PARTIAL MODIFICATIONS OF HYDROXY GROUPS IN 5-METHYL-5β-ESTR-9-ENE DERIVATIVES*

Alexander KASAL and Milos BUDESINSKY

Institute of Organic Chemistry and Biochemistry,
Academy of Sciences of the Czech Republic, 166 10 Prague 6, Czech Republic

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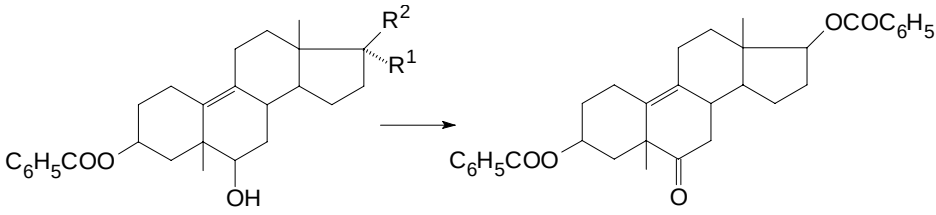
In compounds of the Westphalen type the substituent in position 6 has been removed: the 6β-hydroxyl in 3β,17β-dibenzoyloxy-5-methyl-5β-estr-9-en-6β-ol (**1**) by oxidation to ketone **2** and Huang Minlon reduction, the 6β-chlorine atom in 3β-acetoxy-6β-chloro-5-methyl-5β-estr-9-en-17-one (**13**) by reduction with tributyltin hydride. Androstenedione, testosterone and methyltestosterone analogues **4**, **5**, and **16**, respectively, were prepared from 3β,17β-dihydroxy-5-methyl-5β-estr-9-ene (**3**) by partial oxidation or partial acylation followed by oxidation. Alternatively, these derivatives were prepared from compound **13** without the need of partial transformations.
Key words: Steroids; Conformational analysis; Hormone analogues.

The Westphalen rearrangement of steroid 5-hydroxy derivatives[2,3] affords 5β-steroids with methyl group in position 5 which are interesting from the viewpoint of biological activities. Thus, e.g., a progesterone analogue of this type (5-methyl-19-nor-5β-pregn-9-ene-3,20-dione[4]) affects reproduction[5]: the compound induces abort in rabbits, however, its effect is not antigestagenic[6] because it is not bonded to the gestagenic receptor[7]. With this in mind, we decided to prepare similar analogues of other sex hormones – androgens, in which the position of the Δ^4-double bond and the angular 10β-methyl group is interchanged in an analogous way. In the present study we describe the preparation and properties of such analogues of androstenedione, testosterone and 17-methyltestosterone.

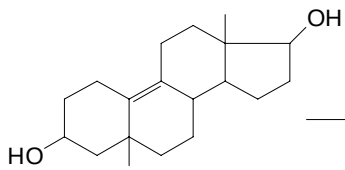
As the starting compound for their preparation we have chosen the easily accessible[8] 3β,17β-dibenzoyloxy-5-methyl-5β-estr-9-en-6β-ol (**1**) (see Scheme 1) which was oxidized to give ketone **2**. Huang Minlon reduction of compound **2** with simultaneous hydrolysis of both the benzoate groups afforded derivative **3** with free hydroxy groups in positions 3 and 17. As shown by the ^{1}H NMR spectrum (Table I), the 3-hydroxy group was axial (in an analogous way, Mousseron-Canet[9] proved the axial character of 3β-hydroxyl in

* Part CCCLXXX in the series On Steroids; Part CCCLXXIX: see ref.[1].



	R^1	R^2
1	H	$OCOC_6H_5$
17	H	OH
19	O	

2



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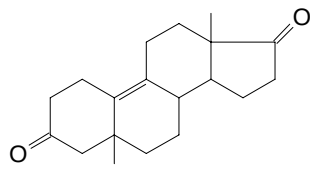

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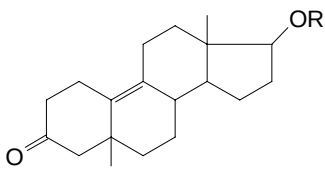
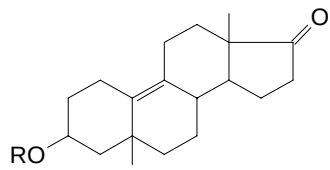
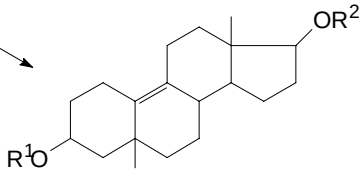


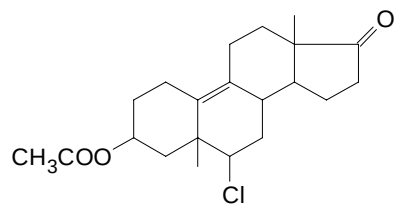
5, R = H
10, R = CH_3CO
12, R = $(CH_3)_3CCO$



6, R = H
11, R = CH_3CO



	R^1	R^2
7	H	CH_3CO
8	CH_3CO	H
9	CH_3CO	CH_3CO



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SCHEME 1

compounds similar to the 6β-alcohol **1**) which offered the possibility of partial transformations of the compound.

Partial oxidation of the diol **3** was realized in several ways: with *N*-bromoacetamide or *N*-bromosuccinimide, as well as by Oppenauer or Jones oxidation. Invariably, the axial 3β-hydroxyl was oxidized faster than the quasiequatorial one in position 17β. Preparatively the simplest method was the oxidation of compound **3** with one equivalent of Jones reagent in dilute acetone solution at low temperatures which gave ketone **5** in 47% yield. In addition, we obtained the 17-ketone **6** (12%) and diketone **4** (19%); some amount of the starting compound (22%) was recovered. The structure of the products was determined on the basis of their ^{1}H NMR and IR spectra (Table I and Experimental, respectively).

The selective acylation of the hydroxy groups in compound **3** was proved by acetylation with acetic anhydride in a mixture of pyridine and toluene. The equatorial 17β-hydroxyl was attacked preferentially and the acetate **7** was obtained in 37% yield whereas its isomer **8** in only 7% yield (the reaction mixture also contained 45% of the starting compound and 10% of the diacetate **9**). The structures were assigned on the

TABLE I
Characteristic parameters of 200 MHz ^{1}H NMR spectra of compounds **2–16** in $CDCl_3$

Compound	13β-Me[a]	5β-Me[a]	H-3[b]	H-17[c]	Other protons
2	1.05	1.49	5.43	4.89	7.52 m, 8.05 m (C_6H_6)
3	0.86	1.25	4.79	3.64	
4	0.89	1.05	–	–	
5	0.88	1.02	–	3.65	
6	1.00	1.29	4.14	–	
7	0.91	1.25	4.12	4.60	2.04 s (OAc)
8	0.86	1.17	3.64	5.07	2.06 s (OAc)
9	0.91	1.17	4.60	5.07	2.04 s (2 × OAc)
10	0.92	1.01	–	4.62	2.04 s (OAc)
11	0.99	1.19	5.06	–	2.06 s (OAc)
12	0.94	1.01	–	4.58	1.21 s ($C(CH_3)_3$)
13	1.01	1.28	5.09	–	2.07 s (OAc); 3.97 dd (H-6; J = 12.5 and 3.8 Hz)
14	0.99	1.21	4.15	–	1.27 s (17-Me)
15	0.99	1.18	5.08	–	1.20 s (17-Me); 2.06 s (OAc)
16	0.99	1.01	–	–	1.22 s (17-Me)

[a] Singlet, 3 H. [b] Quintet, ΣJ = 15 Hz. [c] Triplet, J = 8 Hz.

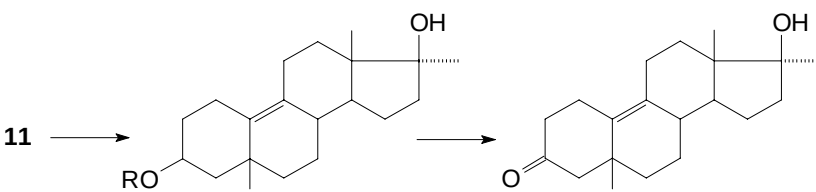
basis of characteristic chemical shifts of the C**H**OR signals in ^{1}H NMR spectrum before and after the acylation.

Both the monoacetates **7** and **8** were oxidized to the isomeric acetoxy ketones **10** and **11** which were hydrolyzed to give the above-described hydroxy ketones **5** and **6**. The former isomer represents the desired analogue of testosterone and was characterized by conversion into the corresponding pivalate **12**.

Since the observed difference in reactivity of the hydroxy groups in diol **3** was surprisingly small, we tried an alternative way, starting with the 6β-chloro derivative **13** (ref.[10]) which already bears different functionalities in the positions 3 and 17. The chlorine atom in compound **13** was removed by reduction with tributyltin hydride[11] to give the above-mentioned ketone **11** in 96% yield.

For the preparation of the corresponding 17-methyltestosterone analogue **16** the reaction of ketone **11** with methyllithium seemed the method of choice. It is known, however, that with easily enolizable 17-ketones the reaction gives considerable amount of lithium enolate products and therefore catalysis with cerium chloride, which favours the desired addition to the carbonyl group, is recommended[12]. We performed the reaction of ketone **11** with methylmagnesium iodide in boiling benzene and the addition to the carbonyl proceeded in high yield even in the absence of cerium chloride (see Scheme 2): the 17-methyl derivative **14** crystallized directly from benzene in 84% yield, a further amount (9%) being obtained on chromatography of the mother liquors. On the other hand, the use of methyllithium in ether (also in the absence of cerium catalyst) resulted in recovery of 39% of the starting ketone (because of limited solubility, the chromatographic separation was performed after conversion into the acetates **11** and **15**). Compound **14** was then oxidized with Jones reagent to give the desired analogue **16**.

For the 6β-hydroxy derivative **1** and the 6-deoxy derivative **8** we tried to find the energetically most advantageous conformations of the rings A and B using the MOPAC method (ref.[13]). The results were compared with the experimental NMR data. For the ring A the calculations gave invariably a chair form with axial substituent in position 3.



14, R = H
15, R = CH_3CO
16

SCHEME 2

The best conformation of the ring B appeared to be a half-chair form $_6HC^7$ (Fig. 1) whose geometry was not seriously affected by substitution in position 6β. The alternative half-chair form $^6HC_7$ (Fig. 1) in the 6β-hydroxy derivative **1** is apparently destabilized by steric interaction of the axial 6β-hydroxyl with the 5β-methyl group (the calculated energy difference between both forms being about 13 kJ). For the 6-deoxy

TABLE II
Interproton torsion angles of ring B in half-chair conformation and the observed ^3J(H,H) in 6β-hydroxy derivatives **1**, **17–19** and 6-deoxy derivative **8**

Protons	Interproton torsion angles, °						*J*, Hz for **1**, **17–19** and **8**	
	from MOPAC (for **1** and **8**)				from electron diffraction[a]			
	6β-OH		6-deoxy		cyclohexene		6β-OH	6-deoxy[b]
	$_6HC^7$	$^6HC_7$	$_6HC^7$	$^6HC_7$	$_6HC^7$	$^6HC_7$		
6α,7α	–68	53	–62	60	–60	60	3.8	3.1 (2.9)
6α,7β	175	–63	180	–57	–177	–56	12.0	9.2 (9.3)
6β,7α	–	–	54	175	56	177	–	8.5 (7.7)
6β,7β	–	–	–62	58	–60	60	–	3.2 (3.0)
7α,8β	–79	180	–82	180	–73	–162	2.0	5.4 (5.5)
7β,8β	38	–61	34	–61	45	–43	7.1	5.7 (5.8)

[a] Calculated from data in ref.[14]. [b] *J*-Values calculated using generalized Karplus equation (according ref.[16]) and the torsion angles calculated with MOPAC for the equilibrium mixture of $_6HC^7$ and $^6HC_7$ in the ratio 60 : 40 are given in parentheses.

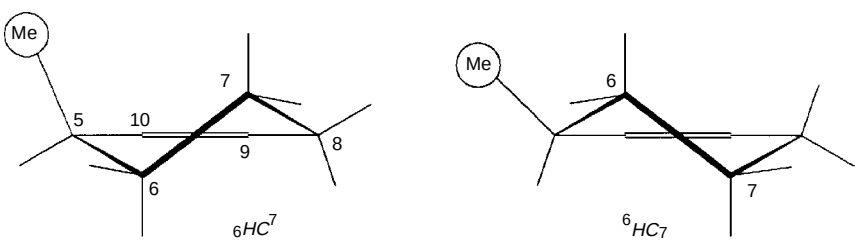
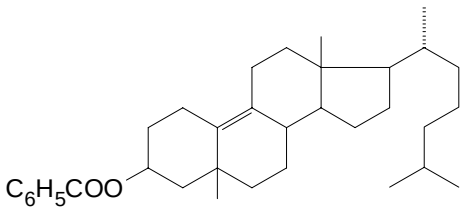


FIG. 1
Schematic representation of half-chair conformations $_6HC^7$ and $^6HC_7$ of ring B in 5-methyl-5β-estr-9-ene derivatives

derivative **8** we obtained a substantially lower energy difference (about 1.3 kJ in favour of the $_6HC^7$ form). The calculated dihedral angles are very similar to those found by electron diffraction for cyclohexene[14] (Table II).



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These results were compared with the ^{1}H NMR data obtained from 500 MHz spectra of the 6β-hydroxy derivatives **1**, **17–19** and the 6-deoxy derivative **8** in which we assigned all the proton signals (Table III) and determined almost all the coupling constants. For the structural assignment of the interacting protons we made use of 2D-COSY spectra. In some cases the multiplets of partly overlapping protons were verified by 2D-J-resolved spectra. The stereospecific assignment of protons H-6 and H-7 in the 6-deoxy derivative **8** was made on the basis of 2D-ROESY spectrum; assignment of protons H-4 was based on the characteristic long-range coupling between equatorial protons, $J(2\beta,4\beta)$ = 2.6 Hz. Compounds **1** and **17**, and the previously prepared[8,15] compounds **18** and **19**, were studied in order to verify a possible effect of substitution in position 17 on the conformation of the rings A and B. Analysis of the NMR data has shown that for all the studied 6β-hydroxy derivatives **1** and **17–19** the coupling constants of protons on the rings A and B are the same within the experimental error and that the effect of substituent in position 17 is negligible. The observed vicinal coupling constants ($J(1\alpha,2\alpha)$ = 4.5, $J(1\alpha,2\beta)$ = 2.9, $J(1\beta,2\alpha)$ = 13.0, $J(1\beta,2\beta)$ = 4.2, $J(2\alpha,3\alpha)$ = 3.9, $J(2\beta,3\alpha)$ = 2.6, $J(3\alpha,4\alpha)$ = 3.9 and $J(3\alpha,4\beta)$ = 2.6 Hz) and long-range coupling constants ($J(2\beta,4\beta)$ = 2.6, $J(1\beta,8\beta)$ = 2.5 and $J(1\beta,11\beta)$ = 1.4 Hz) show unequivocally that, in solution, the ring A in all the studied compounds **1** and **17–19** assumes the chair form with axial substituent in position 3, in accord with the above-mentioned energy calculations.

As concerns the conformation of the ring B, the values of vicinal coupling constants for the 6β-hydroxy derivatives **1** and **17–19** differ markedly from those for the 6-deoxy derivative **8** (Table II). Application of the generalized Karplus relation between the torsion angles and coupling constants[16] shows that for the 6β-hydroxy derivatives **1** and **17–19** the set of the observed values ^3J(H,H) fits the half-chair conformation $_6HC^7$ (but not $^6HC_7$), in accord with the above-discussed energy calculations (Fig. 1). On the other hand, in the case or the 6-deoxy derivative **8** the experimental ^3J(H,H) values fit neither the form $_6HC^7$ nor the form $^6HC_7$. The found values, $J(6\alpha,7\alpha)$ = 3.1, $J(6\alpha,7\beta)$ = 9.2,

TABLE III

Proton chemical shifts of 6β-hydroxy derivatives **1**, **17–19** and 6-deoxy derivative **8** in $CDCl_3$ (from 500 MHz ^1H NMR spectra)

Proton	Chemical shifts				
	1[a]	**17**[b]	**18**[b,c]	**19**[b]	**8**[d]
1α	2.58	2.58	2.57	2.58	2.50
1β	~2.27	2.30	2.28	2.32	2.21
2α	~1.60	1.61	1.57	~1.61	1.45
2β	2.10	2.09	2.08	~2.09	1.92
3α	5.39	5.37	5.36	5.36	5.07
4α	~1.60	1.59	1.60	1.58	1.55
4β	2.33	2.30	2.30	2.32	1.70
6α	3.59	3.57	3.58	3.59	1.35
6β	–	–	–	–	1.28
7α	1.59	1.56	1.56	1.68	1.19
7β	1.82	1.79	1.78	1.87	1.65
8β	~2.28	2.21	2.15	2.34	1.96
11α	2.63	2.63	2.54	2.72	2.65
11β	1.93	1.92	1.93	1.93	1.93
12α	1.22	1.02	~1.10	1.22	1.02
12β	1.86	185	2.01	1.84	1.82
14α	1.56	~1.37	1.42	~1.61	1.18
15α	~1.81	1.70	1.68	2.04	1.62
15β	1.48	~1.37	1.28	~1.61	1.31
16α	1.70	1.49	1.85	2.11	1.45
16β	2.31	2.09	~1.14	2.49	2.07
17α	4.88	3.68	~1.13	–	3.64
13β-Me	1.09	0.90	0.81	1.02	0.87
5β-Me	1.27	1.26	1.25	1.27	1.18

[a] Other signals of two C_6H_5COO: 8.06 and 8.07 (H-2′,6′), 7.45 and 7.46 (H-3′,5′), 7.56 and 7.57 (H-4′). [b] Other signals of C_6H_5COO: 8.07 (H-2′,6′), 7.46 (H-3′,5′), 7.57 (H-4′). [c] Other signals: 0.87 d (3 × H-26 and 3 × H-27), 0.90 d (3 × H-21), 1.39 (H-20), 0.99 and 1.32 (2 × H-22), 1.12 (H-23), 1.63 and 1.12 (2 × H-24), 1.51 (H-25). [d] Other signal: 2.07 s (CH_3COO).

$J(6\beta,7\alpha)$ = 8.5, $J(6\beta,7\beta)$ = 3.2, $J(7\alpha,8\beta)$ = 5.4 and $J(7\beta,8\beta)$ = 5.7 Hz, indicate a possible averaging due to conformational equilibrium between the forms ${}_6HC^7$ and ${}^6HC_7$. Actually, the assumption of such an equilibrium between ${}_6HC^7$ and ${}^6HC_7$ in the ratio of about 60 : 40 leads to a very good accord between the calculated and observed values of ^3J(H,H) for the derivative **8** (see Table II). The preference of conformer ${}_6HC^7$ agrees with our calculations (the energy difference of about 1.3 kJ corresponds to the ratio of about 75 : 25 in favour of the form ${}_6HC^7$).

The bonding of the synthesized compounds to an androgenic receptor and their other properties will be the subject of a separate communication[17].

EXPERIMENTAL

Melting points were determined on a micro melting point apparatus Boetius (Germany) and are uncorrected. Optical rotations and infrared spectra (wavenumbers in cm^{-1}) were measured in chloroform unless stated otherwise. ^{1}H NMR spectra were measured on an FT NMR spectrometer Varian UNITY-200 (200 MHz) in deuteriochloroform with tetramethylsilane as internal standard. Proton 1D and 2D-COSY spectra of compounds **1**, **8**, **17–19** and 2D-ROESY spectrum of **8** were recorded on a Varian UNITY-500 instrument (500 MHz). Thin-layer chromatography was performed on silica gel (ICN Biochemicals), column chromatography on silica gel 60–120 μm.

3β,17β-Dibenzoyloxy-5-methyl-5β-estr-9-en-6-one (**2**)

Jones reagent was added dropwise at 0 °C to a solution of 6β-alcohol **1** (10 g, 19.4 mmol, ref.[8]) in acetone (80 ml) to constant orange coloration. After further 5 min the excess reagent was destroyed with methanol and the mixture was poured into saturated aqueous solution of potassium hydrogen carbonate. The precipitated product was taken up in chloroform and the extract was washed with water. After drying, the solvent was evaporated in vacuo and the residue was crystallized from ether to give 8.36 g (84%) of the product, m.p. 162–165 °C, $[\alpha]_D$ +41° (*c* 1.6). IR spectrum: 1 712, 1 279 (BzO); 1 712, (C=C); 1 603, 1 585, 1 491, 1 452, 1 315, 1 176, 1 117, 1 070, 1 027 (arom). For $C_{33}H_{36}O_5$ (512.6) calculated: 77.32% C, 7.08% H; found: 77.19% C, 7.11% H.

5-Methyl-5β-estr-9-ene-3β,17β-diol (**3**)

Ketone **2** (29.0 g, 56.6 mmol) was refluxed with hydrazine monohydrate (99%, 290 ml, 6 mol). After 4 h, ground potassium hydroxide (29.0 g, 0.52 mol) and triethylene glycol (500 ml) were added and volatile products were distilled from the mixture until its temperature reached 200 °C. The mixture was refluxed for 3 h, cooled and poured into saturated solution of sodium chloride (2 l). The deposited product (20.9 g) was crystallized from toluene to give 3.9 g of compound **3**; chromatography of the mother liquors on silica gel (200 g, 20% ether in benzene) and subsequent crystallization from toluene gave further 3.27 g of compound **3** (total yield 44%). M.p. 172–174 °C, $[\alpha]_D$ + 58° (*c* 1.0). IR spectrum (KBr): 3 300 (OH); 1 100, 1 057, 1 027 (C–O). For $C_{19}H_{30}O_2$ (290.4) calculated: 78.57% C, 10.41% H; found: 78.20% C, 10.63% H.

Oxidation of 3β,17β-dihydroxy-5-methyl-5β-estr-9-ene (**3**)

A) According to Oppenauer: A solution of diol **3** (250 mg, 0.86 mmol) in toluene (18 ml) and cyclohexanone (6 ml, 59 mmol) was distilled until 10 ml of azeotrope was collected and then alumi-

nium isopropoxide (300 mg, 3.12 mmol) was added. During 45 min 6.5 ml of the distillate was collected. After cooling, the mixture was diluted with chloroform, washed with dilute hydrochloric acid (5%) and water, and the volatiles were steam-distilled. Thin-layer chromatography afforded:

*5-Methyl-5*β*-estr-9-ene-3,17-dione* (**4**, 41 mg, 17%), m.p. 130–132 °C (methanol), $[\alpha]_D$ +110° (*c* 1.1). IR spectrum (CCl_4): 1 743 (5-membered ring ketone); 1 714 (6-membered ring ketone). For $C_{19}H_{26}O_2$ (286.4) calculated: 79.68% C, 9.15% H; found: 79.36% C, 9.13% H.

*3*β*-Hydroxy-5-methyl-5*β*-estr-9-en-17-one* (**6**, 12 mg, 5%), m.p. 167–168 °C (acetone), $[\alpha]_D$ +172° (*c* 0.9). IR spectrum: 3 615 (OH); 1 732 (C=O). For $C_{19}H_{28}O_2$ (288.4) calculated: 79.12% C, 9.78% H; found: 79.07% C, 9.86% H.

*17*β*-Hydroxy-5-methyl-5*β*-estr-9-en-3-one* (**5**, 105 mg, 42%), m.p. 123–125 °C (ether–heptane), $[\alpha]_D$ +14° (*c* 1.5). IR spectrum: 3 613, 3 458 (OH); 1 703 (C=O); 1 041 (C–O). For $C_{19}H_{28}O_2$ (288.4) calculated: 79.12% C, 9.78% H; found: 79.35% C, 10.00% H. Starting diol **3** (18 mg, 7%).

B) With Jones reagent: Jones reagent (two drops) was added at –68 °C to a stirred solution of diol **3** (50 mg, 0.172 mmol) in acetone (20 ml). After 5 min the cooling bath was removed and the stirring was continued for another 30 min. The excess reagent was destroyed with methanol (10 drops) and the mixture was filtered. The solid on the filter was washed with acetone and the combined filtrates were concentrated in vacuo to about 0.2 ml. Saturated aqueous solution of potassium hydrogen carbonate was added and the deposited product was extracted with chloroform. The extract was washed, concentrated in vacuo and subjected to preparative TLC on silica gel (3 plates 20 × 20 × 0.1 cm, ether–benzene 1 : 1). Extraction of four zones afforded: dione **4** (9.4 mg, 19%), 3-hydroxy derivative **6** (6.1 mg, 12%), 17-hydroxy derivative **5** (23.1 mg, 47%), and the starting diol **3** (10.9 mg, 22%). The compounds were identical (IR, ^{1}H NMR) with the compounds prepared above.

Acetylation of 5-Methyl-5β-estr-9-en-3β,17β-diol (**3**)

A solution of diol **3** (2.1 g, 7.23 mmol) in toluene (90 ml) was distilled and 70 ml of azeotrope was collected. Pyridine (9 ml, 111 mmol) and acetic anhydride (5.5 ml, 58.3 mmol) were added at 20 °C and after standing for 2.5 h the mixture was diluted with methanol (5.5 ml, 135.8 mmol) and set aside overnight. The solution was concentrated in vacuo, the dry residue was dissolved in chloroform and washed successively with dilute hydrochloric acid, water, potassium hydrogen carbonate solution and again water, and dried over sodium sulfate. The mixture was separated by chromatography on silica gel (100 g) in 10% toluene in light petroleum, toluene, and finally 10% ether in toluene. In addition to the starting diol **3**, the following compounds were obtained:

*3*β*,17*β*-Diacetoxy-5-methyl-5*β*-estr-9-ene* (**9**, 213 mg, 10%), m.p. 113–115 °C (methanol), $[\alpha]_D$ +67° (*c* 1.0). IR spectrum (CCl_4): 1 737, 1 241 (AcO). For $C_{23}H_{34}O_4$ (374.5) calculated: 73.76% C, 9.15% H; found: 73.81% C, 9.09% H.

*17*β*-Acetoxy-5-methyl-5*β*-estr-9-en-3*β*-ol* (**7**, 767 mg, 37%), m.p. 146–148 °C (acetone–heptane), $[\alpha]_D$ +70° (*c* 0.95). IR spectrum: 3 613, 3 505, 3 424 (OH); 1 722, 1 256 (AcO); 1 027 (C–O). For $C_{21}H_{32}O_3$ (332.5) calculated: 75.86% C, 9.70% H; found: 75.66% C, 9.59% H.

*3*β*-Acetoxy-5-methyl-5*β*-estr-9-en-17*β*-ol* (**8**, 144 mg, 7%), m.p. 129–131 °C (acetone–heptane), $[\alpha]_D$ +68° (*c* 1.05). IR spectrum: 3 612 (OH); 1 725, 1 711 sh, 1 247 (AcO). For $C_{21}H_{32}O_3$ (332.5) calculated: 75.86% C, 9.70% H; found: 75.90% C, 9.66% H.

17β-Acetoxy-5-methyl-5β-estr-9-en-3-one (**10**)

Jones reagent was added dropwise at room temperature to a solution of compound **7** (2.66 g, 8.0 mmol) in a mixture of chloroform (5 ml) and acetone (15 ml) until the orange coloration persisted. After further 7 min the excess reagent was destroyed with methanol, the precipitate was filtered and the filtrate concentrated to one fifth of the original volume. The product was precipitated by addition of

saturated aqueous solution of sodium chloride, collected on filter and washed with water. Crystallization from acetone and heptane afforded compound **10** (2.42 g, 91%), m.p. 116–117 °C, $[\alpha]_D$ +15° (*c* 1.4). IR spectrum (CCl_4): 1 738, 1 245 (AcO); 1 715 (C=O). For $C_{21}H_{30}O_3$ (330.5) calculated: 76.33% C, 9.15% H; found: 76.17% C, 9.27% H.

17β-Hydroxy-5-methyl-5β-estr-9-en-3-one (**5**)

Acetate **10** (205 mg, 0.62 mmol) was dissolved in methanolic solution of potassium hydroxide (*c* 0.12 mol l^{-1}, 15 ml). After standing for 18 h under argon, acetic acid (0.1 ml, 1.75 mmol) was added. The solution was concentrated in vacuo to one fifth of the original volume, the product was precipitated by addition of water, collected and washed with water (170 mg, 95%). Crystallization afforded compound **5**, m.p. 124–125 °C (acetone–heptane), $[\alpha]_D$ +15° (*c* 0.9), identical in all respects with the product obtained by direct oxidation of diol **3**.

3β-Acetoxy-5-methyl-5β-estr-9-en-17-one (**11**)

A) A solution of chloro derivative[10] **13** (2.63 g, 7.21 mmol) in toluene (20 ml) and 2,2′-azobis(2-methylpropionitrile) (5 mg) were added to a stirred solution of tributyltin hydride (*c* 1 mol l^{-1}) and the solution was refluxed for 7 h under nitrogen. The mixture was concentrated in vacuo and the residue was partitioned between ether and 10% aqueous solution of potassium fluoride. The ethereal phase was dried over sodium sulfate and purified by flash chromatography on a column of silica gel (120 g, 12% ether in light petroleum). The product (2.28 g, 96%) was crystallized from acetone, m.p. 159–161 °C, $[\alpha]_D$ +153° (*c* 1.1). IR spectrum (CCl_4): 1 741, 1 241 (AcO), 1 741 (C=O). For $C_{21}H_{30}O_3$ (330.5) calculated: 76.33% C, 9.15% H; found: 76.06% C, 9.30% H.

B) Compound **8** (350 mg, 1.05 mmol) was oxidized with Jones reagent as described for the preparation of compound **10**. Yield 302 mg (86%) of compound **11**, m.p. 158–161 °C, undepressed on admixture with the compound prepared by procedure *A*.

17β-Pivaloyloxy-5-methyl-5β-estr-9-en-3-one (**12**)

Pivaloyl chloride (1.0 ml, 8.1 mmol) was added under cooling with ice to a solution of hydroxy ketone **5** (310 mg, 1.07 mmol) in pyridine (1 ml). After standing at room temperature for 18 h, the mixture was poured into water with ice (10 ml), the product was taken up in ether and the extract was successively washed with 1% hydrochloric acid, saturated aqueous potassium hydrogen carbonate solution and water. The solution was dried over sodium sulfate, the solvent was evaporated and the product (335 mg, 84%) was crystallized from acetone and heptane. M.p. 133–135 °C, $[\alpha]_D$ +22° (*c* 1.2). For $C_{24}H_{36}O_3$ (372.6) calculated: 77.38% C, 9.74% H; found: 77.19% C, 9.80% H.

5,17-Dimethyl-5β-estr-9-ene-3β,17β-diol (**14**)

A) A solution of ketone **11** (3.0 g, 9.08 mmol) in benzene (150 ml) was added dropwise to a stirred solution of methylmagnesium iodide, prepared from magnesium (2.25 g, 92.6 mmol) and methyl iodide (6.0 ml, 96.4 mmol) in ether (48 ml). The stirred mixture was heated until 200 ml of distillate came over. Then the mixture was refluxed for 3 h, cooled and poured on a mixture of ice (100 g) and concentrated hydrochloric acid (10 ml, 120 mmol). The product was taken up in benzene, the extract was washed successively with water, sodium thiosulfate, potassium hydrogen carbonate and water. After drying over sodium sulfate, the solution was concentrated and the crystalline product (2.37 g, 86%) collected, m.p. 114–116 °C, $[\alpha]_D$ +40° (*c* 1.5). IR spectrum (CCl_4): 3 613, 3 450 (OH). For $C_{20}H_{32}O_2$ (304.5) calculated: 78.90% C, 10.59% H; found: 78.87% C, 10.62% H. Chromatography of

the mother liquors afforded further portion (237 mg) of the product 14 making the total yield 94%. Also ketone **6** was isolated (51 mg, 1.8%).

B) A solution of methyllithium in ether (*c* 1.6 mol l^{-1}, 0.6 ml) was added at 20 °C to a solution of compound **14** (100 mg, 0.30 mmol) in tetrahydrofuran (0.2 ml). After 18 h the mixture was decomposed by pouring on a mixture of ice (5 g) and concentrated hydrochloric acid (0.2 ml) and the product was extracted with chloroform. The extract was washed with water, potassium hydrogen carbonate solution and again with water, and dried over sodium sulfate. According to thin-layer chromatography, the product consisted of compounds **6** and **14**; their ratio was determined after acetylation with acetic anhydride (0.4 ml) in pyridine (0.4 ml). Preparative thin-layer chromatography afforded acetate **11** (39 mg, 39%) and acetate **15** (57 mg, 54%).

17β-Hydroxy-5,17-dimethyl-5β-estr-9-en-3-one (**16**)

Jones reagent was added dropwise at room temperature to a stirred solution of diol **14** (2.26 g, 7.42 mmol) in acetone (70 ml). After 10 min the mixture was worked up as described for the compound **10**. The product **16** (2.16 g, 95%) was crystallized from acetone and heptane, m.p. 98–99 °C, $[\alpha]_D$ –10° (*c* 1.1). IR spectrum: 3 612, 3 475 (OH); 1 702 (C=O). For $C_{20}H_{30}O_2$ (302.4) calculated: 79.42% C, 10.00% H; found: 79.57% C, 9.84% H.

3-β-Benzoyloxy-5-methyl-5β-estr-9-ene-6β,17β-diol (**17**)

Sodium borohydride (60 mg, 1.6 mmol) was added at 0 °C to a stirred solution of compound **19** (ref.[13], 210 mg, 0.51 mmol) in ethanol (5 ml). After stirring for 15 min, the mixture was set aside at room temperature for 2 h and then poured into 1% hydrochloric acid (25 ml). The precipitate was collected, washed with water and crystallized from acetone to give 146 mg (69%) of product **17**, m.p. 238–240 °C, $[\alpha]_D$ +136° (*c* 1.1). For $C_{26}H_{34}O_4$ (410.6) calculated: 76.06% C, 8.35% H; found: 75.95% C, 8.40% H.

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