THE SYNTHESIS OF 3β,11β,17,21-TETRAHYDROXY-Δ^5-PREGNENE-20-ONE AND ITS 11-KETO ANALOG[1]

by

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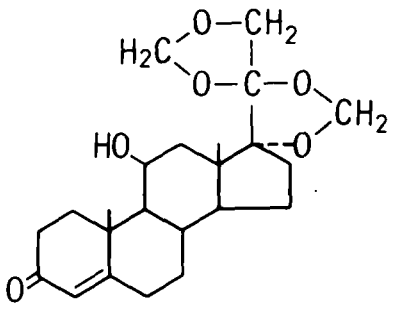
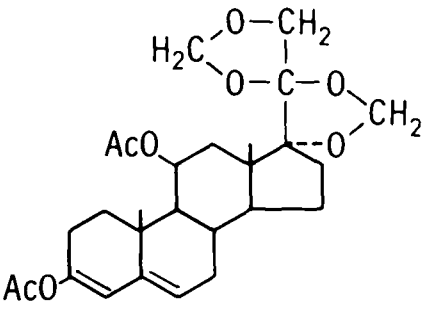
3β,11β,17,21-Tetrahydroxy-Δ^5-pregnene-20-one and its 11-keto analog have been synthesized from hydrocortisone-BMD. Sodium bismuthate oxidation of the unsaturated tetrolone yielded 3β,11β-dihydroxy-5,6α-oxidoandrostane-17-one as well as the expected 3β,11β-dihydroxy-Δ^5-androstene-17-one. The 5α,6α-oxide was identical with the major product from the monoperphthalic acid oxidation of 3β,11β-dihydroxy-Δ^5-androstene-17-one.

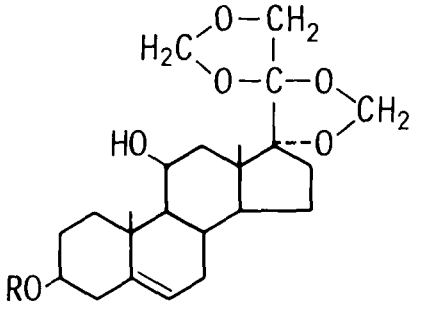
The synthesis of 3β,11β,17,21-tetrahydroxy-Δ^5-pregnene-20-one, a compound structurally related to hydrocortisone, was undertaken in order to study the role this 3β-hydroxy-Δ^5-analog may have in the metabolism of adrenal steroids. Hydrocortisone-BMD (17;20;20;21-bismethylenedioxy-11β-hydroxy-Δ^4-pregnene-3-one, I) was employed as the starting material. Treatment of I with acetic anhydride and acetyl chloride afforded the $\Delta^{3,5}$-diene-3,11-diacetoxy derivative II. The crude product II was first reduced with sodium borohydride giving rise to the 3β-



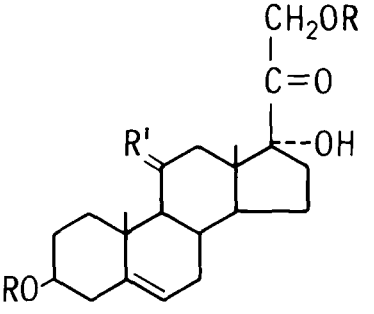
I



II



III a) R=H
b) R=Ac



IV a) R=H R'= 
b) R=Ac R'= 
c) R=Ac R'=O

hydroxy-Δ^5-group. The 11β-acetate group which is difficult to saponify was then reductively cleaved with lithium aluminum hydride. The resulting 17:20;20:21-bismethylenedioxy-Δ^5-pregnene-3β,11β-diol (IIIa) was purified by chromatography. Acid hydrolysis of IIIa afforded 3β,11β,17,21-tetrahydroxy-Δ^5-pregnene-20-one (IVa). This Δ^5-tetrolone and its 3,21-diacetate IVb have been previously synthesized from $\Delta^{5,17(20)}$-pregnadiene-3β,11β,21-triol 3,21-diacetate (1). Chromic acid oxidation of IVb in pyridine yielded 3β,17,21-trihydroxy-Δ^5-pregnene-11,20-dione

3,21-diacetate (IVc) which had the same m.p. as the 11β-hydroxy analog but the m.p. of the mixture of the two steroids was depressed.

In order to verify the structure of 3β,11β,17,21-tetrahydroxy-Δ^5-pregnene-20-one (IVa), the compound was oxidized with sodium bismuthate in aqueous acetic acid to yield the known 3β, 11β-dihydroxy-Δ^5-androstene-17-one. The principal product from this reaction, however, was more polar when chromatographed on Silica Gel G with ethyl acetate. The same polar compound was also formed on treating 3β,11β-dihydroxy-Δ^5-androstene-17-one with sodium bismuthate in aqueous acetic acid. The unknown product was found to be identical with the major product of monoperphthalic acid oxidation of 3β,11β-dihydroxy-Δ^5-androstene-17-one and therefore was 3β,11β-dihydroxy-5,6α-oxidoandrostane-17-one. The assignment of the 5α,6α-orientation of the oxide was made by analogy with the peracid oxidation of dehydroisoandrosterone (3β-hydroxy-Δ^5-androstene-17-one) which is known to give rise to the 5α,6α-oxide as the principal isomer. Molecular rotatory difference ΔM_D ($\Delta^5 \rightarrow$ 5α,6α-epoxide) of +65 for the 11β-hydroxy derivatives and +62 for dehydroisoandrosterone afforded confirmatory evidence for the α-oxide.

The formation of 5,6-oxide of dehydroisoandrosterone with sodium bismuthate in aqueous acetic acid was suggested by Plantin and co-workers (2) and Breuer and Nocke (3) presented evidence from paper chromatographic mobility and sulfuric acid spectrum. In the present investigation evidence of the formation of 3β-hydroxy-5,6α-oxidoandrostane-17-one from dehydroisoandrosterone

and sodium bismuthate has been obtained by melting point determination and infrared spectrometry. The epoxidation of the 5,6-double bond in this reaction may have been due to peracetic acid formed in situ since sodium bismuthate has been reported to liberate active oxygen readily with acids (4).

EXPERIMENTAL[2]

17;20;20;21-Bismethylenedioxy-Δ^5-pregnene-3β,11β-diol (IIIa).

A solution of 3.7 g of hydrocortisone-BMD (5) in 10 ml of acetic anhydride and 10 ml of acetyl chloride was refluxed under nitrogen atmosphere for 90 minutes. The reagents were removed in vacuo to yield 4.5 g of enol acetate of hydrocortisone BMD (**II**). The crude product was dissolved in 10 ml of benzene and 150 ml of 95% ethanol and chilled to 5°C. A cold solution of 1.5 g of sodium borohydride in 30 ml of 95% ethanol was added and the mixture was allowed to stand at 5°C for 1 hour and then at room temperature for an additional 4 hours. Excess sodium borohydride was destroyed with acetic acid and the reduction product was extracted with ethyl acetate to yield 3.79 g of a mixture of 17;20;20;21-bismethylenedioxy-Δ^5-pregnene-3β,11β-diol (IIIa) and its 11-monoacetate. The mixture was reduced with 1 g of lithium aluminum hydride in 300 ml of ether and 3.3 g of product was obtained. Chromatography on 150 g of acid washed alumina and elution with ethyl acetate-benzene yielded 1.10 g of 17;20;20:21-bismethylenedioxy-Δ^5-pregnene-3β,11β-diol (IIIa) m.p. 240-250°. Recrystallization from ethyl acetate and then acetone afforded IIIa, m.p. 243-250°;

$[\alpha]_D^{22}$ = -135°; ν_{max}^{KBr} 3480,1670,1099,1087,1061,944-34,838 cm^{-1}

Anal. Calcd. for: $C_{23}H_{34}O_6$; C, 67.95; H, 8.43

Found: C, 68.02; H, 8.52

The 3-monoacetate was prepared with acetic anhydride and pyridine (IIIb), m.p. 198-204°; $[\alpha]_D^{24}$ = -124°, reported m.p. 198-199° (6); $\nu_{max}^{CS_2,\ CCl_4}$ 3620,1737,1672,1240,1099,1087, 1029,945 cm^{-1}. Anal. Calcd. for: $C_{25}H_{36}O_7$; C, 66.94; 8.08

Found: C, 66.80; 8.05

3β,11β,17,21-Tetrahydroxy-Δ^5-pregnene-20-one (IVa).

A solution of 590 mg of 17;20;20;21-bismethylenedioxy-Δ^5-pregnene-3β,11β-diol (IIIa) in 100 ml of 50% aqueous acetic acid was refluxed for one hour. On cooling to room temperature, an equal volume of 10% sodium chloride solution was added and the mixture was extracted with ethyl acetate. The organic extract was washed with base and brine and dried over sodium sulfate, and the solvent removed to give 521 mg of product. Chromatography on 20 g of Florisil and elution with 10% ethanol in chloroform yielded 247mg of 3β,11β,17,21-tetrahydroxy-Δ^5-pregnene-20-one (IVa). Recrystallization from methanol yielded IVa, m.p. 222-235°; $[\alpha]_D^{22}$ = -9° (ethanol); ν_{max}^{KBr} 3550 (3500-3320), 1710, 1688, 1041, 948, 862 cm^{-1}; reported m.p. 231-236° (1).

Anal. Calcd. for: $C_{21}H_{32}O_5$: C, 69.20; H, 8.85

Found: C, 69.33; H, 8.87

Acetylation with acetic anhydride and pyridine gave the 3,21-

diacetate IVb, m.p. 201-207°; $[\alpha]_D^{26} = -6.6°$; ν_{max}^{KBr} 3530, 3445, 1751, 1723-18, 1672, 1270, 1245-34, 1031, 921, 839 cm^{-1}; reported m.p. 193-203° (1).

Anal. Calcd. for: $C_{25}H_{36}O_7$: C, 66.94; H, 8.08
Found: C, 67.19; H, 8.21

3β,17,21-Trihydroxy-Δ^5-pregnene-11,20-dione 3,21-diacetate (IVc)

A solution of 28 mg of chromic oxide in 3 ml of pyridine was added to 28 mg of 3β,11β,17,21-tetrahydroxy-Δ^5-pregnene-20-one 3,21-diacetate (IVb) in 3 ml of pyridine. The mixture was stored at room temperature for 16 hours, poured into water and extracted with ether. The ether solution was washed with dilute acid, sodium bisulfite solution, dilute base and water. After drying the ether solution, the solvent was evaporated to give 27 mg of the oxidation product. Recrystallizations from acetone-petroleum ether and methanol afforded 14 mg of 3β,17,21-trihydroxy-Δ^5-pregnene-11,20-dione 3,21-diacetate (IVc), m.p. 201-205°; $[\alpha]_D^{27} = 14.7°$; ν_{max}^{KBr} 3500, 1742(sh), 1735, 1719, 1700, 1670, 1252(sh), 1248, 1104, 1047, 1031, 927, 918, 909, 808 cm^{-1}.

Anal. Calcd. for $C_{25}H_{34}O_7$: C, 67.24; H, 7.68
Found: C, 67.14; H, 7.70.

3β,11β,17,21-Tetrahydroxy-Δ^5-pregnene-20-one and sodium bismuthate.

A solution of 16 mg of 3β,11β,17,21-tetrahydroxy-Δ^5-pregnene-20-one (IVa) in 10 ml of 50% aqueous acetic acid

was shaken with 480 mg of sodium bismuthate in the dark for 3 hours. After filtering off the sodium bismuthate with the aid of Celite, the filtrate was extracted with ethyl acetate. The ethyl acetate solution was washed with dilute base and brine, dried and the solvent evaporated. The product upon thin layer chromatography on Silica Gel G with ethyl acetate showed the presence of two compounds with R_f = 0.40 and 0.60. Recrystallization of the crude product from methanol yielded 3β,11β-dihydroxy-5,6α-oxidoandrostane-17-one, m.p. 250-260°; R_f = 0.40. The infrared spectrum was identical with that of the synthetic compound.

The mother liquor of the above recrystallization was chromatographed on thin layer in ethyl acetate and the less polar material, R_f = 0.60, was eluted. The product proved difficult to crystallize and was acetylated with pyridine and acetic anhydride. Recrystallization from cyclohexane-ethyl acetate and ethyl acetate gave 3β-acetoxy-11β-hydroxy-Δ^5-androstene-17-one, m.p. 221-234°. The infrared spectrum was identical with that of an authentic sample[3], m.p. 230-232° (7); ν_{max}^{KBr} 3465, 1733, 1672, 1251-44, 1090, 1024, 949 cm^{-1}.

3β,11β-Dihydroxy-5,6α-oxidoandrostane-17-one.

A solution of 65 mg of monoperphthalic acid in 3 ml of ether was added at 0°C to a solution of 18 mg of 3β,11β-dihydroxy-Δ^5-androstene-17-one in 10 ml of chloroform. The mixture was stored at 0°C for two hours and extracted with ethyl acetate. The ethyl acetate solution was washed with dilute base and

brine, dried and the solvent evaporated to give 19 mg of product. Two compounds with R_f = 0.39 and 0.36 were found to be present by thin layer chromatography on Silica Gel G. The principal product was less polar. Recrystallization of the crude oxidation product from ethyl acetate-methanol afforded 3β,11β-dihydroxy-5,6α-oxidoandrostane-17-one, m.p. 254-263°; $[\alpha]_D^{26}$ = + 1.3° (ethanol); R_f = 0.39; ν_{max}^{KBr} 3485, 3465, 1725, 1074, 1031, 904, 855 cm^{-1}.

Anal. Calcd. for: $C_{19}H_{28}O_4$: C, 71.21; H, 8.88
Found: C, 70.96; H, 8.98

The 3-monoacetate prepared with pyridine and acetic anhydride melted at 204-205°.

Reaction of sodium bismuthate and 3β,11β-dihydroxy-Δ^5-androstene-17-one.

A mixture of 10 mg of 3β,11β-dihydroxy-Δ^5-androstene-17-one in 5 ml of 50% aqueous acetic acid and sodium bismuthate was shaken for 3 hours at room temperature in a dark bottle. The product was isolated as above and was chromatographed on a thin layer of Silica Gel G. The substance with R_f = 0.38 was eluted. The infrared spectrum was identical with that of 3β,11β-dihydroxy-5,6α-oxidoandrostane-17-one prepared with monoperphthalic acid.

Reaction of sodium bismuthate and dehydroisoandrosterone.

A mixture of 500 mg of dehydroisoandrosterone in 200 ml of 50% aqueous acetic acid and 15 g of sodium bismuthate was shaken in a dark bottle for 3 hours at room temperature. The

reaction mixture was worked up as described above to yield 539 mg of product. Column chromatography on 55 g of acid washed alumina and elution with 2% ethyl acetate in benzene gave 150 mg of dehydroisoandrosterone. Elution with 50% ethyl acetate in benzene afforded 113 mg of 3β-hydroxy-5,6α-oxidoandrostane-17-one. Recrystallizations from ethyl acetate and from methanol yielded the oxide, m.p. 230-230.5°. The infrared spectrum was identical with that of an authentic sample prepared from dehydroisoandrosterone and monoperphthalic acid and there was no depression of the m.p. with an authentic sample, m.p. 227-229°.

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Footnotes

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2. The melting points were taken on a micro-hot stage and are corrected. The optical rotations were determined in chloroform unless otherwise specified. The infrared spectra were determined on a Perkin-Elmer Model 21 spectrophotometer; calcium fluoride prism 4000-2750 cm^{-1}, 1800-1600 cm^{-1}, 1500-1280 cm^{-1}; sodium chloride prism 1300-650 cm^{-1}; sh = shoulder.

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