DIHYDROTESTOSTERONE WITH AN AMMONIUM CENTRE IN THE POSITION 16β*

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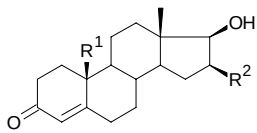
In an alternative synthesis of 17β-hydroxy-16β-(piperidin-1-yl)-5α-androstan-3-one (**4**), neighbouring group participation between a 17β-carbonyloxy group and the 16β-amino group was used and a high yield partial hydrolysis of 3β,17β-diacetoxy-16β-(piperidin-1-yl)-5α-androstane (**11**) was developed. Interference of the neighbouring group participation was also apparent in another 17β-acetoxy derivative – in oxidation of compound **12** to **13**. Compound **4** was converted into water-soluble derivatives, *i.e.* quaternary ammonium derivatives **17** to **20**.

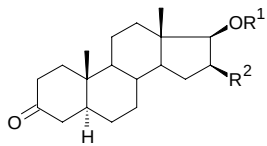
Key words: Neighbouring group participation; Hormone analogues; Quaternary ammonium salts.

Antiandrogenic activity[2] has been sought for many years and several more, or less active compounds[3,4] have been found. One of them, 16β-ethyl-17β-hydroxy-19-norandrost-4-en-3-one (TSAA291, **1**) has[5] dual action: it inhibits the activity of 5α-reductase in a competitive way and binds to an androgen receptor. The ethyl group in the 16β-position apparently converted an androgen (**2**) into its antagonist (**1**).

We envisaged that introduction of a dialkylamino group into a molecule of dihydrotestosterone (**3**) could produce a similar effect. Moreover, the products formed, *e.g.* compound **4**, could be quaternized and thus converted into water-soluble salts.

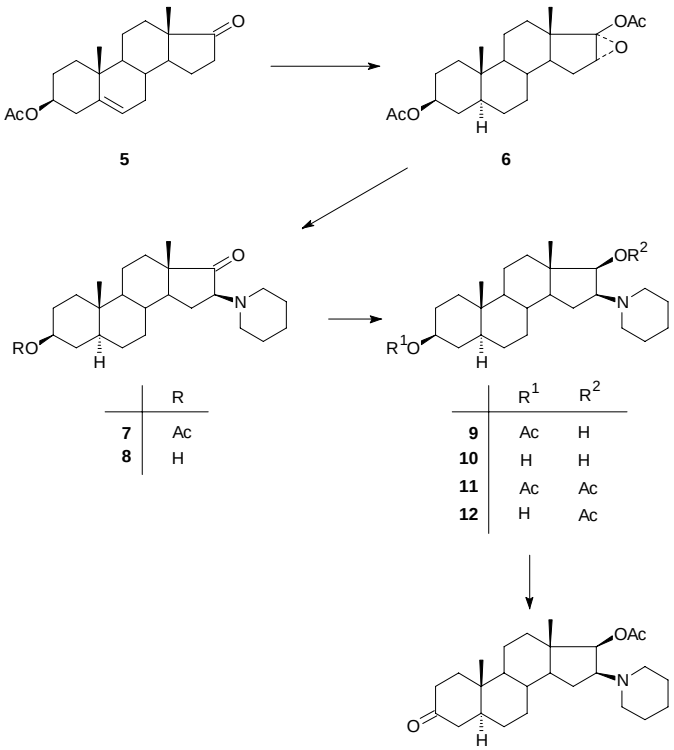


	R^1	R^2
1	H	C_2H_5
2	CH_3	H



	R^1	R^2
3	H	H
4	H	piperidin-1-yl

* Part CCCLXXXIX in the series On Steroids; Part CCCLXXXVIII see ref.[1].



SCHEME 1

A synthesis of **4** has already been described[6], however, Hewett's original procedure contained low-yield steps of partial acetalization of oxo groups in positions 3 and 17. Our improved synthesis of **4** is described further.

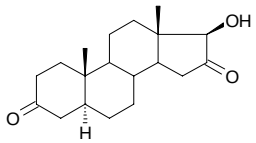
3β-Acetoxyandrost-5-en-17-one (**5**) was converted[7] into epoxide **6** in the conventional manner. The use of methodology previously applied in the production of pipecuronium bromide[8], *i.e.* the treatment of epoxide **6** with aqueous piperidine, afforded 16β-piperidino derivative **7** (*cf.* ref.[9]) along with the corresponding 3β-hydroxy derivative **8** (*cf.* ref.[6]) which had been prepared by another route (see Scheme 1).

Due to the presence of bulky substituents in vicinal positions, sodium borohydride reduction of the 17-oxo group in compounds **7** and **8** proceeded mainly from the α-side yielding predominantly 17β-alcohols **9** and **10**. Acetylation of both compounds to 3,17-diacetate **11** had apparently presented problems to earlier authors[9] and proceeded in poor yields in our hands as well. We found, however, that the low yields originated within the work-up of the reaction mixture. Apparently, neighbouring group participation between the 17β-acetoxy group and the piperidine nitrogen atom increased the sensitivity of the 17β-acetoxy group towards hydrolytic reagents. In a model experi-

ment, diacetate **11** was easily deacetylated to **9** by protic solvents (*e.g.* methanol, water) under mild acidic catalysis (*e.g.* silica gel, see Experimental). When, however, the acetylation and the work-up of the mixture were carried out with the least exposure to protic solvents in the presence of weak acids, diacetate **11** could be isolated in good yields.

Selective hydrolysis of the 3β-acetoxy group in diacetate **11** was cleanly carried out by acid-catalyzed tranesterification with methanol. The neighbouring group participation of the amino group was neutralized with strong acid (perchloric acid) and then the ester group in the position 3 was removed first: monoacetate **12** was produced in 70% yield, its structure is supported by its ^{1}H NMR spectrum (see Table I).

The above mentioned neighbouring group participation interfered in the process once more: in the oxidation of alcohol **12** to ketone **13**. Several methods (chromium(VI) oxide in pyridine, *N*-bromoacetamide in acetic acid, Jones reagent) were tested. A number of side products always accompanied compound **13**. The structure of some of them, apparent from NMR spectra, prove that hydrolysis of the acetoxy group had taken place and was followed by transformation to compound **14**. The best yields of ketone **13** were achieved by Jones oxidation as long as it was carried out rapidly to prevent the hydrolysis and subsequent reactions. For this purpose, the excess of the reagent had to be reduced by fast (*i.e.* inorganic) agents.



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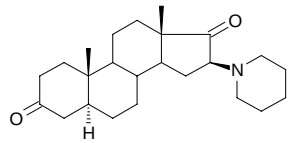

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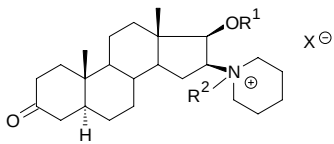

	R^1	R^2	X
16	Ac	CH_3	Br
17	H	CH_3	I
18	H	CH_3	Br
19	H	H	Br
20	H	CH_3	OH

Hydrolysis of ketone **13** produced the title compound, 17β-hydroxy-16β-piperidino-5α-androstan-3-one (**4**). Quaternary ammonium salts **16** to **18** were prepared from piperidino derivatives **13** and **4**, respectively, using the corresponding methyl halide. For

spectral comparison, hydrobromide **19** was prepared in a routine way. The action of wet silver oxide converted iodide **17** into compound **20**. ^{13}C NMR spectra of the quaternary salts, listed in Table II, support the ascribed structures. Some missing signals in room-temperature spectra of compounds **4** and **16** were detected in the spectra measured at 50 °C as very broad signals (35 Hz). The broadening may be due to hindered rotation around the C(16)–N bond. IR spectra of hydroxy compounds **4**, **19**, **17** and **16** exert bands of ν(OH) between 3 400 and 3 248 cm^{-1}.

In spite of its 16,17-substituents, methobromide **18** exerts no neuromuscular blocking activity[8]. The free base **4** shows no significant binding to steroid hormone receptors (androgenic, gestagenic, glucocorticoid, mineralocorticoid and estrogenic), compound **4**, **16** and **20** exert no inhibitory activity of 5α-reductase[10].

TABLE I
Characteristic ^1H NMR parameters (δ, ppm) of compounds **4** and **6–20** in $CDCl_3$

Compound	H-18[a]	H-19[a]	H-3[b]	H-16	H-17	CH_2NCH_2	OAc[a]	OH[c]	NCH_3[a]
4	0.69	1.02	–	2.77[d]	3.40[e]	2.52[f]	–	–	–
6	0.80	0.85	4.64	3.82[g]	–	–	2.04, 1.98	–	–
7	0.83	0.84	4.67	3.11[h]	–	2.65, 2.45[i]	2.01	–	–
8	0.83	0.84	3.60	3.12[h]	–	2.65, 2.45[i]	–	–	–
9	0.66	0.83	4.67	2.75[d]	3.37[e]	2.52[f]	2.02	–	–
10	0.65	0.80	3.57	2.75[d]	3.37[e]	2.50[f]	–	–	–
11	0.80	0.83	4.70	3.05[d]	4.80[e]	2.50[f]	2.10, 2.02	–	–
12	0.80	0.81	3.60	3.05[d]	4.80[e]	2.46[f]	2.10	–	–
13	0.83	1.02	–	3.06[d]	4.80[e]	2.50[f]	2.12	–	–
15	0.87	1.04	–	3.12[h]	–	2.65, 2.45[i]	–	–	–
16	0.85	1.04	–	4.71[j]	5.31[k]	3.97, 3.73[i]	2.19	–	3.44
17	0.82	1.02	–	4.25[j]	4.38[l]	3.99, 3.56[i]	–	4.77	3.31
18	0.88	1.02	–	4.25[j]	4.38[l]	4.01, 3.52[i]	–	5.78	3.33
19	0.93	1.03	–	3.41[m]	4.06[e]	3.90, 3.66[i]	–	–	–
20	0.86	1.05	–	3.95[j]	4.10[l]	3.75, 3.42[i]	–	–	3.16

[a] Singlet, 3 H. [b] Multiplet, 1 H ($W \approx 30$ Hz). [c] Doublet, 1 H ($J = 6.3$ Hz). [d] Doublet of triplets, 1 H ($J = 7.8$, 8.6 and 10.4 Hz). [e] Doublet, 1 H ($J = 8.6$ Hz). [f] Multiplet, 4 H. [g] Singlet, 1 H. [h] Doublet of doublets, 1 H ($J = 8.0$ and 10.0 Hz). [i] 2 × multiplet, 2 × 2 H. [j] Doublet of triplets, 1 H ($J = 9.1$, 9.5 and 9.5 Hz). [k] Doublet, 1 H ($J = 10.1$ Hz). [l] Doublet of doublets, 1 H ($J = 9.1$ and 6.3 Hz). [m] Multiplet, 1 H ($W = 28$ Hz).

TABLE II
Carbon-13 NMR chemical shifts (δ, ppm) of compounds **4**, **13** and **16** in $CDCl_3$

Atom	**13**	**4**		**17**	
	T = 20 °C	*T* = 20 °C	*T* = 50 °C[a]	*T* = 20 °C	*T* = 50 °C[a]
1	38.33	38.40	38.40	38.28	38.16
2	38.04	38.07	37.89	37.98	37.77
3	211.90	212.10	212.48	212.67	212.10
4	44.58	44.59	44.44	44.47	44.30
5	46.50	46.57	46.57	46.34	46.29
6	28.73	28.74	28.70	28.47	28.43
7	31.69	31.81	31.75	31.36	31.25
8	34.07	34.32	34.35	33.92	33.95
9	53.66	53.78	53.86	53.48	53.42
10	35.72	35.71	35.70	35.71	35.67
11	20.96	21.13	21.08	20.83	20.80
12	38.10	38.41	37.89	37.05	36.81
13	42.64	43.22	43.17	44.12	44.03
14	48.22	48.32	48.35	45.99	45.88
15	25.04	27.07	26.99	26.85	26.81
16	65.23	65.70	65.73	[b]	71.83[c]
17	81.82	77.52	77.57	[b]	78.00[c]
18	13.33	13.04	12.80	12.80	12.38
19	11.40	11.39	11.23	11.37	11.18
2′,6′[d]	52.74	[b]	53.33[c]	[b]	61.50; 60.82[c]
3′,5′[d]	26.55	26.29	26.17	20.31; 20.22	20.08; 20.06
4′[c]	24.51	24.28	24.17	20.79	20.78
N–CH_3	–	–	–	[b]	44.97[c]
OAc, C=O	170.82	–	–	–	–
OAc, CH_3	21.25	–	–	–	–

[a] For high temperature spectra *ca* 10% of CD_3OD was added to the $CDCl_3$ solution. [b] Signals were not observed. [c] Very broad signals (*ca* 35 Hz). [d] Piperidine moiety.

EXPERIMENTAL

Melting points were determined on a micro melting point apparatus Boetius (Germany). Optical rotations were measured at 25 °C on a Perkin–Elmer 141 MC polarimeter in chloroform unless stated otherwise. Infrared spectra (wavenumbers in cm^{-1}) were recorded on a Bruker IFS 88 spectrometer in tetrachloromethane, unless stated otherwise. ^1H NMR spectra were taken on a Varian UNITY-200 (200 MHz) spectrometer at 23 °C in deuteriochloroform, with tetramethylsilane as an internal standard. Chemical shifts are given in ppm (δ-scale), coupling constants (*J*) and width of multiplets (*W*) in Hz. ^{13}C NMR spectra were measured using Varian UNITY-500 spectrometer (at 125.7 MHz) and solvent, and referenced to the signal of solvent (δ($CHCl_3$) 77.0). The purity of products and reaction courses were checked by thin-layer chromatography (TLC) performed on silica gel G (ICN Biochemicals), detection was carried out by spraying with sulfuric acid and heating. Preparative thin-layer chromatography (PLC) was carried out on 200 × 200 mm plates of the same silica gel; thickness of the layer was 0.6 mm. Column chromatography was performed on silica gel (60–120 μm).

17β-Hydroxy-16β-(piperidin-1-yl)-5α-androstan-3-one (**4**)

Acetate **13** (6.5 g, 15.64 mmol) was refluxed in a solution of potassium hydroxide in methanol (2%, 150 ml) for 1 h. The solution was concentrated under reduced pressure to a quarter of its volume and the saturated aqueous solution of sodium chloride was added (80 ml). The product was extracted into chloroform, the extract was washed with a saturated aqueous solution of sodium chloride, dried over anhydrous sodium sulfate and evaporated to dryness. The product (5.5 g, 94%) crystallized from acetone–heptane; m.p. 174–176 °C (ref.[6] records 177 °C), $[\alpha]_D$ +31° (*c* 1.2). IR spectrum: 3 400 (O–H); 2 800, 2 740 (C–H), heterocycle); 1 718 (C=O). NMR spectra: see Tables I and II.

17-Oxo-16β-(piperidin-1-yl)-5α-androstan-3β-yl Acetate (**7**)

A solution of epoxide[7] **6** (10 g, 25.6 mmol) in piperidine (100 ml) and water (30 ml) was refluxed for 7 h. Volatile components of the mixture were evaporated under reduced pressure and the residue (10.2 g) was chromatographed on 500 g of silica gel, elution with ammonia-treated chloroform with 10% of toluene. Evaporation of the solvent yielded compound **7** (3.1 g, 31%), which was crystallized from acetone, m.p. 131–134 °C (ref.[9] records 132–134 °C).

3β-Hydroxy-16β-(piperidin-1-yl)-5α-androstan-17-one (**8**)

A) From the reaction mixture: More polar product **8** of the above chromatography (5.8 g, 61%) crystallized from acetone–heptane; m.p. 171–175 °C, $[\alpha]_D$ +110° (*c* 1.15), (ref.[6] records 170–175 °C and $[\alpha]_D$ +113°). IR spectrum: 3 620 (O–H); 2 801, 2 754 (C–H, heterocycle); 1 740 (C=O). For $C_{24}H_{39}NO_2$ (373.6) calculated: 77.16% C, 10.52% H, 3.75% N; found: 76.89% C, 10.57% H, 3.87% N.

B) By hydrolysis: acetate **7** (2 g, 4.81 mmol) was hydrolyzed by refluxing it with a solution of potassium hydroxide in methanol (2%, 40.3 ml, 14.38 mmol) for 1 h. The solution was concentrated under reduced pressure to a quarter of its volume and crude compound **8** was precipitated by the addition of water. The precipitate was filtered off, dissolved in chloroform, washed with water and dried over anhydrous sodium sulfate. Evaporation of solvents under reduced pressure yielded 1.53 g (85%) of compound **8** identical with the sample prepared above.

17β-Hydroxy-16β-(piperidin-1-yl)-5α-androstan-3β-yl Acetate (**9**)

Sodium borohydride (0.6 g, 15.86 mmol) was added under stirring at 0 °C to a solution of **7** (1 g, 2.41 mmol) in methanol (15 ml). After 1 h at room temperature, the solution was poured into a satu-

rated aqueous solution of sodium chloride and extracted with chloroform. The organic layer was washed with water and dried over anhydrous sodium sulfate. Evaporation of solvent yielded **9** (0.771 g, 77%) which crystallized from methanol, m.p. 134–136 °C (ref.[9] records 135–136 °C).

16β-(Piperidin-1-yl)-5α-androstane-3β,17β-diol (**10**)

Compound **8** (0.85 g, 2.28 mmol) was reduced with sodium borohydride (0.45 g, 12 mmol) in methanol (6 ml). After 1 h, the solution was concentrated under reduced pressure to a quarter of its volume, a saturated aqueous solution of sodium chloride was added. A precipitate was extracted to chloroform, the extract was dried over anhydrous sodium sulfate. Evaporation of solvent gave compound **10** (0.73 g, 85%) which crystallized from methanol–water. M.p. 184–186 °C, $[\alpha]_D$ +9° (*c* 1.0), (ref.[6] records 185 °C and $[\alpha]_D$ +13°). IR spectrum: 3 622, 3 400 (O–H); 2 800, 2 740 (C–H, heterocycle).

16β-(Piperidin-1-yl)-5α-androstane-3β,17β-diyl Diacetate (**11**)

Diol **10** (3.0 g, 8.0 mmol) was acetylated with acetic anhydride (9.0 ml, 89 mmol) in pyridine (15 ml) at room temperature. After 18 h, the solution was evaporated to dryness under reduced pressure and the residue quickly crystallized from methanol (temperature did not exceed 35 °C, mostly it was under –10 °C). Yield: 3.13 g (85%); m.p. 193–195 °C, $[\alpha]_D$ –3° (*c* 0.8) (ref.[9] records 195–197 °C). IR spectrum: 2 800, 2 740 (C–H, heterocycle); 1 739 (C=O); 1 243 (C–O).

Stability of Diacetate **11**

a) On silica gel: compound **11** (30 mg) was applied on a PLC plate. After 48 h, the plate was developed with ammonia-treated chloroform and two components were isolated: starting material **11** (21 mg, 70%) and compound **9** (7.1 mg, 26%).

b) In boiling methanol: compound **11** (10 mg) in methanol (20 ml) was refluxed for 20 min. Evaporation of the solvent to dryness and purification on PLC plate (7 × 10 cm) yielded 6.1 mg (68%) of monoacetate **9**.

c) In boiling acetone: compound **11** (10 mg) in acetone (20 ml) was refluxed for 20 min. Evaporation of the solvent to dryness yielded compound **11** only, no hydrolysis was observed.

3β-Hydroxy-16β-(piperidin-1-yl)-5α-androstan-17β-yl Acetate (**12**)

Diacetate **11** (2.53 g, 5.50 mmol) was dissolved in chloroform (10 ml) and a solution (31 ml, prepared by mixing 1 ml of 72% perchloric acid with 49 ml of methanol) was added. After 4 days at room temperature, the solution was concentrated under reduced pressure at 30 °C to a quarter of its volume. Ammonium hydroxide (10 ml) was added and the precipitate was extracted with chloroform. The extract was dried over anhydrous sodium sulfate, evaporated under reduced pressure and crystallized from acetone–heptane. Yield: 1.96 g (70%). M.p. 185–186 °C, $[\alpha]_D$ +13° (*c* 1.2). IR spectrum: 3 622 (O–H); 2 799, 2 741 (C–H, heterocycle); 1 736 (C=O); 1 243, 1 031 (C–O); 1 036 (C–OH). For $C_{26}H_{43}NO_3$ (417.6) calculated: 74.78% C, 10.38% H, 3.35% N; found: 74.48% C, 10.41% H, 3.62% N.

3-Oxo-16β-(piperidin-1-yl)-5α-androstan-17β-yl Acetate (**13**)

Jones reagent (6 ml) was added to a solution of alcohol **12** (2.6 g, 6.23 mmol) in acetone (180 ml). After 2 min, a saturated aqueous solution of sodium metabisulfite (20 ml) was added and the solution was concentrated under reduced pressure to a quarter of its volume. The product was extracted into

chloroform, the extract was washed with water, dried over anhydrous sodium sulfate, and the solvent was evaporated to dryness. Compound **13** crystallized from acetone–heptane (2.05 g, 80%), m.p. 202–206 °C, $[\alpha]_D$ +18° (*c* 0.59). IR spectrum: 2 799, 2 741 (C–H, heterocycle); 1 736, 1 716 (C=O); 1 243, 1 232, 1 030 (C–O). For $C_{26}H_{41}NO_3$ (415.6) calculated: 75.14% C, 9.94% H, 3.37% N; found: 75.44% C, 10.05% H, 3.45% N. Chromatography of mother liquors (0.4 g) on silica gel (20 g) in ammonia-treated chloroform with 10% of toluene afforded an additional crop of compound **13** (0.15 g, 5.8%).

Stability of Compound **13**

Compound **13** (30 mg) was applied on one PLC plate. After 48 h, the plate was developed with ammonia-treated chloroform and two components were isolated: starting material **13** (22 mg, 73%) and hydroxy derivative **4** (6.3 mg, 23%).

16β-(Piperidin-1-yl)-5α-androstane-3,17-dione (**15**)

Chromatography of mother liquors (0.4 g) from the preparation of ketone **13** yielded 0.23 g (9.9%) of compound **15**, m.p. 136–137 °C, $[\alpha]_D$ +130° (*c* 1.1) (ref.[6] records 137 °C, $[\alpha]_D$ +132°). IR spectrum: 2 801, 2 753 (C–H, heterocycle); 1 740, 1 716 (C=O).

N-(17β-Acetoxy-3-oxo-5α-androstan-16β-yl)-*N*-methylpiperidinium Bromide (**16**)

A solution of methyl bromide (0.28 g, 2.95 mmol) in ether (2 ml) was added to a solution of compound **13** (0.1 g, 0.24 mmol) in acetone (0.5 ml) and benzene (0.5 ml). After 48 h, a solid product was filtered off, mother liquors after evaporating yielded starting material **13** (0.07 g, 56%). The solid product was crystallized from acetone (0.035 g, 28%); m.p. 243–244 °C, $[\alpha]_D$ –17° (*c* 0.8). IR spectrum: 1 757, 1 707 (C=O); 1 238, 1 024 (C–O); 914 ($R^1R^2R^3R^4N^+$). For $C_{27}H_{44}BrNO_3$ (510.6) calculated: 63.52% C, 8.69% H, 15.65% Br, 2.74% N; found: 64.29% C, 8.67% H, 15.43% Br, 2.68% N.

N-(17β-Hydroxy-3-oxo-5α-androstan-16β-yl)-*N*-methylpiperidinium Iodide (**17**)

Methyl iodide (0.5 ml, 8.03 mmol) was added to a solution of compound **4** (0.7 g, 1.87 mmol) in benzene (3 ml). After 18 h, a solid product was filtered off and crystallized from acetone. Yield: 0.516 g (53%); m.p. 273–274 °C, $[\alpha]_D$ +8° (*c* 1.1). IR spectrum: 3 307 (O–H); 1 707 (C=O); 1 027 (C–OH); 941 ($R^1R^2R^3R^4N^+$). For $C_{25}H_{42}INO_2$ (515.5) calculated: 58.25% C, 8.15% H, 24.66% I, 2.72% N; found: 58.03% C, 8.21% H, 24.36% I, 2.72% N.

N-(17β-Hydroxy-3-oxo-5α-androstan-16β-yl)-*N*-methylpiperidinium Bromide (**18**)

A solution of methyl bromide (0.51 g, 5.3 mmol) in ether (4 ml) was added to a solution of compound **4** (0.5 g, 1.34 mmol) in acetone (2 ml) and benzene (2 ml). After 48 h, a solid product was filtered off and crystallized from acetone (0.358 g, 57%); m.p. 280–283 °C, $[\alpha]_D$ +1° (*c* 1.2). IR spectrum: 3 248 (O–H); 1 709 (C=O); 1 027 (C–OH); 942 ($R^1R^2R^3R^4N^+$). For $C_{25}H_{42}BrNO_2$ (468.5) calculated: 64.09% C, 9.04% H, 17.06% Br, 2.99% N; found: 63.90% C, 9.02% H, 16.08% Br, 3.02% N.

N-(17β-Hydroxy-3-oxo-5α-androstan-16β-yl)piperidinium Hydrobromide (**19**)

Compound **4** (10 mg, 0.03 mmol) in chloroform (0.3 ml) was treated with hydrobromic acid (0.11 ml, 1 mmol) to give **19** (7.5 mg, 62%). M.p. 291–293 °C. IR spectrum: 3 363 (O–H); 2 645 (N^+–H);

1 707 (C=O). For $C_{24}H_{40}BrNO_2$ (454.50) calculated: 63.43% C, 8.87% H, 17.58% Br, 3.08% N; found: 63.54% C, 9.18% H, 17.12% Br, 3.34% N.

N-(17β-Hydroxy-3-oxo-5α-androstan-16β-yl)-*N*-methylpiperidinium Hydroxide (**20**)

Compound **17** (0.33 g, 0.64 mmol) in H_2O (15 ml) was refluxed with silver oxide (0.5 g, 4 mmol) for 30 min. The solution was filtered, concentrated to 3 ml and kept at 0 °C for 5 days to give compound **20** (0.062 g, 24%). M.p. 237–241 °C. For $C_{25}H_{43}NO_3$ (405.6) calculated: 74.03% C, 10.69% H, 3.45% N; found: 73.85% C, 10.47% H, 3.35% N.

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