SYNTHESIS OF 17α-HYDROXY STEROIDS: B-NOREPITESTOSTERONE*

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The key intermediate *VI* was prepared by two ways: by B ring contraction of an androst-5-ene-3β,17α-diol derivative *I* and by configurational inversion of the 17β-hydroxy group in a B-norandrost-5-ene-3β,17β-diol derivative *XII*. B-Norepitestosterone (*IX*) and its potential metabolite *X* were then prepared by standard methodology. Both these compounds appear to be inhibitors of 5α-reductase.

Within the framework of studies of biological properties of 17α-hydroxysteroids[1] which could find application in treatment of diseases of some androgen-dependent tissues[2] we decided to prepare 17α-hydroxy derivatives of several androgen analogs with modified B ring that had already been studied earlier. B-Normethyltestosterone[3,4], the first clinically applied antiandrogen, was for the first time prepared in this Laboratory[5,6] and therefore as the first modification of structure of epitestosterone and its derivatives we have chosen contraction of the B ring in these compounds, i.e., the synthesis of B-norepitestosterone *IX*.

As starting compound we used androst-5-ene-3β,17α-diyl 3-acetate 17-benzoate (*I*), an intermediate from the preparation of labelled epitestosterone[1]. This was oxidized with chromium trioxide in acetic acid. In accord with the previous findings[7], the neutral portion of the reaction mixture consisted mainly of the corresponding 7-keto derivative *II*: the oxidation introduced a keto group in the neighbourhood of the double bond (an IR band at 1 678 cm^{-1} due to ν(C=O) and a downfield shift of H-6 proton in the NMR spectrum). The acidic portion of the oxidation mixture contained the desired 5-oxo-5,6-seco-6-oic acid *III* as evidenced by its physical (IR, ^1H NMR spectra) as well as chemical (different R_F values in TLC in acidic or ammonia systems; see Experimental) properties. Under conditions of benzoylation in pyridine, this seco acid underwent

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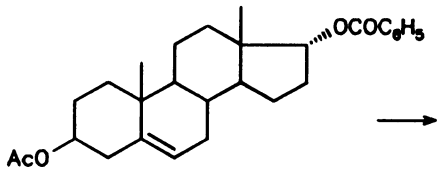
the expected condensation to β-hydroxy acid which was dehydrated[8,9] to give β-lactone *IV* (originally, in the cholestane series the corresponding β-lactone was formulated as "enollactone". This assumption was accepted[10] as late as in 1956). The β-lactone structure was confirmed inter alia by the strong ν(C=O) band at 1 818 cm^{-1} in the IR spectrum of compound *IV* (measured in chloroform; for the analogous β-lactone of the cholestane series, this band was observed at 1 825 cm^{-1}). Pyrolysis of the β-lactone *IV* at 190 °C afforded the desired decarboxylation product[8], B-nor-5-androstene-3β,17α-diyl 3-acetate 17-benzoate (*V*), in 85% yield (see Scheme 1).

Both intermediates of the above-mentioned reaction sequence (*III*, *IV*) were amorphous substances; this made their purification difficult and lowered the yields. Therefore, the key compound *V* was also prepared in an alternative way, the starting compound being 17-oxo-B-nor-5-androsten-3β-yl acetate (*XI*, ref.[6]), accessible by an analogous procedure from the commercially available 17-oxo-5-androsten-3β-yl acetate. Reduction of the 17-keto group in compound *XI* with sodium borohydride led to the corresponding 17β-hydroxy derivative *XII* (ref.[6]) whose tosylate *XIII* was solvolyzed[11] by treatment with potassium nitrite in dimethyl sulfoxide at 140 °C. The most polar component of the reaction mixture, obtained in 42% yield by chromatography on silica gel, exhibited spectral characteristics of the desired 17α-hydroxy olefin *VI* (particularly the doublet of 17β-proton at δ 3.73, J = 6.1 Hz, in the ^1H NMR spectrum). The medium lipophilic component of the mixture was identical with the product of α-elimination, ketone *XI* (16%), and the lipophilic component (17%) was assigned the structure of Δ^{16}-olefin *XIV* on the basis of two signals in the vinyl proton region (see Table I). Surprisingly, neither compound *XIV* nor the corresponding 3-hydroxy derivative *XV* have the characteristic smell of the boar pheromone, typical for many Δ^{16}-derivatives[12]. Benzoylation of the principal solvolysis product *VI* afforded diester *V*, identical with the product prepared by the former reaction sequence.

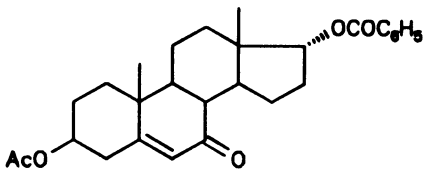
Further transformations of compound *V* consisted in clasical procedures, such as partial hydrolysis of the acetoxy group in the presence of benzoyloxy group (formation of compound *VII*), Oppenauer oxidation of 3β-hydroxy derivative *VII* (to give conjugated ketone *VIII*) and alkaline hydrolysis of the 17α-benzoyloxy group (leading to the desired B-norepitestosterone *IX*).

One of the expected metabolic products[13] of compound *IX* is its dihydro derivative *X*; we prepared this compound by hydrogenation of *IX* over palladium on carbon in tetrahydrofuran. The 5β-configuration of product *X* was confirmed by its CD spectrum: the observed negative Cotton effect of compound *X* ($\Delta\varepsilon_{289}$ −1.29) corresponds to the B-nor-5β-cholestan-3-one model[14] ($[\alpha]_{310}$ −430°, $[\alpha]_{265}$ +1 030°; calculation[15] from these values leads to $\Delta\varepsilon_{288}$ −1.36) because the corresponding 5α-isomers show a positive Cotton effect[16].

Chemical and physicochemical properties of the prepared B-norsteroid derivatives are very similar to those of the analogous compounds with classical steroid skeleton



I



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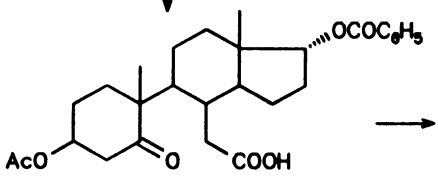
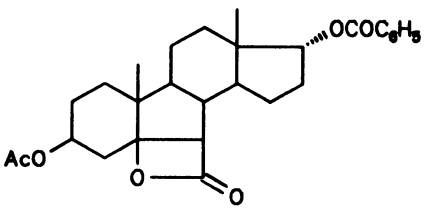
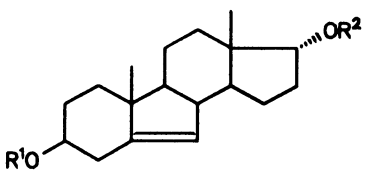


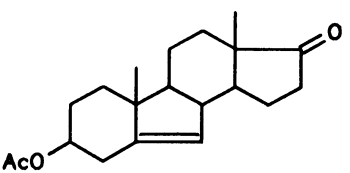
III



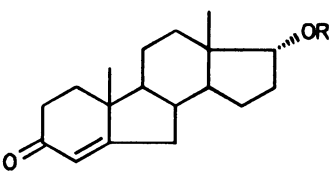
IV



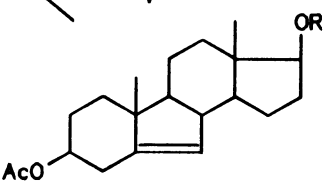
V, R^1 = Ac; R^2 = COC_6H_5
VI, R^1 = Ac; R^2 = H
VII, R^1 = H; R^2 = COC_6H_5



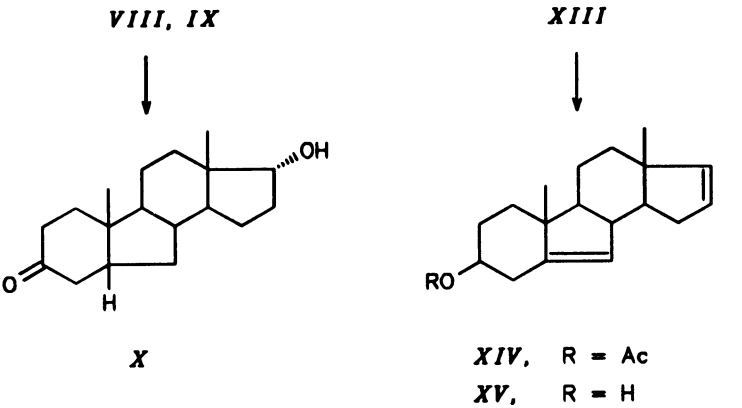
XI



VIII, R = COC_6H_5
IX, R = H



XII, R = H
XIII, R = Ts



SCHEME 1

TABLE I
Selected ^{1}H NMR spectral data of compounds *I* to *XV*, for other conditions see Experimental

Compound	H-18[a]	H-19[a]	H-3[b]	H-17	C=CH	Other[c]
I	0.84	1.04	4.60	5.06[d]	5.41[e]	2.04[f]
II	0.84	1.23	4.72	5.02[d]	5.77[g]	2.06[f]
III	0.86	1.08	5.40[h]	5.07[d]	–	2.02[f], 3.21[i]
IV	0.86	1.04	5.06	5.10[d]	–	2.06[f], 3.27[j]
V	0.84	0.92	4.65	5.07[d]	5.46[k]	2.05[f], 2.65[l]
VI	0.68	0.91	4.61	3.74[d]	5.42[k]	2.04[f], 2.64[l]
VII	0.84	0.91	3.62	5.04[d]	5.44[k]	2.64[l]
VIII	0.88	1.10	–	5.09[d]	5.79[m]	
IX	0.72	1.09	–	3.79[d]	5.79[m]	
X	0.67	0.95	–	3.75[d]	–	
XI	0.91	0.92	4.62	–	5.47[k]	2.05[f], 2.67[l]
XII	0.77	0.91	4.62	3.68[m]	5.39[k]	2.04[f], 2.63[l]
XIII	0.82	0.87	4.57	4.31[m]	5.35[k]	2.03[f], 2.45[a]
XIV	0.76	0.91	4.66	5.88[o]	5.42[k]	2.04[f], 5.72[p]
XV	0.77	0.99	3.70	5.88[o]	5.40[k]	5.72[p], 2.62[l]

[a] Singlet, 3 H. [b] Multiplet, unless otherwise stated, W = 38. [c] All benzoates exert multiplets of aromatic protons at 7.47 and 8.04; tosylates exert two doublets of aromatic protons at 7.33 and 7.79. [d] Doublet, J = 6.1. [e] Doublet, J = 4.9. [f] Acetate. [g] Doublet, J = 1.5, H-6. [h] Multiplet, W = 18. [i] Doublet of doublets, J = 4 and 14.5. [j] Doublet, J = 7.5, H-6. [k] Multiplet, $W_{1/2}$ = 5.5, C=CH. [l] Doublet of doublets of doublets, J = 13.7 and 4.9 and 1.8, H-4α. [m] Broad singlet, $W_{1/2}$ = 4. [n] Doublet of doublets, J = 9 and 7. [o] Doublet of doublets of doublets, J = 5.6 and 2.3 and 1.2. [p] Doublet of doublets, J = 5.6 and 1.7 and 2.9, H-16.

(cf., e.g., the NMR parameters of homologous compounds *I* and *V* in Table I): the only exception being the 4α-proton signal in the Δ^5-unsaturated derivatives: contrary to normal steroids, in B-norsteroids the allylic 4β-hydrogen is oriented perpendicularly to the C=C bond plane and assumes antiperiplanar position relative to the 3α-proton, whereas the 4α-proton is coplanar with the double bond and synclinal to the 3α-proton. As the result, the 4α-proton signal is shifted downfield into well observable region. A decoupling experiment with compound *XII* has shown that the signal at δ 2.63 (H-4α) does not interact with the vinyl proton but collapses into a doublet of doublets (J(gem) = 13.4 Hz, $J(2\alpha,4\alpha)$ = 2.2 Hz) upon irradiation of the 3α-proton. On the other hand, the signal at δ 2.07 (H-4β) does interact with the vinyl proton ($J(4\beta,6)$ = 2.4 Hz) and also interacts with the geminal 4α-proton and the vicinal 3α-proton.

Preliminary biologic assays (inhibition of 5α-reductase, antiandrogenic activity) indicate that pharmacodynamic properties of B-norepitestosterone (*IX*) are similar to those of natural epitestosterone and that its dihydro derivative (B-nor-5β-androstan-17α-ol-3-one, *X*) is a surprisingly strong inhibitor of 5α-reductase. The full results will be published elsewhere[17].

EXPERIMENTAL

Melting points were determined on a Kofler block and are uncorrected. Optical rotations and IR spectra (Zeiss UR 20 instrument) were measured in chloroform unless stated otherwise; wavenumbers are given in cm^{-1}. ^1H NMR spectra were taken in deuteriochloroform with tetramethylsilane as internal standard at 23 °C on Varian XL-200 (200 MHz, FT-mode) and Varian UNITY 500 (500 MHz, FT-mode) instruments. Chemical shifts are given in ppm (δ-scale), coupling constants J in Hz. All parameters were obtained by first order analysis. Mass spectra were measured on a VG-ZAB-EQ spectrometer (in parentheses relative intensities, referenced to the base peak, and in some cases also assignments). Identity of compounds prepared by different procedures was proved by mixture melting points and comparison of IR spectra. Reaction course and purity of the compounds were followed by thin-layer chromatography (TLC) on silica gel (Woelm DC, detection by spraying with sulfuric acid and heating). Compounds were separated by flash chromatography on a column of silica gel Silpearl (Kavalier, Votice, The Czech Republic) or on a thin layer of silica gel (PLC, 200 × 200 × 0.7 mm, ICN DC, inspection at 254 nm after spraying with 0.02% solution of morin in methanol). Steroids used as starting material were purchased from Steraloids (Wilton, N.H., U.S.A.).

3β-Acetoxy-17α-benzoyloxy-5-oxo-5,6-secoandrostan-6β-oic Acid (*III*)

A solution of chromium trioxide (4.6 g, 46.0 mmol) in 50% aqueous acetic acid (14 ml) was added during 1 h at 55 °C to a stirred solution of androst-5-ene-3β,17α-diyl 3-acetate 17-benzoate[1] (*I*; 5.6 g, 12.8 mmol) in acetic acid (60 ml). After stirring at room temperature for 1 h, the excess oxidizing agent was destroyed by addition of methanol (6 ml) and the solvent was evaporated at 45 °C in vacuo. The dry residue was partitioned between ether and water, the combined ethereal phases were extracted with saturated aqueous potassium hydrogen carbonate solution (10 × 25 ml) and with water, and the solvent was evaporated in vacuo. The remaining oil (3.5 g) consisted predominantly of the corresponding 7-oxo derivative *II*; IR spectrum (CCl_4): 1 739, 1 238 (acetate); 1 720, 1 273 (benzoate); 1 678, 1 634 (C=C–C=O). The alkaline aqueous washings (solution of potassium salt of seco

acid *III*) were washed with ether, acidified with hydrochloric acid (18%) and the liberated acid *III* was taken up in ether. The extract was washed with water, dried over anhydrous sodium sulfate and concentrated in vacuo to give 2.4 g (38.6%) of noncrystalline acid *III*; $[\alpha]_D^{20}$ +8° (*c* 1.2). IR spectrum: 3 512, 3 400 – 2 500, 1 698 (COOH); 1 734, 1 250 (acetate); 1 707, 1 280 (benzoate); 1 707 (C=O). For $C_{28}H_{36}O_7$ (484.6) calculated: 69.40% C, 7.49% H; found: 69.11% C, 7.39% H.

3β-Acetoxy-17α-benzoyloxy-5-hydroxy-B-nor-5β-androstane-6β-carboxylic Acid, β-Lactone (*IV*)

Benzoyl chloride (4.0 ml, 34.5 mmol) was added to a solution of seco acid *III* (3.58 g, 7.4 mmol) in pyridine (12 ml). After standing at room temperature for 48 h, the mixture was poured in an ice–water mixture, the product was extracted with benzene, the extract was washed with dilute hydrochloric acid (5%), water, aqueous solution of potassium hydrogen carbonate, again with water, and dried by filtration through a layer of sodium sulfate. After evaporation, the residue solidified to an amorphous mass, m.p. 55 – 65 °C, $[\alpha]_D^{20}$ 0° (*c* 0.9). IR spectrum: 1 818, 1 097 (β-lactone); 1 728 sh, 1 252 (acetate); 1 713, 1 277, 1 603, 1 585, 1 491, 1 452 (benzoate). For $C_{28}H_{34}O_6$ (466.6) calculated: 72.08% C, 7.35% H; found: 71.73% C, 7.00% H.

B-Norandrost-5-ene-3β,17α-diyl 3-Acetate 17-Benzoate (*V*)

A) A 250 ml flask, containing β-lactone *IV* (2.65 g, 6.27 mmol), was evacuated (water pump) and kept at 190 °C for 15 min in a bath of Wood's metal. After cooling, the reaction mixture was dissolved in benzene (about 20 ml) and mixed with silica gel (20 ml). The flask was attached to a rotatory evaporator and benzene was evaporated in vacuo. The product, adsorbed on silica gel, was layered on a column of silica gel (6.5 × 24 cm). Flash chromatography in benzene afforded 2.04 g (85%) of olefin *V*; $[\alpha]_D^{20}$ –88° (*c* 0.9). IR spectrum (CCl_4): 1 734, 1 242 (acetate); 1 719, 1 274 (benzoate). For $C_{27}H_{34}O_4$ (422.6) calculated: 76.74% C, 8.11% H; found: 76.40% C, 7.89% H.

B) A solution of compound *VI* (2.5 g, 7.85 mmol) in pyridine (5 ml) was mixed at 0 °C with benzoyl chloride (2.5 ml, 21.5 mmol). After standing at room temperature for 20 h, the excess reagent was decomposed by pouring into stirred warm water (55 °C, 120 ml). The solution was kept in a refrigerator overnight, the deposited product was collected on a filter, washed with water and dissolved in ether. The solution was washed with an aqueous solution of potassium hydrogen carbonate, water, dried over sodium sulfate and the solvent was evaporated. The residue was chromatographed on silica gel in benzene to give 2.9 g (87%) of an oily substance, identical (IR spectrum) with the sample prepared by procedure *A*.

17α-Hydroxy-B-norandrost-5-en-3β-yl Acetate (*VI*)

A solution of tosylate *XIII* (9.11 g, 19.3 mmol) in dimethyl sulfoxide (250 ml) was stirred with sodium nitrite (31 g, 0.45 mol) at 130 – 140 °C in a nitrogen atmosphere. After 4 h the mixture was cooled, poured into a solution of ammonium sulfate and the product was filtered and washed with water. The filtrate was partitioned between water and chloroform, the organic layer was dried over sodium sulfate and applied onto a column of silica gel (4.5 × 17 cm, Silpearl). Elution with toluene–ether (10 : 1) afforded in succession: B-norandrosta-5,16-dien-3β-yl acetate (*XIV*, 980 mg, 17%), IR spectrum (CCl_4): 3 037, 1 637 (C=C); 3 052 sh, 1 641 sh (other C=C); 1 735, 1 242 (acetate); 17-oxo-B-norandrost-5-en-3β-yl acetate (*XI*; 984 mg, 16%), IR spectrum (CCl_4): 3 037, 1 635 (C=C), 1 743 (C=O), 1 735, 1 241, 1 031 (acetate), identical with that of an authentic sample; 17α-hydroxy-B-norandrost-5-en-3β-yl 3-acetate (*VI*; 2.564 g, 42%), m.p. 91 – 92 °C, $[\alpha]_D^{20}$ –142° (*c* 1.3). For $C_{20}H_{30}O_3$ (318.5) calculated: 75.43% C, 9.50% H; found: 75.28% C, 9.68% H.

3β-Hydroxy-B-norandrost-5-en-17α-yl Benzoate (*VII*)

Concentrated hydrochloric acid (1 ml, 12 mmol) was added to a solution of diester *V* (3.0 g, 7.1 mmol) in a mixture of chloroform (4 ml) and methanol (50 ml). After standing at room temperature for 48 h, the acidity was destroyed by addition of sodium hydrogen carbonate (0.7 g) and the solution was concentrated in vacuo to 1/10 of the original volume. The residue was partitioned between ether and an aqueous potassium hydrogen carbonate solution, the ethereal solution was washed with water, dried over sodium sulfate and concentrated in vacuo. The obtained product *VII* did not crystallize in usual solvents; $[\alpha]_D^{20}$ −142° (*c* 1.2). IR spectrum (CCl_4): 3 612 (OH); 1 720, 1 274 (benzoate); 1 635 (C=C). For $C_{25}H_{32}O_3 \cdot H_2O$ (298.6) calculated: 75.34% C, 8.60% H; found: 75.16% C, 8.41% H.

3-Oxo-B-norandrost-4-en-17α-yl Benzoate (*VIII*)

A mixture of hydroxy derivative *VII* (2.7 g, 7.1 mmol), toluene (90 ml) and cyclohexanone (25 ml, 241 mmol) was distilled until 28 ml of the azeotropic distillate was collected. Solid aluminium isopropoxide (1.5 g, 7.3 mmol) was then added to the residue and the mixture was boiled so as to obtain 50 ml of distillate during 1 h. The remaining mixture was diluted with chloroform, washed with dilute hydrochloric acid (5%), water, solution of potassium hydrogen carbonate, and again water. The volatile components were removed by steam-distillation, the product was dissolved in chloroform, the solution dried over sodium sulfate and filtered through a layer of alumina. After concentration in vacuo, the product was crystallized from acetone, m.p. 172 – 173 °C; yield 1.9 g (70%). Preparative TLC of the mother liquors (8 plates, 200 × 200 × 1 mm, benzene–ether 5 : 1) afforded another portion of the product *VIII* (470 mg, 17%). $[\alpha]_D^{20}$ −44° (*c* 1.1). IR spectrum (CCl_4): 1 720, 1 274 (benzoate); 1 672, 1 639 (C=C–C=O); 1 603, 1 586 (arom.). For $C_{25}H_{30}O_3$ (378.5) calculated: 79.33% C, 7.99% H; found: 79.01% C, 8.11% H.

17α-Hydroxy-B-norandrost-4-en-3-one (*IX*)

Benzoate *VIII* (300 mg, 0.8 mmol) was hydrolyzed with ethanolic potassium hydroxide (5%, 5 ml). After standing for 48 h, the mixture was neutralized with hydrochloric acid (1.5 ml, 5%) and the solution was concentrated in vacuo to 1/4 of the original volume. The residue was partitioned between water and chloroform, the organic phase was dried over sodium sulfate and the solvent was evaporated to dryness. Crystallization of the residue afforded 165 mg (76%) of compound *IX*, m.p. 186 – 188 °C (acetone–heptane); $[\alpha]_D^{20}$ −42° (*c* 0.9). For $C_{18}H_{26}O_2$ (274.4) calculated: 78.79% C, 9.55% H; found: 78.60% C, 9.39% H.

17α-Hydroxy-5β-B-norandrostan-3-one (*X*)

Ketone *IX* (43 mg, 0.16 mmol) was hydrogenated in tetrahydrofuran (3 ml) over palladium on charcoal (10%, 10 mg). After 2.5 h, the hydrogenation was interrupted, the catalyst filtered off and washed, and the filtrate concentrated in vacuo. The dry residue was crystallized from acetone and heptane; m.p. 120 – 121 °C (32 mg, 74%); $[\alpha]_D^{20}$ −25° (*c* 0.9). IR spectrum: 3 616, 1 040 (OH); 1 707 (C=O). CD spectrum: $\Delta\varepsilon_{289}$ −1.29 (methanol). For $C_{18}H_{28}O_2$ (276.4) calculated: 78.21% C, 10.21% H; found: 77.95% C, 10.19% H.

17β-Hydroxy-B-norandrost-5-en-3β-yl Acetate (*XII*)

The title compound was prepared according to ref.[18]. ^{1}H NMR spectrum (500 MHz; selected signals): 1.64 m, 1 H (H-2β); 1.84 m, 1 H (*J* = 2.2 and 3.9 and 7.6 and 12.0, H-2α); 2.07 m, 1 H (*J*(4β,6) = 2.4, *J*(4β,3α) = 11.5, *J*(4β,4α) = 13.4, H-4β); 2.30 tdd, 1 H (*J* = 1.5 and 4.6 and 11 and 11, H-8);

2.63 ddd, 1 H ($J(4\alpha,3\alpha)$ = 5.1, $J(4\alpha,2\alpha)$ = 2.2, $J(4\alpha,4\beta)$ = 13.4, H-4α); 3.69 dd, 1 H (J = 7.8 and 9.0, H-17β); 4.63 tt, 1 H ($J(3\alpha,4\alpha)$ = 5.1, $J(3\alpha,4\beta)$ = 11.5, $J(3\alpha,2\alpha)$ = 4.0, $J(3\alpha,2\beta)$ = 11.5, H-3α); 4.63 m, 1 H (J = 2.4 and 1.5, H-6).

B-Norandrost-5-ene-3β,17β-diyl 3-Acetate 17-Tosylate (*XIII*)

p-Toluenesulfonyl chloride (2.0 g, 10.5 mmol) was added at 0 °C to a solution of 17β-alcohol *XII* (ref.[18]; 800 mg, 2.51 mmol) in pyridine (4 ml). After standing at room temperature for 64 h, the mixture was poured in a stirred saturated sodium chloride solution. The product was taken up in ether, the extract was washed successively with dilute hydrochloric acid (5%), water, aqueous potassium hydrogen carbonate and water, and dried over anhydrous sodium sulfate. After evaporation of the solvent, the product was crystallized from acetone, m.p. 143 – 145 °C; yield 1.15 g, 96%); $[\alpha]_D^{20}$ −96° (*c* 0.95). IR spectrum (CCl_4): 1 734, 1 242 (tosylate); 1 374, 1 189, 1 178 (acetate). For $C_{27}H_{36}O_5S$ (472.6) calculated: 68.61% C, 7.68% H; found: 68.39% C, 7.71% H.

B-Norandrosta-5,16-dien-3β-ol (*XV*)

Concentrated hydrochloric acid (0.1 ml, 1.2 mmol) was added to a solution of acetate *XIV* (100 mg, 0.33 mmol) in a mixture of chloroform (0.2 ml) and methanol (3 ml). After standing at room temperature for 48 h, the solution was concentrated in vacuo to 1/10 of the original volume and partitioned between ether and aqueous potassium hydrogen carbonate; the ethereal solution was washed with water, dried over sodium sulfate and concentrated in vacuo. The product (73 mg, 85%) was crystallized from heptane; m.p. 125 – 126 °C. For $C_{18}H_{26}O$ (258.4) calculated: 83.66% C, 10.14% H; found: 83.49% C, 9.88% H.

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