SYNTHESIS OF ANDROST-4-EN-3β-OL-11,17-DIONE

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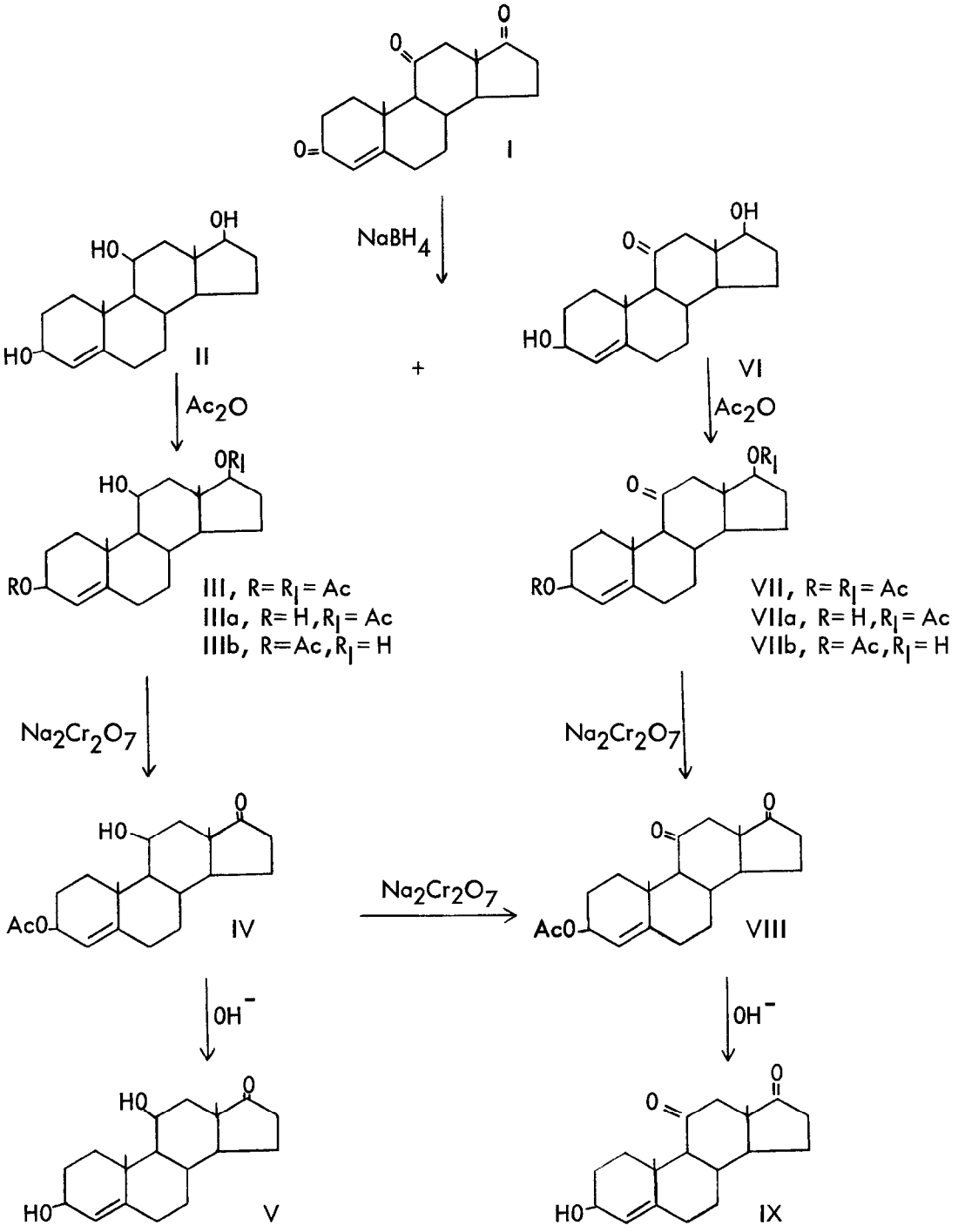
ABSTRACT

The synthesis of androst-4-ene-3β,11β-diol-17-one (V) from androst-4-ene-3,11,17-trione is described. Oxidation of the acetate of (V) and deacetylation provided androst-4-en-3β-ol-11,17-dione (IX) which was also prepared from androst-4-ene-3β,17β-diol-11-one (VI).

Current studies in this laboratory are being directed at the conversion products of cortisone arising from the in vivo metabolism in adrenalectomized and oophorectomized women with cancer of the breast and from breast tumor slices when incubated with cortisone. In the course of this work, attention has been directed toward the possible presence of androst-4-en-3-ol's and the chemical synthesis outlined here was designed to provide reference standards for this study.

The synthesis of (V) and its 3α epimer from pregn-4-ene-11β,17α,21-triol-3,20-dione (cortisol) by lithium aluminum hydride reduction and cleavage with periodate has been reported by Fukushima (1).

Reduction of androst-4-ene-3,11,17-trione (I) with sodium borohydride gave a mixture of androst-4-ene-3α,11β,17β-triol, its 3β isomer (II) (2), and androst-4-ene-3β,17β-diol-11-one (VI) which was separated into its components by column chromatography. Compound (II) was acetylated with one molar equivalent of acetic anhydride in pyridine to give androst-4-ene-3β,11β,17β-triol 3-acetate (IIIb), the 17-acetate (IIIa) and the 3,17-diacetate (III).


I
NaBH4
II
VI
Ac2O
Ac2O
III, R= R1= Ac
IIIa, R= H, R1= Ac
IIIb, R=Ac, R1= H
VII, R= R1= Ac
VIIa, R= H, R1= Ac
VIIb, R= Ac, R1= H
Na2Cr2O7
Na2Cr2O7
IV
Na2Cr2O7
VIII
OH-
OH-
V
IX

Oxidation of (IIIb) with sodium dichromate in acetic acid gave androst-4-ene-3β,11β-diol-17-one 3-acetate (IV), which was identical in all respects to the compound prepared from cortisol acetate. Hydrolysis of the acetate (IV) gave the free alcohol (V).

The conversion of cortisol acetate was accomplished by reduction with excess sodium borohydride and subsequent cleavage of the side chain with lead tetraacetate to give compound (V) in a manner similar to the reported synthesis (1). Acetylation of compound (VI) gave androst-4-ene-3β,17β-diol-11-one 17-acetate (VIIa), the 3-acetate (VIIb) and the 3,17-diacetate (VII).

Oxidation of the 3-acetate (VIIb) with sodium dichromate in glacial acetic acid gave androst-4-en-3β-ol-11,17-dione 3-acetate (VIII) which was also prepared from the 3-acetate of androst-4-ene-3β,11β-diol-17-one (IV). Hydrolysis of compound (VIII) gave the free alcohol, androst-4-en-3β-ol-11,17-dione (IX) which was characterized by its oxidation to androst-4-ene-3,11,17-trione (I) by 2,3-dichloro-4,5-dicyanobenzoquinone (DDQ) and by its reduction to androst-4-ene-3β,11β,17β-triol (II) by sodium borohydride.

EXPERIMENTAL

Melting points are uncorrected. Infrared spectra were taken of nujol mulls on a Perkin-Elmer Infracord. The adsorbents for column chromatography were silica gel, 100-200 mesh from Will Scientific, Inc., and chromatographic alumina F-20 from the Aluminum Company of America.

Reduction of Androst-4-ene,3,11,17-trione (I). - To a solution of androst-4-ene-3,11,17-trione (5 g.) in methanol (1 l.) was added over a period of 15 minutes sodium borohydride (5 g.). After standing at 25° for 1 hour, the solution was evaporated in vacuo. To the residue was added ethyl acetate (100 ml.) and water (50 ml.). Extraction of the water with ethyl acetate (100 ml.) and evaporation of the combined organic solvents gave a white crystalline mass. The solid material was dissolved in boiling benzene (150 ml.) by the dropwise addition of pyridine. Cooling to room temperature precipitated 2.51 g. of androst-4-ene-3β,17β-diol-11-one (VI). A

recrystallized sample from ethyl acetate melted at 223-225°, infrared 2.97, 5.97μ.

Anal. calcd. for $C_{19}H_{28}O_3$: C, 74.96; H, 9.27. Found: C, 74.78; H, 9.40.

The filtrate was evaporated in vacuo, dissolved in ethyl acetate and adsorbed on a 4.5 x 50 cm. column of silica gel. Elution of the column with ethyl acetate gave, respectively, androst-4-ene-3β,17β-diol-11-one (0.55 g.) (VI), androst-4-ene-3β,11β,17β-triol (0.405 g.) (II), m.p. 214-217°, and androst-4-ene-3α,11β,17β-triol (0.210 g.), m.p. 206-213°. Reduction of androst-4-en-11β-ol-3,17-dione by Slaunwhite et al. gave (II), m.p. 214-217° and the 3α isomer, m.p. 126-127° (2).

Acetylation of Androst-4-ene-3β,11β,17β-triol (II). - A mixture of androst-4-ene-3β,11β,17β-triol (1.02 g.) (II) in pyridine (25 ml.) and acetic anhydride (340 mg.) was evaporated in vacuo after standing at 25° for 18 hours. The remaining syrup was dissolved in benzene (10 ml.) and adsorbed on a 4.5 x 35 cm. column of alumina. The column was eluted with benzene (500 ml.), 25% ethyl acetate in benzene (2 l.) and ethyl acetate (1.5 l.) to yield in order of their elution, androst-4-ene-3β,11β,17β-triol 3,17-diacetate (III), androst-4-ene-3β,11β,17β-triol 17-acetate (IIIa), and androst-4-ene-3β,11β,17β-triol 3-acetate (IIIb).

(III) 182 mg., m.p. 150-151°, infrared 2.86, 5.87, 8.10μ.

Anal. calcd. for $C_{23}H_{34}O_5$: C, 70.74; H, 8.78. Found: C, 70.59; H, 8.80.

(IIIa) 188.6 mg., m.p. 111-112°, infrared 2.85, 5.98, 7.96μ.

Anal. calcd. for $C_{21}H_{32}O_4$: C, 72.38; H, 9.26. Found: C, 71.99; H, 9.05.

(IIIb) 88.6 mg., m.p. 149.5-151°, infrared 2.89, 5.90, 8.08μ.

Anal. calcd. for $C_{21}H_{32}O_4$: C, 72.38: H, 9.26. Found, C, 72.13; H, 9.40.

Oxidation of androst-4-ene-3β,11β,17β-triol 17-acetate (40 mg.) (IIIa) by DDQ (32.6 mg.) (3) in benzene gave androst-4-ene-11β,17β-diol-3-one 17-acetate (31.1 mg.), m.p. 149-150° (4).

Androst-4-ene-3β,11β,-diol-17-one 3-Acetate (IV). - To a solution of androst-4-ene-3β,11β,17β-triol 3-acetate (120 mg.) (IIIb) in glacial acetic acid (25 ml.) was added a solution of sodium dichromate dihydrate (34 mg.) in glacial acetic acid (1 ml.). After standing at 25° for 1 hour, the mixture was evaporated in vacuo and the residue triturated with hot benzene (10 ml.). The benzene solution was evaporated to 5 ml. and was adsorbed on a column of alumina 1.5 x 30 cm. Elution of the column with 20%

ethyl acetate in benzene gave androst-4-ene-3β,11β-diol-17-one 3-acetate (70 mg.) (IV), m.p. 178-180°, infrared 2.97, 5.76, 5.82, 8.02μ.

Anal. calcd. for $C_{21}H_{30}O_4$: C, 72.80; H, 8.73. Found: C, 72.65; H, 8.92.

Hydrolysis of 72 mg. (IV) in a solution of 10 ml. ethanol and 1 ml. 1 N NaOH gave 30 mg. (V), m.p. 183-184°.

Reduction and Side Chain Cleavage of Pregn-4-ene-3,20-dione-11β,17α,21-triol 21-Acetate. - A solution of pregn-4-ene-3,20-dione-11β,17α,21-triol 21-acetate (2.13 g.)and sodium borohydride (6 g.) in methanol (600 ml.) was stirred at 25° for 30 minutes and evaporated in vacuo. The solid residue was dissolved in ethyl acetate (200 ml.), extracted with water (100 ml.) and the aqueous layer extracted three times with ethyl acetate (200 ml.). The ethyl acetate was dried over sodium sulfate and evaporated to give 1.416 g. of reduced products of cortisol. The product was oxidized by dissolving 900 mg. in glacial acetic acid (25 ml.) and adding, over a period of 5 minutes a solution of lead tetraacetate (2 g.) in benzene (150 ml.). After standing at 25° for 30 minutes, propylene glycol (10 ml.) was added and the solution was allowed to stand an additional 10 minutes. The solution was then diluted with water (100 ml.) and extracted twice with ethyl acetate (100 ml.), dried over sodium sulfate and evaporated in vacuo. The residue was dissolved in a solution of 8% pyridine in benzene (10 ml.), adsorbed on a 4.5 x 30 cm. column of silica gel and eluted with 8% pyridine in benzene (1 l.) and 20% pyridine in benzene to give androst-4-ene-3β,11β-diol-17-one (V), (130 mg.), m.p. 183-184°, infrared 2.94, 5.84μ.

Acetylation in acetic anhydride and pyridine gave the 3-acetate (IV), m.p. 178-180°. Fukushima reports a m.p. of 164-169°, 171° for this compound. A mixed melting point with a sample prepared by dichromate oxidation of (IIIb) showed no depression.

Acetylation of Androst-4-ene-3β,17β-diol-11-one (VI). - Androst-4-ene-3β,17β-diol-11-one (1.0 g.) was treated in exactly the same manner as (II) to give, in order of their elution, androst-4-ene-3β,17β-diol-11-one 3,17-diacetate (VII), androst-4-ene-3β,17β-diol-11-one 17-acetate (VIIa) and androst-4-ene-3β,17β-diol-11-one 3-acetate (VIIb).

(VII) 176.4 mg., m.p. 177-178°, infrared 5.79, 5.90, 8.04μ.

Anal. calcd. for $C_{23}H_{32}O_5$: C, 71.10; H, 8.30. Found: C, 71.10; H, 8.37.

(VIIa) 146.2 mg., m.p. 116-117°, infrared 2.95, 5.81, 5.94, 8.14μ.

Anal. calcd. for $C_{21}H_{30}O_4$: C, 72.80; H, 8.73. Found: C, 72.96; H, 8.90.

(VIIb) 143 mg., m.p. 187-189°, infrared 2.82, 5.88, 5.96, 8.06μ.

Anal. calcd. for $C_{21}H_{30}O_4$: C, 72.80; H, 8.73. Found: C, 72.69; H, 8.58.

Oxidation of androst-4-ene-3β,17β-diol-11-one 17-acetate (40 mg.) (VIIa) and DDQ (32.6 mg.) in benzene gave androst-4-en-17β-ol-3,11-dione 17-acetate (28.1 mg.), m.p. 162-163° (4).

Androst-4-en-3β-ol-11,17-dione 3-Acetate (VIII). - To a solution of androst-4-ene-3β,11β-diol-17-one 3-acetate (30 mg.) (VIIb) in glacial acetic acid (20 ml.) was added a solution of sodium dichromate dihydrate (8.6 mg.) in glacial acetic acid (1 ml.). After standing at 25° for 1 hour, the mixture was evaporated in vacuo and the residue triturated with hot benzene (10 ml.). The benzene solution was evaporated to 5 ml. and adsorbed on a 1.5 x 20 cm. column of alumina. Elution of the column with 20% ethyl acetate in benzene and recrystallization of the product from ethyl acetate gave androst-4-en-3β-ol-11,17-dione 3-acetate (13 mg.) (VIII), m.p. 177-178°, infrared 5.82, 5.90, 8.15μ.

Anal. calcd. for $C_{21}H_{28}O_4$: C, 73.22; H, 8.19. Found. C. 72.75; H, 8.54.

Identical treatment of androst-4-ene-3β,17β-diol-11-one 3-acetate (720 mg.) (IV) with sodium dichromate dihydrate (205 mg.) as above and adsorption on a 2 x 30 cm. column of alumina gave 365 mg. compound (VIII), m.p. 177-178°. A mixed melting point of the two compounds showed no depression and the infrared spectra were superimposable.

Androst-4-en-3β-ol-11,17-dione (IX). - To a solution of androst-4-en-3β-ol-11,17-dione 3-acetate (60 mg.) (VIII) in ethanol (20 ml.) was added 1 N sodium hydroxide (0.5 ml.) and the mixture was evaporated in vacuo after standing at 25° for 3 hours. The residue was triturated with benzene (10 ml.), evaporated to 5 ml., adsorbed on an alumina column 1.5 x 15 cm. and eluted with 20% ethyl acetate in benzene. Recrystallization of the produce from ethyl acetate-heptane gave androst-4-en-3β-ol-11,17-dione (30 mg.) (IX), m.p. 172-173°, infrared 3.03, 5.85, 6.03μ.

Anal. calcd. for $C_{19}H_{26}O_3$: C, 75.46; H, 8.67. Found: C, 75.34; H, 8.80.

Oxidation of (IX) with DDQ in benzene gave androst-4-ene-3, 11,17-trione, m.p. 216-222° and reduction with sodium borohydride in methanol gave androst-4-ene-3β,11β,17β-triol, m.p. 214-217°.

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