Synthesis of 17α-Methyl-4-androstene-3β,17β-diol

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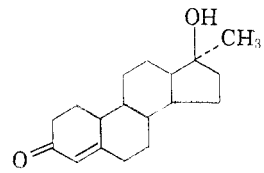
R. I. Dorfman[1] has recently found that the diacetate of 4-androstene-3β(or α)17β-diol was a highly potent long acting androgen, comparable in activity to testosterone esters. This observation was of some interest in view of the finding of Butenandt and coworkers[2] that the parent compound, 4-androstene-3β,17β-diol,[3] exhibited very little activity in the capon comb test. In view of the work by Dorfman which indicated that hormone activity could be maintained with a Δ^4-3-ol grouping in the molecule, it was decided to prepare the unknown 17α-methyl-4-androstene-3β,17β-diol (IIa) for a comparative study of its androgenic activity especially with methyl testosterone (I) and 17α-methyl-5-androstene-3β,17β-diol.

Methyl testosterone (I) on reduction with sodium borohydride[4] in methanol-ethyl acetate gave in 70% yield 17α-methyl-4-androstene-3β,17β-diol (IIa), which was isolated and purified by crystallization directly from the reduction mixture. The β-configuration at C3 was assigned on the basis of digitonide formation. The digitonide on decomposition with pyridine gave back the 3β,17β-diol IIa identical with the starting material. This established that the product IIa was not contaminated with the chemically possible 3α,17β-diol. The presence of the latter in the purification mother liquors was not investigated.

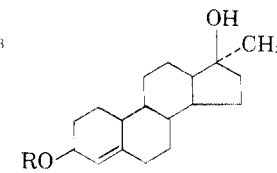
The 3-acetate IIb and 3-propionate IIc were prepared in the usual manner. It was interesting to observe that both derivatives exhibited in the infrared two bands in the C=O stretching region, *i.e.* at 1748 cm.$^{-1}$ and 1730 cm.$^{-1}$ for the acetate IIb, and at 1745 cm.$^{-1}$ and 1727 cm.$^{-1}$ for the propionate IIc. This may possibly be attributed to the acyloxy groups being in the allylic position to the Δ^4-double bond.

Bioassays.[5] 17α-Methyl-4-androstene-3β,17β-diol (IIa) proved to be a highly active androgen in a number of assays.

In the baby chick comb assay (inunction method, propylene glycol, 1 week) compound IIa exhibited an activity of the same order as methyl testosterone (I).



I



IIa, R = H
b, R = CH_3CO
c, R = CH_3CH_2CO

Orally as measured by the weight of the ventral prostate in the castrated male rat (compound incorporated in the diet, 1 week) compound IIa was approximately one quarter to one half as active as methyl testosterone. In the same assay 17α-methyl-5-androstene-3β,17β-diol was only about one quarter as active as methyl testosterone.

Subcutaneously as measured by the weight of the ventral prostate in the castrated male rat (single dose in sesame oil, 72 hr.) compound IIa was equal in activity to testosterone propionate, whereas both testosterone and methyl testosterone (I) were only about one quarter as active.

EXPERIMENTAL

Melting points. All melting points are uncorrected and were determined with uncalibrated Anschütz thermometers.

Infrared absorption spectra. The spectra (pressed potassium bromide) were determined with a Perkin-Elmer spectrophotometer (Model 21).

17α-Methyl-4-androstene-3β,17β-diol (IIa). To a solution of methyl testosterone (I, 1 g.) in methanol (40 ml.) and ethyl acetate (10 ml.) was added a solution of sodium borohydride (0.25 g.) in methanol (40 ml.) and ethyl acetate (10 ml.). The mixture was allowed to stand at room temperature for 24 hr. when water (1 ml.) was added, and the *p*H was adjusted to 7.0 by the slow addition of acetic acid. The mixture was concentrated to near dryness under reduced pressure with mild heating (45–50°). Water was added, and the resultant precipitate was collected by filtration. Several crystallizations from acetone afforded 0.43 g. of the diol IIa, m.p. 166–170°; $\lambda_{max}^{abs.\ EtOH}$ none; ν_{max} 3509, 3311, 1675, 1653, 1091, and 1053 cm.$^{-1}$; $[\alpha]_D^{24}$ +14° (c, 1.345, methanol). The product was very hygroscopic.

Anal. Calcd. for $C_{20}H_{32}O_2$ (304.46): C, 78.89; H, 10.59. Found: C, 76.14; 77.05, 77.30; H, 10.71, 10.66, 10.94.

Compound IIa gave a precipitate with digitonin in 90% (w/w) alcohol. The digitonide on decomposition with pyridine gave back IIa, m.p. 166–168°. Its infrared absorption spectrum was identical with that of starting material.

In another run with methyl testosterone (I, 5 g.) there was obtained 3.52 g. (70% yield) of IIa, m.p. 165–168°.

3β-Acetoxy-17α-methyl-4-androsten-17β-ol (IIb). To a solution of IIa, (0.3 g.) in pyridine (3 ml.) was added acetic anhydride (1 ml.), and the mixture was allowed to stand at room temperature overnight. The solution was poured into ice water, and the resultant solid was collected by filtration, and washed with water. Two crystallizations from ether–petroleum ether (b.p. 60–70°) yielded 0.1 g. of the 3-acetate (IIb), m.p. 115.5–117°; ν_{max} 3571, 3484, 1748, 1730, 1667, 1242, and 1093 cm.$^{-1}$; $[\alpha]_D^{24}$ −17° (c, 0.950, chloroform).

Anal. Calcd. for $C_{22}H_{34}O_3$ (346.49): C, 76.26; H, 9.89. Found: C, 76.15; H, 9.90.

3β-Propionoxy-17α-methyl-4-androsten-17β-ol (IIc). To a solution of 17α-methyl-4-androstene-3β,17β-diol (IIa, 0.20

(1) Private communication.

(2) A. Butenandt, K. Tscherning, and G. Hanisch, *Ber.*, **68**, 2097 (1935).

(3) The German workers prepared this compound by the reduction of testosterone with aluminum isopropoxide, a preparative method which generates both C3 epimers. The homogeneity of the reduction product was not established.

(4) For the reduction of a Δ^4-3-ketone with sodium borohydride to afford a Δ^4-3-ol see W. W. Zorbach, *J. Am. Chem. Soc.*, **75**, 6344 (1953), and B. Camerino and C. G. Alberti, *Gazz. Chim. Ital.*, **85**, 51 (1955).

(5) We are indebted to Drs. F. I. Dessau and E. De Renzo and their associates for these results.

g.) in pyridine (2 ml.) was added propionic anhydride (1 ml.), and the mixture was allowed to stand at room temperature overnight. Addition of water gave an oil which solidified on standing (ice cooling). The solid was collected by filtration and washed with water. Several crystallizations from methanol–water, followed by two crystallizations from ether–petroleum ether gave 0.05 g. of the 3-propionate IIc; m.p. 105–106.5°; ν_{max} 3509, 1745, 1727, 1667, 1205, and 1089 cm.$^{-1}$; $[\alpha]_D^{24}$ −18° (c, 1.360, chloroform).

Anal. Calcd. for $C_{23}H_{36}O_3$ (360.52): C, 76.62; H, 10.07. Found: C, 76.22, H, 10.09.

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Esters of 17α-Ethinylandrostane-3β,17β-diol and 17α-Ethinylandrost-5-ene-3β,17β-diol

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As part of a continuing endocrinological screening program being carried out in these laboratories, an extensive investigation has been made of two series of ester derivatives based upon 17α-ethinylandrostane-3β,17β-diol and 17α-ethinylandrost-5-ene-3β,17β-diol, respectively. A number of these compounds have been shown to possess outstanding activity as pituitary inhibitors.[1]

The parent 17α-ethinyl steroid diols and their acetates were originally prepared by Ruzicka and Hoffmann;[2] the pituitary inhibiting properties of these types apparently have heretofore not been observed. In the present work it was found that while the known diols and their 3-monoacetates were active pituitary inhibitors, this activity was negated by a high degree of estrogenicity. An increase in the size of the ester group in the 3-monoesters led to a greatly increased activity ratio (defined as the ratio of pituitary inhibition to estrogenicity). The most favorable activity ratio was found with 17α-ethinylandrost-5-ene-3β,17β-diol 3-(3-cyclohexylpropionate) (Ethandrostate). The 3,17-diesters were found to be nearly inactive as pituitary inhibitors; apparently a free 17β-hydroxy is a prerequisite for activity in this series.

The new 3-monoesters were prepared by standard procedures; such minor modifications as were used were induced by the ease of diesterification with acylating agents such as the acyl halides. Frequently it was necessary to purify the esters by chromatography during the initial preparations, but it was subsequently found that experimental conditions could be worked out for each individual ester (usually an adjustment of the mole ratio of reactants and the time of reaction) which would lead to a high yield of pure product by direct recrystallization. The new esters are summarized in Tables I and II and in the Experimental Section.

EXPERIMENTAL[3]

3-Mono-esters of 17α-ethinylandrostane-3β,17β-diol and 17α-ethinylandrost-5-ene-3β,17β-diol. The 3-mono esters were prepared from the parent diols by acylation with either an acid anhydride or an acid chloride in pyridine solution, as shown in examples below.

Method A. Acid anhydrides. To a solution of 31.45 g. (0.100 mole) of 17α-ethinylandrost-5-ene-3β,17β-diol in 150 ml. of C.P. pyridine was added 44.1 g. (0.150 mole) of cyclohexylpropionic anhydride. The resulting clear solution was allowed to stand at room temperature for 60 to 70 hr., after which period it was quenched in 1500 ml. of water. After 1 hr., the mixture was extracted three times with methylene dichloride and the extracts were washed with dilute sulfuric acid and sodium bicarbonate solutions. After drying, the methylene dichloride was evaporated *in vacuo*, the residue was dissolved in 500 ml. of hot *n*-hexane, and the solution was filtered[4] and concentrated to 300 ml. for crystallization. One additional recrystallization from *n*-hexane gave 38.22 g. (86%) of the pure 3-(3-cyclohexylpropionate), crystallizing in rosettes of large, fernlike masses.

With acid anhydrides of lower molecular weight the time of reaction and the proportion of anhydride were both reduced; *e.g.*, with propionic anhydride there was used 1.3 moles of anhydride and a time of 17 hr. (83% yield).

Method B. Acid chlorides. To a cold (0°) solution of 3.16 g. (0.01 mole) of 17α-ethinylandrostane-3β,17β-diol in 20 ml. of pyridine was slowly added 1.48 g. (0.011 mole) of α-ethyl-*n*-butyryl chloride. The resulting deeply colored heterogenous mixture was held at room temperature for 5 hr. and then quenched in 500 ml. of water. After 1 hr. the resulting slurry was filtered and the semicrystalline material was washed thoroughly with water and dried at 50° *in vacuo*. The product was chromatographed on 240 g. of silica gel as usual. Elution with 5 to 10% ether—pentane mixtures gave a trace amount of the diester; further elution with a 20% ether—pentane mixture gave the 3-mono-ester. One recrystallization from methanol resulted in pure material, in about 50% over-all yield.

17α-Ethinylandrost-5-ene-3β,17β-diol 3-acid succinate. A mixture of 3.14 g. (0.01 mole) of 17α-ethinylandrost-5-ene-3β,17β-diol, 1.50 g. (0.015 mole) of succinic anhydride and 25 ml. of C.P. pyridine was refluxed for 3 hr. After quenching in 500 ml. of water, the greyish solid was filtered off, washed thoroughly with water and dried at 70°. Two recrystallizations from methanol gave 2.56 g. of material, crystallizing in clusters of flattened needles.

The *diethanolamine salt*, prepared by mixing equimolecular amounts of the components in hot acetone, formed slender,

(1) A. L. Beyler and R. O. Clinton, *Proc. Soc. Exper. Biol. Med.*, **92**, 404 (1956).

(2) L. Ruzicka and K. Hoffmann, *Helv. Chim. Acta*, **20**, 1280 (1937).

(3) All melting points are corrected; they were determined in a modified Hershberg apparatus using total immersion N.B.S.—calibrated thermometers. The analyses were done by Mr. K. D. Fleischer and staff.

(4) Insoluble material at this point is the starting diol.