[CONTRIBUTION FROM THE ORGANIC CHEMICAL RESEARCH SECTION, LEDERLE LABORATORIES, A DIVISION OF AMERICAN CYANAMID CO.]

16-Hydroxylated Steroids. XXI.[1] The Preparation and Epimerization of 16β,21-Diacetoxy-9α-fluorocorticoids

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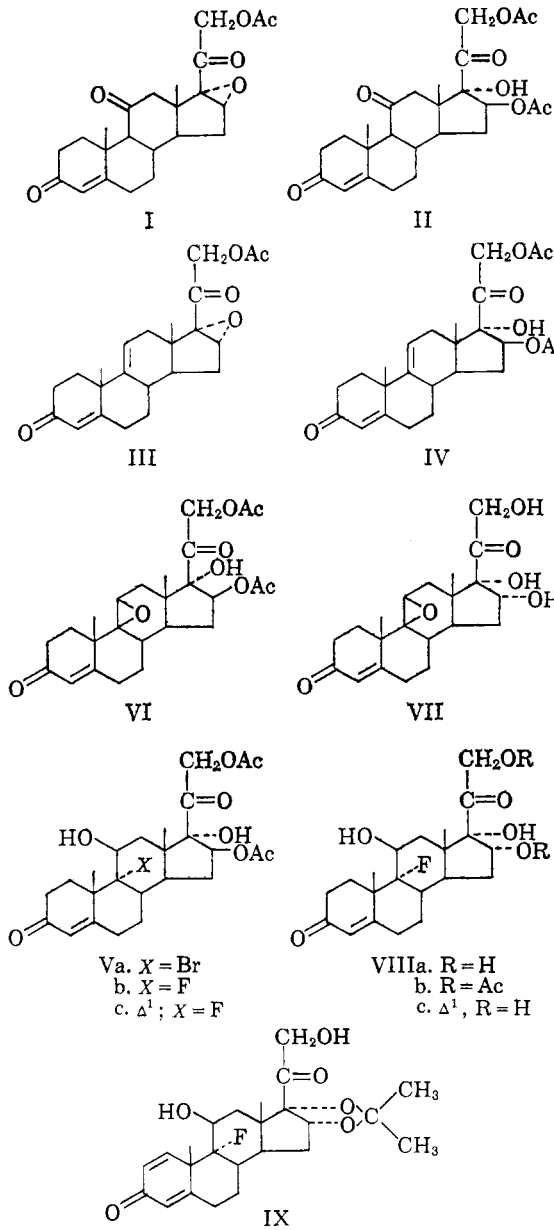
The preparation of 16β-21-diacetoxy-9α-fluoro-11β,17α-dihydroxypregn-1,4-diene-3,20-dione (Vc) and its epimerization to triamcinolone (VIIIc) are discussed.

In a continuation of the previous report[1] some 11,16β-dioxygenated corticoids were prepared for pharmacological evaluation. First, 21-acetoxy-16α,17α-epoxypregn-4-ene-3,11,20-trione (I)[2] was treated with sulfuric acid in acetic acid to give 16β,21 - diacetoxy - 17α - hydroxypregn - 4 - ene-3,11,20-trione (II), which had physical characteristics consistent with the proposed structure and was clearly different from the 16α-acetoxy epimer.[3]

For preparing 9α-halo analogs, 21-acetoxy-16α,-17α - epoxypregn - 4,9(11) - diene - 3,20 - dione (III)[2b,4] was treated with sulfuric acid–acetic acid to give 16β,21 - diacetoxy - 17α - hydroxypregn - 4,9-(11)-diene-3,20-dione (IV). The procedures for elaborating the C ring halohydrin substituents outlined by Fried and Sabo[5] were then employed. Addition of the elements of hypobromous acid to the $\Delta^{4,9(11)}$-diene-3,20-dione IV afforded Va which did not lend itself to purification but which, on treatment with potassium acetate in ethanol, yielded pure 16β,21-diacetoxy-9β,11β-epoxy-17α-hydroxypregn-4-ene-3,20-dione (VI). The latter compound was then treated with hydrogen fluoride in methylene chloride and tetrahydrofuran to give the fluorohydrin Vb. The reaction of Vb with selenium dioxide[6] in *t*-butyl alcohol afforded 16β,21 - diacetoxy - 9α - fluoro - 11β,17α - dihydroxypregn - 1,4 - diene - 3,20 - dione (Vc).

In the manner expected from the results in the previous paper,[1] alkaline treatment of the 9β,11β-epoxide VI gave 9β,11β - epoxy - 16α,17α,21-trihydroxypregn-4-ene-3,20-dione (VII).[7] In a similar fashion, the fluorohydrin Vb gave 9α-fluoro-



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11β,16α,17α,21 - tetrahydroxypregn - 4 - ene - 3,20-dione (VIIIa),[7] which was further characterized as the diacetate VIIIb. Additionally, Δ^1-analog Vc yielded triamcinolone (9α-fluoro-11β,16α,17α,21-tetrahydroxypregn - 1,4 - diene - 3,20 - dione, VIIIc),[7] which was characterized as the acetonide IX.[7] This formally constitutes a new synthesis of triamcinolone *via* appropriate 16β-acetoxy intermediates.

Bioassay.[8] 16β,21 - Diacetoxy - 9α - fluoro-11β,17α - dihydroxypregn - 1,4 - diene - 3,20-dione (Vc) was inactive in a liver glycogen deposition and thymus involution assay (less than 0.5 times the activity of hydrocortisone at a 500 γ dose level).

EXPERIMENTAL

Melting points. All melting points are uncorrected.

Absorption spectra. The ultraviolet spectra were determined in alcohol; the infrared spectra were determined in a potassium bromide disk.

Petroleum ether. The fraction used (unless otherwise noted) had a b.p. of 60–70°.

16β,21-Diacetoxy-17α-hydroxypregn-4-ene-3,11,20-trione (II). To a solution of 1.05 g. of 21-acetoxy-16α,17α-epoxypregn-4-ene-3,11,20-trione (I) in 20 ml. of acetic acid was added 2.5 ml. of a 4:1 (v./v.) solution of acetic acid-sulfuric acid. The mixture was allowed to stand for 65 hr. at room temperature and then poured into ice water. The resulting crude solid (800 mg.) was submitted to partition chromatography on a Celite[9] column using the system 7,5,2; petroleum ether (b.p. 90–100°), methylene chloride, ethylene glycol. Hold-back volume two was evaporated, and the residue was extracted with methylene chloride. The extract was washed with water, dried, and evaporated to give a solid (440 mg.). Three crystallizations from methanol yielded 95 mg. of II; m.p. 220–221.5°; positive Blue Tetrazolium ketol test; λ_{max} 237 mμ (ε 16,000); ν_{max} 3400, 1756, 1747, 1718, 1677, 1640, 1240 cm.$^{-1}$; $[\alpha]_D^{25}$ +170° (chloroform).

Anal. Calcd. for $C_{25}H_{32}O_8$ (460.51): C, 65.20; H, 7.00. Found: C, 65.14; H, 7.13.

16β,21-Diacetoxy-17α-hydroxypregn-4,9(11)-diene-3,20-dione (IV). A solution of 0.5 g. of 21-acetoxy-16α,17α-epoxypregn-4,9(11)-diene-3,20-dione (III) in 10 ml. of glacial acetic acid was treated with 1 ml. of a 20% (v./v.) solution of sulfuric acid in acetic acid and allowed to stand at room temperature for 24 hr. The resulting brown solution was poured into ice water and extracted several times with ethyl acetate. The combined extracts were washed with aqueous sodium bicarbonate and finally with water until the washings were neutral. The extract was dried and evaporated. The resulting oil was submitted to partition chromatography on a Celite[9] column with the system 5,2,3,2; petroleum ether (b.p. 90–100°), ethyl acetate, methanol, water. Hold-back volumes two and part of three were evaporated to give a white semisolid which crystallized from acetone-petroleum ether to give 280 mg. of IV, m.p. 172–174°. Three crystallizations from acetone–petroleum ether afforded 160 mg.; m.p. 173–175° λ_{max} 239 mμ (ε 15,700); ν_{max} 3440, 1755, 1740, 1650, 1620, 1238 cm.$^{-1}$; $[\alpha]_D^{25}$ +73° (chloroform).

Anal. Calcd. for $C_{25}H_{32}O_7$ (444.51): C, 67.55; H, 7.26. Found: C, 67.78; H, 7.56.

9α-Bromo-16β,21-diacetoxy-11β,17α-dihydroxypregn-4-ene-3,20-dione (Va). To a solution of 1.64 g. of IV in 82 ml. of dioxane (peroxide free) and 16 ml. of water cooled to 15° were added 0.7 g. of *N*-bromoacetamide and 3.5 ml. of 10% aqueous perchloric acid. After standing for 30 min. at room temperature, the solution was treated with aqueous sodium sulfite until the color was discharged and the solution became slightly alkaline. Dilution with water gave a semisolid (1 g.) which could not be purified further.

16β,21-Diacetoxy-17α-hydroxy-9β,11β-epoxypregn-4-ene-3,20-dione (VI). To a solution of 1.0 g. of bromohydrin Va in 500 ml. of absolute ethanol was added 3.0 g. of dried potassium acetate and the mixture was refluxed for 24 hr. After evaporation to dryness, the residue so obtained was dissolved in ethyl acetate, washed with water, dried, and evaporated. The resulting oil was dissolved in 20 ml. of pyridine and treated with 4 ml. of acetic anhydride overnight at room temperature. The acetylation mixture was evaporated to give 0.65 g. of oil which was submitted to partition chromatography on a Celite[9] column using the system 4:2:3:2; petroleum ether (b.p. 90–100°), ethyl acetate–methanol–water. Hold-back volumes three and part of two were evaporated to give an oil which on treatment with acetone–petroleum ether furnished 120 mg. of VI, m.p. 192–197°. Three crystallizations from acetone–petroleum ether gave 60 mg.; m.p. 200–202°; λ_{max} 243–244 mμ (ε 15,200); ν_{max} 3390, 1740, 1718, 1655, 1619, 1235 cm.$^{-1}$; $[\alpha]_D^{25}$ +3° (chloroform).

Anal. Calcd. for $C_{25}H_{32}O_8$ (460.51): C, 65.20; H, 7.00. Found: C, 65.28; H, 7.28.

16β,21-Diacetoxy-9α-fluoro-11β,17α-dihydroxypregn-4-ene-3,20-dione (Vb). To a solution of 200 mg. of the 9,11-epoxide (VI) in 15 ml. of methylene chloride at −60°, was added a solution of 1 ml. of hydrogen fluoride in 2 ml. of tetrahydrofuran at −60°. The mixture was allowed to stand at −5° for 4 hr. and then poured slowly into a mixture of 50 ml. of saturated aqueous sodium bicarbonate and 50 ml. of methylene chloride. The methylene chloride layer was separated and the aqueous phase was extracted three times with methylene chloride. The combined extracts were washed until neutral with water, dried, and evaporated to give 200 mg. of oil. Trituration with ether–petroleum ether gave 130 mg., m.p. 197–212°. Six crystallizations from acetone–petroleum ether gave 45 mg. of Vb; m.p. 239–241.5°; λ_{max} 239 mμ (ε 16,500); ν_{max} 3540, 3420, 1755, 1738, 1718, 1669, 1627, and 1250 cm.$^{-1}$; $[\alpha]_D^{25}$ +106° (acetone).

Anal. Calcd. for $C_{25}H_{33}O_8F$ (480.51): C, 62.49; H, 6.92; F, 3.95. Found: C, 62.66; H, 7.11; F, 4.05.

16β,21-Diacetoxy-9α-fluoro-11β,17α-dihydroxypregn-1,4-diene-3,20-dione (Vc). To a solution of 1.62 g. of Vb in 175 ml. of *t*-butyl alcohol was added 2 ml. of water. The solution was then flushed with nitrogen and evacuated on a water pump. This sequence was repeated three times to ensure removal of air. Selenium dioxide (2.0 g.) was added and the solution was refluxed under a stream of nitrogen for 23 hr., at which time it was evaporated. The residue was dissolved in ethyl acetate, the insolubles were filtered off, and the solution was washed with aqueous sodium bicarbonate and finally with water. After being dried, the solution was evaporated and the residue was dissolved in 50 ml. of methanol. To the methanol solution was added 1 teaspoon of deactivated Raney nickel[10] and the mixture was shaken for 1 hr. and filtered. The dark red solution was evaporated and the residue was dissolved in ethyl acetate. The ethyl acetate solution was washed twice with 10% aqueous acetic acid, then with sodium bicarbonate solution, and finally with water until the washings were neutral. The solution was dried and evaporated to give 1.2 g. of yellow glass which was submitted to partition chromatography on a Celite[9] column using the sys-

(8) The assay was done by the Metabolic Chemotherapy Department of these Laboratories.

(9) Celite is Johns-Manville's registered trade mark for diatomaceous silica products.

(10) Three teaspoons of W-2 Raney nickel were shaken with 300 ml. of 10% aqueous acetic acid for 15 min., the acid decanted, the Raney nickel shaken with 200 ml. of water, and the water decanted. The catalyst was washed twice more with water, twice with ethanol, and finally twice with methanol.

tem 2:3:3:2; petroleum ether (b.p. 90–100°)–ethyl acetate–methanol–water. Hold-back volume two was evaporated to give 330 mg. of semisolid which on treatment with acetone–petroleum ether afforded 220 mg. of Vc; m.p. 228–236°. Three crystallizations from acetone–petroleum ether gave 55 mg.; m.p. 233.5–236°; λ_{max} 238 mμ (ε 13,000); ν_{max} 3490, 3320, 1755, 1733, 1713, 1660, 1620, 1608, and 1245 cm.$^{-1}$; $[\alpha]_D^{25}$ +76.5° (acetone).

Anal. Calcd. for $C_{25}H_{31}O_8F$ (478.49): C, 62.75; H, 6.53; F, 3.97. Found: C, 63.13; H, 6.53; F, 3.62.

9β,11β-Epoxy-16α,17α,21-trihydroxypregn-4-ene-3,20-dione (VII). To a solution of 200 mg. of VI in 20 ml. of methanol, cooled to 0° and flushed with nitrogen, was added a solution of 80 mg. of potassium hydroxide in 5 ml. of methanol. After standing for 1 hr. at room temperature, the solution was neutralized with acetic acid and evaporated *in vacuo* at 35–40°. The residue was dissolved in ethyl acetate, and the solution was washed to neutral with water, dried and evaporated to yield 150 mg. of oil. Trituration with acetone–petroleum ether gave 50 mg.; m.p. 178–200°. Two crystallizations from acetone-petroleum ether raised the m.p. to 207.5–210.5°. A mixed melting point determination with an authentic sample of VII gave no depression. Its infrared spectrum was identical to that of the authentic sample.

9α-Fluoro-11β,16α,17α,21-tetrahydroxypregn-4-ene-3,20-dione (VIIIa). To a solution of 160 mg. of Vb in 20 ml. of methanol, cooled to 0°, and flushed with nitrogen, was added a solution of 56 mg. of potassium hydroxide in 5 ml. of methanol. After standing for 1 hr. at room temperature, the solution was neutralized with acetic acid and evaporated *in vacuo* at 35–40°. The crystalline residue was slurried in water, filtered, and washed well with water to yield 50 mg.; m.p. 203–236°. Its infrared spectrum was identical to that of an authentic sample of VIIIa.

The diacetate VIIIb prepared in the usual manner from VIIIa also had an infrared spectrum identical to that of an authentic sample.

9α-Fluoro-11β,16α,17α,21-tetrahydroxypregn-1,4-diene-3,20-dione (VIIIc). To a solution of 240 mg. of Vc in 25 ml. of methanol, cooled to 0°, and flushed with nitrogen, was added a solution of 100 mg. of potassium hydroxide in 5 ml. of methanol. After standing for 1 hr. at room temperature, the solution was neutralized with acetic acid and evaporated *in vacuo* at 35–40°. The residue was treated with acetone–petroleum ether to give a poor-looking solid which was set aside. The mother liquor was evaporated to dryness and submitted to partition chromatography on a Celite[9] column using the system 3:4:3:2; petroleum ether (b.p. 90–100°)–ethyl acetate–methanol–water. Hold-back volumes 6–8 were evaporated to dryness to give a solid. Crystallization from acetone–petroleum ether gave 20 mg., m.p. 265–268°. Mixed melting point determination with an authentic sample of VIIIc showed no depression. The infrared spectra were also identical.

9α-Fluoro-11β,21-dihydroxy-16α,17α-isopropylidenedioxypregn-1,4-diene-3,20-dione (IX). To a suspension of 14 mg. of VIIIc in 5 ml. of acetone was added 5λ of 72% perchloric acid. Solution became complete immediately. The reaction was allowed to stand for 2 hr. at room temperature and was then treated with 3 ml. of water and 0.4 ml. of saturated sodium bicarbonate solution. Evaporation of the acetone at room temperature gave a solid which was filtered off and washed with water to yield 10 mg., m.p. 277–281°. Its infrared spectrum was identical to that of an authentic sample of triamcinolone acetonide IX.

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[CONTRIBUTION FROM THE ORGANIC CHEMICAL RESEARCH SECTION, LEDERLE LABORATORIES DIVISION, AMERICAN CYANAMID CO.]

The Synthesis of Certain 4-Alkyl Derivatives of Hydrocortisone and 9α-Fluorohydrocortisone

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4-Methylhydrocortisone (VI), 4-methyl-9α-fluorohydrocortisone (XI), 4-methyl-9α-fluoroprednisolone (XII), 4-ethyl-9α-fluorohydrocortisone (XVII), and 4,4-dimethyl-9α-fluoro-11β,17α,21-trihydroxy-5-pregnene-3,20-dione (XIX) have been synthesized. The 4-alkyl group was introduced by treatment of a Δ^4-3-ketone with an alkyl iodide in the presence of potassium *t*-butoxide. This alkylation procedure will also cause etherification of a free 21-ol and some oxide ring formation with a ring C fluorohydrin. Introduction of a 4-alkyl group into an active corticoid causes a decrease in thymolytic and glucocorticoid activity and does not reverse the sodium-retaining properties of the 9α-fluoro corticoids.

This paper reports the synthesis of certain 4-alkyl derivatives in the glucocorticoid series. 4-Alkyl, in particular 4-methyl, derivatives of hydrocortisone and its analogs were of considerable interest in view of the important biological effects which result on the introduction of a methyl group at the 2α-,[2] 6α-,[3] 16α-,[4] and 16β-[5] positions of the hydrocortisone molecule.

An attractive procedure for the 4-alkylation of a Δ^4-3-keto system was the method introduced by

(1) To whom inquiries concerning this paper should be addressed.

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