXVII* was calculated using the MM2 method (version 1985, see ref.[12]); the C-ring exists as deformed chair.

$b = 9{\cdot}1716(8)$, $c = 23{\cdot}936(2)$ Å, $V = 1617{\cdot}3(3)$ Å^3, $\varrho_x = 1{\cdot}14$ for $Z = 4$ and $C_{19}H_{28}O_2$, $\varrho_m = 1{\cdot}18(2)$ g cm^{-3} (flotation in aqueous $ZnBr_2$), $\mu = 0{\cdot}7$ mm^{-1}, absorption neglected. Using MoK_α radiation ($\lambda = 0{\cdot}71073$ Å) and $\omega - 2\Theta$ scan mode, intensities of 5 344 reflections were measured in the range $h\langle 0, 10\rangle$, $k\langle 0{\cdot}12\rangle$ and $l\langle 0{\cdot}33\rangle$; three standard reflections monitored periodically during data collection showed no observable crystal decay. From 2 381 symmetrically unique reflections, 1 356 fulfilling the $I > 1{\cdot}96\sigma(I)$ criterion were used in the subsequent data treatment. The structure was solved by direct methods[13]. All H atoms were clearly discernible in a difference map but, since their positions tend to become ill-defined during attempted refinement, they were constrained in calculated places assuming C—H 1·08 Å. Scale factor, coordinates and anisotropic thermal parameters of non-H atoms and group (CH_3, CH_2 and CH) isotropic thermal parameters of H atoms were then refined simultaneously by full-matrix least-squares[14]. The function minimized was $\sum w(|F_o| - |F_c|)^2$ where $w = 0{\cdot}7721(\sigma^2(F_o) + 0{\cdot}0009F^2)$. At convergence, $R = 0{\cdot}043$ and $wR = 0{\cdot}051$. Tables of further experimental details, structure factors, anisotropic thermal parameters and H atom coordiates have been deposited by the author (J.P.) and are available on request.

5,6α-Epoxy-5α-androstane-3β,17β-diol Dibenzoate (*III*)

A solution of crystalline sodium hydrogen phosphate (5·0 g, 18·7 mmol) in water (6 ml), followed by a 34% aqueous solution of peroxyacetic acid (7·5 ml, 34 mmol), was added under stirring to a solution of dibenzoate *I* (5·0 g, 10 mmol) in chloroform (25 ml). After 6 h the organic phase was separated and the aqueous one extracted with chloroform (2 × 25 ml). The combined chloroform phases were washed with aqueous potassium hydrogen carbonate solution and with water, dried over anhydrous sodium sulfate and concentrated in vacuo. The dry residue was crystallized from toluene to give 3·2 g (62%) of *III*, m.p. 232—235°C; $[\alpha]_D$ −7° (*c* 0·9). For $C_{33}H_{38}O_5$ (514·7) calculated: 77·01% C, 7·44% H; found: 76·74% C, 7·28% H. The mother liquors were a mixture of epoxides *II* and *III* (according to ^{1}H NMR spectrum) and were used in the preparation of diol *IV*.

6β-Chloro-4α-androstane-3β,5,17β-triol 3,17-Dibenzoate (*V*)

The epoxide *III* (3·1 g, 6·2 mmol) was vigorously stirred at room temperature with chloroform (14 ml) and hydrochloric acid (14 ml). After 20 min the aqueous phase was separated and extracted with chloroform (2 × 14 ml). The combined chloroform extracts were washed successively with water, aqueous solution of potassium hydrogen carbonate and water, and dried over anhydrous sodium sulfate. The solvent was evaporated in vacuo and the dry residue crystallized from dichloromethane–heptane to give 3·1 g (93%) of chlorohydrin *V*; m.p. 209—216°C; $[\alpha]_D$ −18° (*c* 0·9). IR spectrum: 3 620, 3 595 (OH); 1 718, 1 290 (C_6H_5COO). For $C_{33}H_{39}ClO_5$ (551·1) calculated: 71·92% C, 7·13% H; found: 71·46% C, 6·88% H.

5α-Androstane-3β,5,6β,17β-tetraol 3,17-Dibenzoate (*IV*)

A mixture of epoxide *II* and *III* (20 g, 38·85 mmol) was dissolved in warm dioxane (260 ml) and acetone (130 ml) and cooled. Aqueous perchloric acid (5%, 60 ml) was added to this solution with stirring at 35°C. After 18 h the solution was concentrated in vacuo to one third of the original volume and water was added to precipitate the product which was collected on filter and washed with water; yield of the compound usable in the next step was 18·1 g (87%). An analytical sample was obtained by crystallization from toluene, m.p. 225—228°C, $[\alpha]_D$ +6° (*c* 1·0). For $C_{33}H_{40}O_6$ (532·7) calculated: 74·41% C, 7·57% H; found: 73·67% C, 7·22% H.

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

A solution of the chlorohydrin *V* (2·9 g, 5·3 mmol) in acetic acid (35 ml) and acetic anhydride (70 ml) was distilled at atmospheric pressure. After collecting 17 ml of the distillate, the mixture was cooled to 30°C, acidified with 6 drops of sulfuric acid and kept at 30°C for 30 min and at 25°C for 4 h. The reaction mixture was poured with stirring and ice-cooling into a saturated aqueous sodium chloride solution (400 ml) and, after standing at 0°C for 18 h, the product was filtered and dissolved in ethyl acetate. The solution was washed with water, potassium hydrogen carbonate solution and water, and dried over anhydrous sodium sulfate. Crystallization from dichloromethane–methanol gave 1·67 g (59%) of *VI*, m.p. 186–188°C; $[\alpha]_D$ +192° (*c* 1·6). IR spectrum (CCl_4): 1 726, 1 279 (C_6H_5COO). Pro $C_{33}H_{37}ClO_4$ (533·1) calculated: 74·35% C, 7·00% H; found: 73·85% C, 6·88% H.

5-Methyl-19-nor-5β-androst-9-ene-3β,6β,17β-triol 6-Acetate 3,17-Dibenzoate (*VII*)

The dihydroxy derivative *IV* (20 g, 37·6 mmol) was subjected to Westphalen rearrangement by treatment with sulfuric acid in acetic anhydride (see preceding experiment). On pouring the reaction mixture into brine the product separated as an oil which was set aside for 18 h at 0°C and dissolved in ethyl acetate. The solution was washed with aqueous potassium carbonate solution and with water. The solvent was evaporated and the product purified by chromatography on silica gel (440 g) in ether–light petroleum (1 : 9). Crystallization from methanol afforded 10·9 g (52%) of compound *VII*, m.p. 130–137°C. $[\alpha]_D$ +154° (*c* 1·3). IR spectrum (CCl_4): 1 732, 1 250 (CH_3COO); 1 722, 1 278 (C_6H_5COO). For $C_{35}H_{40}O_6$ (556·7) calculated: 75·51% C, 7·24% H; found: 75·30% C, 7·01% H.

5-Methyl-19-nor-5β-androst-9-ene-3β,6β,17β-triol 3,17-Dibenzoate (*VIII*)

A mixture of acetate *VII* (8·3 g, 14·9 mmol), chloroform (35 ml), methanol (350 ml) and conc. hydrochloric acid (6·5 ml) was allowed to stand at 40°C for 36 h, and then concentrated to a quarter of the original volume. After dilution with a water–ice mixture the separated product was filtered, washed and crystallized from methanol; yield 7·25 g (94%) of *VIII*, m.p. 148–152°C. IR spectrum: 3 615 (OH); 1 713, 1 282, 1 604, 1 586, 1 493 (C_6H_5COO). For $C_{33}H_{38}O_5$ (514·7) calculated: 77·01% C, 7·44% H; found: 77·09% C, 7·38% H.

5-Methyl-19-nor-5β-androst-9-ene-3β,6β,17β-triol 3,17-Dibenzoate 6-Methanesulfonate (*IX*)

Methanesulfonyl chloride (2·0 ml, 26 mmol) was added dropwise at 0°C to a stirred solution of hydroxy derivative *VIII* (2·8 g, 5·44 mmol) in pyridine (9 ml). After standing at 0°C for 2 h and at 20°C for 3 h, the mixture was poured with stirring on ice. The separated product was taken up in chloroform and the extract was washed with dilute hydrochloric acid (5%), water, potassium hydrogen carbonate solution (7%) and again with water. The chloroform was evaporated in vacuo and the residue dissolved in a minimum amount of ether. After standing at 0°C for 18 h the product *IX* (2·1 g, 65%) was collected; m.p. 142–143°C (unchanged on crystallization from dichloromethane–ether; $[\alpha]_D$ +124° (*c* 0·9). IR spectrum (CCl_4): 1 722, 1 281 (C_6H_5·.COO); 1 362, 1 179 (CH_3SO_3). For $C_{34}H_{40}O_7S$ (592·8) calculated: 68·89% C, 6·80% H, 5·41% S; found: 68·31% C, 6·57% H, 5·63% S.

Reduction of 5-Methyl-19-nor-5β-androst-9-ene-3β,6β,17β-triol 3,17-Dibenzoate 6-Methanesulfonate (*IX*)

Lithium tri-tert-butoxyaluminium hydride (800 mg, 3·6 mmol) was added to a solution of methane-

sulfonate *IX* (300 mg, 0·5 mmol) in tetrahydrofuran (4 ml). The mixture was stired at 75°C for 4 h and then poured into dilute hydrochloric acid. The product was extracted with ethyl acetate under argon, the extract was washed with water and dried over sodium sulfate, Preparative thin-layer chromatography on silica gel (4 plates, eluent ethyl acetate–toluene 1 : 10) afforded the following compounds (in the order of increasing polarity):

4a-*Methyleno*-A-*homo*-B,19-*dinor*-5β-*androst*-9-*ene*-3β,17β-*diol dibenzoate* (X; 55 mg, 22%), m.p. 151—153°C (heptane), $[\alpha]_D$ +85° (*c* 1·1); IR spectrum (CCl_4): 1 725, 1 279 (C_6H_5COO); 1 651, 903 (C=CH_2). For $C_{33}H_{36}O_4$ (496·6) calculated: 79·81% C, 7·31% H; found: 79·52% C, 7·27% H.

4a-*Methyleno*-A-*homo*-B,19-*dinor*-3,4-*seco*-5β-*androst*-9-*ene*-3,17β-*diol* 17-*benzoate* (XI, 120 mg, 60%), $[\alpha]_D$ +90° (*c* 1·0): IR spectrum (CCl_4): 3 620 (OH); 1 721, 1 278 (C_6H_5COO); 1 642, 1 650, 895 (C=CH_2). For $C_{26}H_{34}O_3$ (394·6) calculated: 79·15% C, 8·69% H; found: 78·67% C, 8·81% H.

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

a) *Solvolysis of* 6β-*chloride* VI. A suspension of *VI* (2·0 g, 3·75 mmol) and silver acetate (5·0 g, 30 mmol) in acetic acid (150 mg) was refluxed under argon for 18 h, cooled and the solvent was evaporated in vacuo to dryness. The residue was codistilled with toluene, dissolved in chloroform and filtered. The filtrate was washed with water, dried over anhydrous sodium sulfate and the solvent was evaporated in vacuo to dryness. Chromatography of the residue on a silica gel column (60 g) in toluene containing 2% of ethyl acetate afforded 650 mg (35%) of dibenzoate *X*, m.p. 151—153°C (chloroform–heptane); no depression on admixture with the sample prepared by procedure *b*).

b) *Solvolysis of* IX. A suspension of compound *IX* (2·7 g, 4·55 mmol) and silver acetate (2·5 g, 15 mmol) in pyridine (48 ml) was refluxed under argon for 18 h and the solvent was evaporated in vacuo. The residue was coevaporated with toluene, mixed with chloroform, filtered and the filtrate was washed with water, dried over anhydrous sodium sulfate and the solvent was evaporated in vacuo to dryness. Chromatography on a column of silica gel (80 g) in toluene with 4% of ethyl acetate afforded 998 mg (44%) of dibenzoate *X* and 780 mg (34·5%) of A-homo-B,19--dinor-4a-methyl-5β-androsta-4,9-diene-3β,17β-diol dibenzoate (*XII*). M.p. 130—138°C (decomp., light petroleum), $[\alpha]_D$ +95° (*c* 1·0). Mass spectrum (*m/z*): 496·2614 (M^+, $C_{33}H_{36}O_4$, 36%), 374·2231 ($C_{26}H_{30}O_2$, 100%). IR spectrum (CCl_4): 1 729, 1 281 (C_6H_5COO). ^{13}C NMR spectrum: 11·44 (C-18); 23·81 (C-4b); 21·35, 24·22, 25·43, 27·80, 31·44, 33·20, 36·47 and 43·66 (C-1, C-2, C-7, C-11, C-12, C-13, C-15 and C-16); 45·67, 49·91 and 52·80 (C-5, C-8 and C-14); 73·98 and 82·91 (C-3 and C-17); 126·36 (C-4); 130·70 and 130·74 (2 × C-1 of benzoate groups); 128·23 and 128·29 (2 × C-3 and 2 × C-3 of benzoate groups); 129·50 and 129·58 (2 × C-2 and 2 × C-2 of benzoate groups); 132·72 (2 × C-4 of benzoate groups); 133·41, 135·33 and 141·36 (C-4a, C-9 and C-10); 165·89 and 166·49 (2 × COO). ^1H NMR spectrum (200 MHz): 1·02 s, 3 H (3 × H-18); 1·84 m, 3 H (3 × H-4b, $\sum J$ = 5·1); 3·43 d, 1 H (H-5, $J(5\beta, 6\alpha)$ = 9·0); 4·83 dd, 1 H (H-17, $J(17, 16\alpha)$ = 7·5; $J(17, 16\beta)$ = 9·4); 5·50 m, 1 H (H-4, $\sum J$ = 9); 5·73 m, 1 H (H-3, $\sum J$ = 16·6). For $C_{33}H_{36}O_4$ (496·7) calculated: 79·81% C, 7·31% H; found: 79·65% C, 7·23% H.

3β,5,6β-Trihydroxy-5α-androstan-17-one 3-Benzoate (*XIV*)

A solution of 3β-benzoyloxy-5-androsten-17-one (*XIII*, 20 g, 51 mmol) in chloroform (100 ml) was vigorously stirred with a solution of crystalline sodium hydrogen phosphate (20 g, 5 mmol)

in water (25 ml) and aqueous peroxyacetic acid (34%, 30 ml, 134 mmol) was added to the mixture. After stirring for 2 h the organic phase was separated and the aqueous one was extracted with chloroform. The combined extracts were washed with a solution of potassium hydrogen carbonate and water, dried over anhydrous sodium sulfate and the solvent was evaporated in vacuo. The remaining mixture of epoxides was dissolved in warm dioxane (250 ml) and acetone (150 ml), the solution was cooled and stirred with 72% perchloric acid (64 ml). After 3 h the mixture was concentrated in vacuo to a half, diluted with water, the product was filtered, washed with water and dried; yield 19 g (87%). The product *XIV* was used directly in the next step. An analytical sample was obtained by crystallization from toluene; m.p. 242–266°C; $[\alpha]_D$ +29° (*c* 1·0). For $C_{26}H_{34}O_5$ (426·6) calculated: 73·21% C, 8·03% H; found: 72·65% C, 8·11% H.

3β,6β-Dihydroxy-5-methyl-19-nor-5β-androst-9-en-17-one 3-Benzoate 6-Acetate (*XV*)

A solution of diol *XIV* (43·0 g; 0·12 mol) in acetic anhydride (1 000 ml) was distilled. After collection of 180 ml of the distillate the mixture was cooled and sulfuric acid (54 drops) added. After standing at 30°C for 30 min and at 20°C for 2 h, the mixture was poured under cooling and stirring to a saturated aqueous salt solution (4 l). The aqueous phase was decanted from the separated material which was dissolved in ethyl acetate and washed with a solution of potassium hydrogen carbonate and water. After drying over anhydrous sodium sulfate and evaporation of the solvent, the product was crystallized from acetone and heptane and then from acetone. Yield 12·9 g (28·3%) of product *XV*, m.p. 149–151°C; $[\alpha]_D$ +137°C (*c* 1·2); IR spectrum (CCl_4): 1 743, 1 407 ($COCH_2$); 1 743, 1 254 (CH_3COO); 1 724, 1 278 (C_6H_5COO). For $C_{28}H_{34}O_5$ (450·6) calculated: 74·64% C, 7·61% H; found: 74·15% C, 7·97% H.

3β,6β-Dihydroxy-5-methyl-19-nor-5β-androst-9-en-17-one 3-Benzoate (*XVI*)

A solution of conc. hydrochloric acid (10 ml) in methanol (500 ml) was added to a solution of acetate *XV* (12·8 g, 28·4 mmol) in chloroform (50 ml). After standing at 35°C for 60 h, the mixture was concentrated in vacuo to a quarter. The product was precipitated on addition of water, cooled, filtered and washed with water. Crystallization from methanol afforded 9·5 g (82%) of compound *XVI*, m.p. 123–124°C; $[\alpha]_D$ +215° (*c* 1·2); IR spectrum: 3 625 (OH), 1 737, 1 406 ($COCH_2$); 1 711, 1 284 (C_6H_5COO). For $C_{26}H_{32}O_4$ (408·5) calculated: 76·44% C, 7·90% H; found: 76·21% C, 8·04% H.

3β,6β-Dihydroxy-5-methyl-19-nor-5β-androst-9-en-17-one
3-Benzoate 6-Methanesulfonate (*XVII*)

Methanesulfonyl chloride (10 ml, 129 mmol) was added at 0°C to a stirred solution of hydroxy derivative *XVI* (10 g, 24·5 mmol) in pyridine (20 ml). After standing at 0°C for 1 h the mixture was poured under stirring to an ice–water mixture and after 2 h the crystalline precipitate was filtered, washed with water and dissolved in ether. The ethereal solution was washed successively with dilute hydrochloric acid, water, aqueous solution of potassium hydrogen carbonate and water. After drying over anhydrous sodium sulfate the solvent was evaporated in vacuo and the product crystallized from ether–heptane to give 10·7 g (90%) of *XVII*, m.p. 126–128°C; $[\alpha]_D$ +173° (*c* 1·1); IR spectrum: 1 737 (C=O); 1 712, 1 280 (C_6H_5COO); 1 335, 1 176 (CH_3SO_2O). For $C_{27}H_{34}O_6S$ (486·6) calculated: 66·64% C, 7·04% H, 6·59% S; found: 66·78% C, 7·11% H, 6·21% S.

17,17-Ethylenedioxy-5-methyl-19-nor-5β-androst-9-ene-
-3β,6β-diol 3-Benzoate 6-Methanesulfonate (*XIX*)

A mixture of ketone *XVI* (3 g, 7·3 mmol), *p*-toluenesulfonic acid (160 mg, 0·84 mmol), ethylene glycol (10 ml) and benzene (160 ml) was refluxed using a Dean–Stark apparatus. After 6 h the mixture was cooled, washed with aqueous potassium hydrogen carbonate solution and dried over sodium sulfate. (TLC in benzene–ether 1 : 1 R_F of starting compound 0·45, R_F of product *XVIII* 0·60). The solvent was evaporated, the residue was dissolved in pyridine (10 ml) and at 0°C mixed with methanesulfonyl chloride (2·5 ml, 32·3 mmol). After standing at room temperature for 2 h, the mixture was poured onto ice with aqueous potassium hydrogen carbonate and the product was taken up in chloroform. The extract was washed with water, dried over anhydrous sodium sulfate and concentrated in vacuo to dryness. TLC (benzene–ether 5 : 1): R_F before mesylation 0·15, R_F of product 0·45). Yield 3·4 g (87%) of *XIX*; the amorphous product was used without purification in the next step.

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

A solution of methanesulfonate *XIX* (2·10 g, 3·96 mmol) in ether (100 ml) was slowly added dropwise under nitrogen at room temperature to a stirred solution of lithium aluminium hydride (about 600 mg, 16 mmol) in tetrahydrofuran (25 ml). After 5 h the reaction was completed by refluxing for 3 h, the excess hydride was destroyed with moist ether and then with several drops of saturated aqueous solution of sodium sulfate. The inorganic material was removed by filtration through a column of anhydrous sodium sulfate and the filtrate was concentrated in vacuo. The dry residue was acetylated with acetic anhydride (4 ml) in pyridine (6 ml) at 20°C for 18 h under nitrogen. The mixture was decomposed with a water–ice mixture and the product was washed with water, dilute hydrochloric acid and water and the solvent was evaporated. The residue was dissolved in acetone (25 ml) containing *p*-toluenesulfonic acid (400 mg). After standing for 18 h under argon the solution was diluted with the same volume of toluene, concentrated to a half, washed with a solution of potassium hydrogen carbonate, water, dried over anhydrous sodium sulfate and purified by flash chromatography on silica gel (60 g, toluene with 3% of ethyl acetate; yield 560 mg (43%), m.p. 93—95°C (after four crystallizations from dichloromethane–light petroleum) without depression on admixture with an authetic sample[3].

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

A solution of methanesulfonate *XVII* (6·0 g, 12·3 mmol) in pyridine (80 ml) was mixed with silver acetate (6·0 g, 36 mmol) and the mixture was refluxed for 22 h under argon. The inorganic material was filtered off, the filtrate was concentrated in vacuo and the dry residue was repeatedly codistilled with toluene, applied (in toluene) on a column of silica gel (16 × 5 cm) and flash-chromatographed in toluene. The coloured material was eluted with toluene (2·5 ml) and then the compound *XX* was eluted (2·2 g, 46%). TLC (benzene): R_F 0·19. IR spectrum (CCl_4): 1 743, 1 408 ($COCH_2$); 1 721, 1 276 (C_6H_5COO); 1 652, 909 ($CH_2{=}C$). Mass spectrum, *m/z* (%): 390 (M^+, 11); 362 ($M^+ - CO$, 1); 268 ($M^+ - C_6H_5COOH$, 100); 253 ($M^+ - C_6H_5COOH - CH_3$, 17); 240 ($M^+ - C_6H_5COOH - CO$, 25). For $C_{26}H_{30}O_3$ (390·5) calculated: 79·97% C, 7·74% H; found: 79·58% C, 7·83% H.

Hydrogenation of 3β-Hydroxy-4a-methyleno-A-homo-B,19-dinor-5β-androst-9-en-17-one 3β-Acetate (*XXI*)

Diene *XXI* (350 mg, 1·07 mmol) was hydrogenated in acetic acid (10 ml) over Adams catalyst

(100 mg) for 8 h. After filtration, the catalyst was washed with acetic acid and the filtrate concentrated. The residue was dissolved in acetone (5 ml) and oxidized according to Jones (20°C, 10 min). The product was extracted with dichloromethane, the extract washed with potassium hydrogen carbonate and water and dried over anhydrous sodium sulfate. The solvent was evaporated and the residue subjected to preparative TLC (7 plates 200 × 200 × 0·7 mm). The plates were developed twice in toluene–ethyl acetate (97 : 3), detection with morin in the UV light (360 nm). The following two main products were isolated (given in the order of growing polarity):

3β-*Hydroxy*-4aα-*methyl*-A-*homo*-B,19-*dinor*-5β,10α-*androstan*-17-*one* 3-*acetate* (XXII; 106 mg, 30%), m.p. 98–99°C (heptane); $[\alpha]_D$ +19° (*c* 0·9). IR spectrum (CCl_4): 1 742, 1 408 ($COCH_2$); 1 742, 1 250, 1 027 (CH_3COO). For $C_{21}H_{32}O_3$ (332·5) calculated: 75·86% C, 9·70% H; found: 75·64% C, 9·68% H.

3β-*Hydroxy*-4aα-*methyl*-A-*homo*-B,19-*dinor*-5α,9β-*androstan*-17-*one* 3-*acetate* (XXIV; 145 mg, 41%); m.p. 157°C, remelting at 167–175°C (methanol); $[\alpha]_D$ +81° (*c* 1·0). IR spectrum: 1 730, 1 261, 1 026 (CH_3COO); 1 730, 1 408 (CO). For $C_{21}H_{32}O_3$ (332·5) calculated: 75·86% C, 9·70% H; found: 75·51% C, 9·56% H.

Hydrogenation of 3β-Hydroxy-4a-methyleno-A-homo-B,19-dinor-5β-androst-9-en-17-one 3β-Benzoate (*XX*)

Benzoate *XX* (585 mg, 1·5 mmol) was hydrogenated and the product was oxidized according to Jones as described in the preceding experiment. Chromatography on a column of silica gel (90 g) in light petroleum–acetone (99 : 1) afforded the following two main products:

3β-*Hydroxy*-4aα-*methyl*-A-*homo*-B,19-*dinor*-5β,10α-*androstan*-17-*one* 3-*cyclohexanecarboxylate* (XXIII; 210 mg, 35%); m.p. 147–149°C (acetone), $[\alpha]_D$ +25° (*c* 1·0). IR spectrum: 1 729, 1 408 ($COCH_2$); 1 729, 1 712 sh, 1 179 ($C_6H_{11}COO$). For $C_{26}H_{40}O_3$ (400·6) calculated: 77·95% C, 10·07% H; found: 77·81% C, 9·93% H.

3β-*Hydroxy*-4aα-*methyl*-A-*homo*-B,19-*dinor*-5α,9β-*androstan*-17-*one* 3-*cyclohexanecarboxylate* (XXV, 287 mg, 48%), m.p. 114–117°C (ethanol); $[\alpha]_D$ +71° (*c* 1·0). IR spectrum (CCl_4): 1 740, 1 725 sh (CO); 1 740, 1 192, 1 177 ($C_6H_{11}COO$). Mass spectrum, *m/z* (%): 400 (M^+, 6); 356 (M^+ – 44·4); 288 ($M^+ - C_6H_{11}COH$, 16); 272 ($M^+ - C_6H_{11}COOH$, 100); 257 (Y4); high resolution: 400·2880 ($C_{26}H_{40}O_3$). For $C_{26}H_{40}O_3$ (400·6) calculated: 77·95% C, 10·07% H; found: 77·63% C, 10·42% H.

17-Hydroxy-4aα,17α-dimethyl-A-homo-B,19-dinor-5α,9β-androstan-3-one (*XXX*)

A solution of methyllithium in ether (1·4 mol l^{-1}, 2 ml) was added at room temperature to a stirred solution of ketone *XXIV* (150 mg, 0·45 mmol) in tetrahydrofuran (2 ml). After 20 h the mixture was poured into dilute hydrochloric acid (5%, 10 ml), the product was taken up in chloroform and the organic layer washed with aqueous potassium hydrogen carbonate solution and water. The crude product *XXVIII* was oxidized according to Jones at 0°C and the oxidation product was extracted with chloroform. The extract was washed with aqueous potassium hydrogen carbonate solution and then with water. After removal of the solvent the product was purified by preparative TLC (4 plates) in benzene–ether 2 : 1 to give 81 mg (59%) of compound *XXX*. IR spectrum (CCl_4): 3 625, 1 100, 1 080 (OH); 1 704 (CO). For $C_{20}H_{32}O_2$ (304·5) calculated: 78·90% C, 10·59% H; found: 78·46% C, 10·86% H.

4aα-Methyl-A-homo-B,19-dinor-5α,9β-androstane-3,17-dione (*XXVII*)

A mixture of acetate *XXIV* (150 mg, 0·45 mmol), potassium hydroxide (100 mg, 1·8 mmol) and

methanol (5 ml) was refluxed under nitrogen for 1 h and then concentrated in vacuo to a quarter of the original volume. The product was precipitated with water and extracted with ether. The extract was washed with water and dried over anhydrous sodium sulfate, the solvent was evaporated and the crude hydroxy derivative *XXVI* was oxidized in acetone according to Jones (20°C, 10 min). The oxidation product was again extracted with ether, the extract washed with water and dried. Evaporation of the solvent followed by preparative TLC (3 plates) in benzene–ether 5 : 1 afforded 58 mg (45%) of the diketone *XXVII*; m.p. 162—164°C (acetone–heptane); $[\alpha]_D$ +68° (*c* 1·1). Mass spectrum, *m/z* (%): 288 (M^+, 64); 270 ($M^+ - H_2O$, 9); 244 ($M^+ - 44$·40); 229 (10); 149 (64); 135, 100). IR spectrum (CCl_4): 1 743 (C=O in five-membered ring); 1 705 (C=O in six-membered ring), For $C_{19}H_{28}O_2$ (288·4) calculated: 79·12% C, 9·78% H; found: 78·99% C, 9·70% H.

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