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

16-Hydroxylated Steroids. XIX.[1] The Synthesis of 16α-Hydroxy-19-norhydrocortisone

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19-Norhydrocortisone (III), 16α-hydroxy-19-norhydrocortisone (IX), and 11β,21-dihydroxy-16α,17α-isopropylidenedioxy-19-norpregn-4-ene-3,20-dione (X) have been synthesized starting from prednisolone.

19-Norhydrocortisone (III)[2,3] has been shown to have considerably less glucocorticoid activity than the corresponding 10-methyl compound, hydrocortisone, and to exhibit sodium retention. Since it is known that 16α-hydroxylation negates the sodium retaining property of certain steroids, *e.g.* 9α-fluorohydrocortisone,[4] it became of interest to us to synthesize 16α-hydroxy-19-norhydrocortisone (IX).

The proposed route utilized 11β-acetoxy-17α,21-dihydroxy - 3 - methoxy - 19 - norpregna - 1,3,5-(10)-trien-20-one (IVb) as an intermediate. Magerlein and Hogg[2] prepared this compound by a multistep synthesis starting from 11α-hydroxyprogesterone. However, a promising starting material for a less tedious and more direct preparations of compound IVb appeared to be 11β-hydroxy-17,20; 20,-21-bismethylenedioxypregna-1,4-dien-3-one (prednisolone BMD).[5,6] Pyrolysis[2] of this compound in a mineral oil suspension gave 17,20; 20,21-bismethylenedioxy - 19 - norpregna - 1,3,5(10) - triene - 3,11β-diol (Ia) in 15–20% yield. The structure of compound Ia was shown by its conversion to the known compounds, 3,11β,17α,21-tetrahydroxy-19-norpregna-1,3,5(10)-trien-20-one (IVa)[2] and 19-norhydrocortisone (III).[2,3] Thus, hydrolysis of the phenol Ia with dilute acetic acid containing 5,5-dimethyldihydroresorcinol (used as a scavenger for the liberated formaldehyde) afforded compound IVa. Also, the methyl ether Ib, obtained by treating the phenol Ia with methyl iodide and anhydrous potassium carbonate in ethanol, was reduced with lithium in liquid ammonia and ethanol to give 3-methoxy - 17,20; 20,21 - bismethylenedioxy - 19-norpregna-2,5(10)-dien-11β-ol (II) which was not characterized. Dilute acetic acid hydrolysis of the enol ether II gave 19-norhydrocortisone (III).

3 - Methoxy - 17,20; 20,21 - bismethylenedioxy-19 - norpregna - 1,3,5(10) - trien - 11β - ol (Ib) was acetylated to give 11β-acetoxy-3-methoxy-17,20; 20,21 - bismethylenedioxy - 19 - norpregna-1,3,5(10)-triene (Ic). Alternatively, 3,11β-diacetoxy - 17,20; 20,21 - bismethylenedioxy - 19 - norpregna-1,3,5(10)-triene (Id), obtained by acetylation of the phenol Ia, was treated with methyl iodide as above to give compound Ic. This compound was converted into the desired intermediate IVb by dilute acetic acid hydrolysis.

Ketalization of compound IVb gave 11β-acetoxy - 20 - ethylenedioxy - 3 - methoxy - 19 - norpregna-1,3,5(10)-triene-17α,21-diol (Va),[2] acetylation of which yielded 11β,21-diacetoxy-20-ethylenedioxy - 3 - methoxy - 19 - norpregna - 1,3,5(10)-trien-17α-ol (Vb). The diacetate Vb, on treatment with thionyl chloride in pyridine, was transformed into 11β,21-diacetoxy-20-ethylenedioxy-3-methoxy-19-norpregna-1,3,5(10),16-tetraene (VI) in low yield. Oxidation of compound VI using osmium tetroxide in pyridine[7] gave 11β,21-diacetoxy-20-ethylenedioxy - 3 - methoxy - 19 - norpregna-1,3,5(10)-triene-16α,17α-diol (VIIa) in excellent yield. The diol (VIIa) was treated[2] with lithium aluminum hydride to give 20-ethylenedioxy-3-methoxy - 19 - norpregna - 1,3,5(10) - triene-11β,16α,17α,21-tetrol (VIIb) which afforded 20-ethylenedioxy - 3 - methoxy - 19 - norpregna - 2,5-(10)-diene-11β,16α,17α,21-tetrol (VIII) when subjected to reduction by lithium in liquid ammonia and ethanol. The enol ether VIII, which was not characterized, was converted into 16α-hydroxy-19-norhydrocortisone (IX) by hydrolysis with dilute sulfuric acid in methanol. Compound IX was characterized by formation of the acetonide, 11β,21-dihydroxy - 16α,17α - isopropylidenedioxy - 19-norpregn-4-ene-3,20-dione (X).

Bioassays.[8] In the thymus involution assay,[8a] 16α-hydroxy-19-norhydrocortisone (IX) had an activity of $< 0.5 \times$ hydrocortisone at a dose of 2000 γ per rat and showed no sodium retention[8b] at a dose of 16 γ per rat. In the same assays, the

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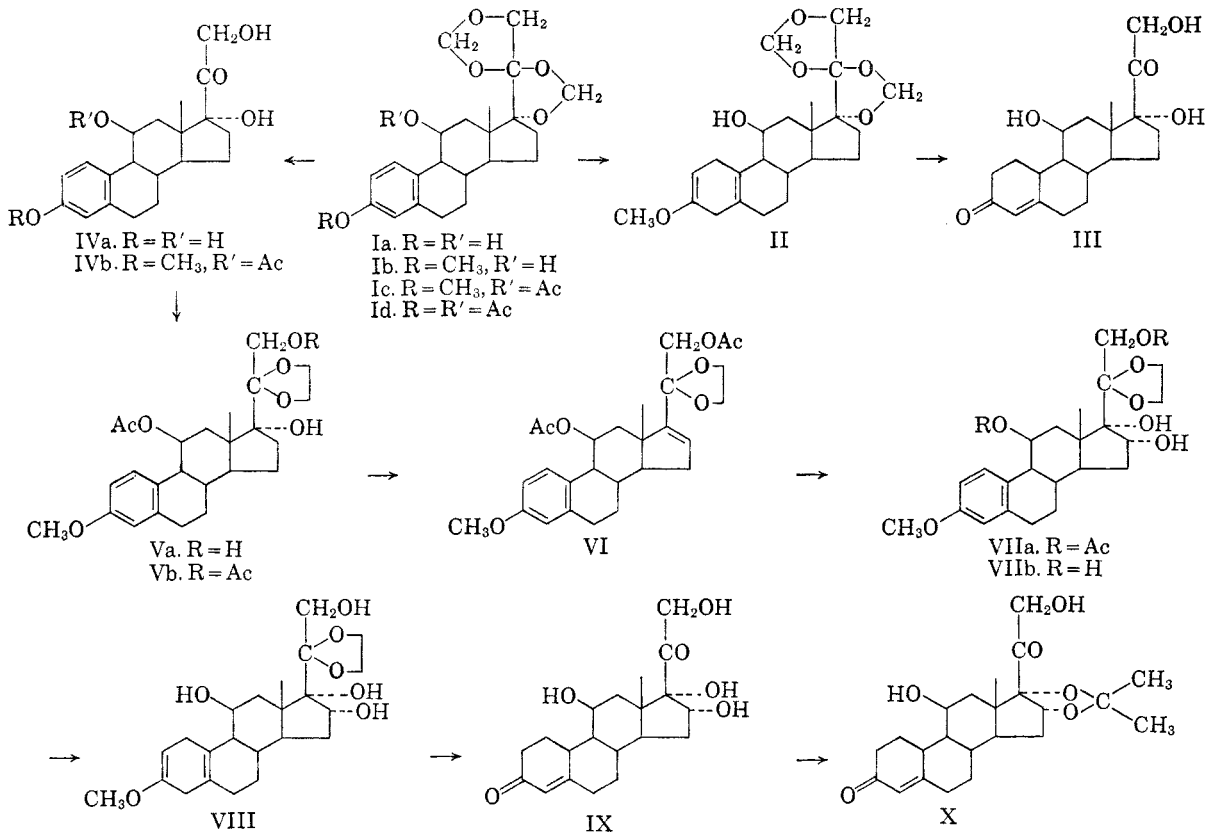

acetonide, 11β,21-dihydroxy-16α,17α-isopropylidenedioxy-19-norpregn-4-ene-3,20-dione (X), had an activity of 0.4 (0.3–0.6; 95% confidence limits) × hydrocortisone at a dose range of 100–2400 γ per rat and showed no sodium retention at a dose of 16 γ per rat.

EXPERIMENTAL[9]

Absorption spectra. The ultraviolet absorption spectra were determined in methanol. The infrared absorption spectra were carried out in pressed potassium bromide.

Melting points. Melting points are uncorrected.

Optical rotations. The rotations are for chloroform solutions unless noted otherwise.

Petroleum ether. The fraction had a b.p. of 60–70°.

17,20;20,21-Bismethylenedioxy-19-norpregna-1,3,5(10)-triene-3,11β-diol (Ia). 11β-Hydroxy-17,20;20,21-bismethylenedioxypregna-1,4-dien-3-one (500 mg.) and mineral oil (50 ml.) were mixed in a Waring blender for 15 min., and the suspension was added dropwise (1 drop/sec.) into a heated vertical Vycor tube (8 mm. i. d.) packed with broken Vycor glass for a length of 34.5 cm. The tube was heated to 550° over 25.5 cm. from the top of the packing, and, during the addition of the mineral oil suspension, a slow stream of nitrogen was passed through the tube. The cooled effluent was extracted with aqueous potassium hydroxide (5%), and the extract was washed with ether. The alkaline solution was acidified (Congo red) with dilute hydrochloric acid (5%), and the solid which separated was extracted in methylene chloride. The extract was washed with water and dried, and the residue obtained by removal of solvent crystallized from acetone to give 17,20; 20,21-bismethylenedioxy-19-norpregna-1,3,5(10)-triene-3,11β-diol as prisms (85 mg.), m.p. 300–305° dec. The analytical sample had a m.p. of 310–313° dec.; $[\alpha]_D^{25}$ −42° (pyridine); λ_{max} 222 (ε 7000), 280 (ε 1240), and 286 mμ (ε 1100); ν_{max} 3497, 3300, 1623, 1585, 1504, 1250, and 1099 cm.$^{-1}$

Anal. Calcd. for $C_{22}H_{28}O_6$ (388.44): C, 68.02; H, 7.27. Found: C, 68.25; H, 7.61.

Yields of 15–20% were obtained by using 50 ml. of mineral oil per gram of steroid.

3,11β,17α,21-Tetrahydroxy-19-norpregna-1,3,5(10)-trien-20-one (IVa). 17,20;20,21-Bismethylenedioxy-19-norpregna-1,3,5(10)-triene-3,11β-diol (Ia, 250 mg.), 5,5-dimethyldihydroresorcinol (370 mg.), acetic acid (12.5 ml.), and water (6.5 ml.) were heated under reflux for 2 hr. The reaction mixture was diluted with water (50 ml.) and was then extracted with methylene chloride. The aqueous phase was neutralized with sodium hydrogen carbonate and extracted with ethyl acetate. The extract was washed with water and dried. Solvent was removed and the residue was crystallized from acetone from which 3,11β,17α,21-tetrahydroxy-19-norpregna-1,3,5(10)-trien-20-one separated as needles (100 mg.), m.p. 256–258°. The compound had $[\alpha]_D^{25}$ +107° (methanol); λ_{max} 220 (ε 8150), 280 (ε 2180) and 286 mμ (ε 1730); ν_{max} 3390, 1715, 1626, 1595, 1511, 1250, and 1106 cm.$^{-1}$ (lit.,[2] m.p. 256–258°).

Anal. Calcd. for $C_{20}H_{26}O_5$ (346.41): C, 69.34; H, 7.57. Found: C, 69.54; H, 7.89.

3-Methoxy-17,20;20,21-bismethylendioxy-19-norpregna-1,3,5(10)-trien-11β-ol (Ib). 17,20;20,21-Bismethylenedioxy-19-norpregna-1,3,5(10)-triene-3,11β-diol (Ia, 500 mg.), anhydrous potassium carbonate (1 g.), methyl iodide (5 g.),

(8) The assays were carried out by Miss E. Heyder and Dr. S. Mauer of the Metabolic Chemotherapy Dept. of these laboratories. The compound, suspended in a modified carboxymethylcellulose medium, was given subcutaneously. (a) The assay was performed on immature female rats and the thymi were removed after 48 hours and weighed. (b) The assay was performed on salt-loaded adrenalectomized male rats. The urine was collected for 5 hours.

(9) Analyses were done by Mr. Louis M. Brancone and associates and the spectra and optical rotations were done by Mr. William Fulmor and associates.

and absolute ethanol (15 ml.) were heated under reflux for 4 hr. The filtered reaction mixture was evaporated, and the residue was collected with the aid of water. The solid so obtained crystallized from methanol to give the product as needles (360 mg.), m.p. 198–200° raised to 201–202° upon further crystallization. The analytical sample had $[\alpha]_D^{25}$ +10.5°; λ_{max} 222 (ϵ 8850), 278 (ϵ 2000), and 286 mμ (ϵ 1960); ν_{max} 3509, 1612, 1575, 1504, 1256, and 1099 cm.$^{-1}$

Anal. Calcd. for $C_{23}H_{30}O_6$ (402.47): C, 68.63; H, 7.51. Found: C, 68.68; H, 7.69.

19-Norhydrocortisone (III). Lithium wire (700 mg.) was added in small pieces to a stirred solution of 3-methoxy-17,-20;20,21-bismethylenedioxy-19-norpregna-1,3,5(10)-trien-11β-ol (Ib, 700 mg.) in liquid ammonia (200 ml.), dioxane (35 ml.), and ethanol (10 ml.). Fifteen minutes after the addition was complete, the lithium had dissolved, and the solution was allowed to evaporate to dryness. The product, 3-methoxy-17,20;20,21-bismethylenedioxy-19-norpregna-2,5(10)-dien-11β-ol (II), was collected by the addition of water followed by filtration. It crystallized as needles (500 mg.), m.p. 139–170°, from methanol. This compound II (250 mg.), acetic acid (12.5 ml.), and water (6.5 ml.) were heated under reflux for 2 hr. The mixture was diluted with water and then neutralized with sodium hydrogen carbonate. The product was extracted in ethyl acetate, and the extract was washed with water and dried. The gum obtained by evaporation of solvent crystallized from methanol–ethyl acetate to give 19-norhydrocortisone as needles (110 mg.), m.p. 250–252°. The analytical sample had m.p. 255–257°; $[\alpha]_D^{25}$ + 110° (methanol); λ_{max} 242 mμ (ϵ 16,700); ν_{max} 3534, 3413, 2989, 1709, 1642, and 1618 cm.$^{-1}$ [lit.,[8] m.p. 255–257°; $[\alpha]_D$ + 112° (methanol); $\lambda_{max}^{C_2H_5OH}$ 241 mμ (ϵ 16,980)].

Anal. Calcd. for $C_{20}H_{28}O_5$ (348.42): C, 68.94; H, 8.10. Found: C, 68.95; H, 8.41.

3,11β-Diacetoxy-17,20;20,21-bismethylenedioxy-19-norpregna-1,3,5(10)-triene (Id). A solution of 17,20;20,21-bismethylenedioxy-19-norpregna-1,3,5(10)-triene-3,11β-diol (Ia, 1.0 g.) in pyridine (5 ml.) and acetic anhydride (5 ml.) was kept at room temperature overnight. The solution was diluted with water, and the product was extracted in methylene chloride. The extract was washed with water, aqueous sodium bicarbonate solution, water, and dried. The residue obtained by evaporation of solvent crystallized from methanol as prisms (940 mg.), m.p. 179–181°, and had $[\alpha]_D^{25}$ −25°; λ_{max} 268 (ϵ 870) and 275 mμ (ϵ 835); ν_{max} 1767, 1736, 1616, 1587, 1502, 1242, 1208, 1096, 1031, and 1013 cm.$^{-1}$

Anal. Calcd. for $C_{28}H_{32}O_8$ (472.52): C, 66.08; H, 6.83. Found: C, 65.78; H, 6.98

11β-Acetoxy-3-methoxy-17,20;20,21-bismethylenedioxy-19-norpregna-1,3,5(10)-triene (Ic). *A.* Acetic anhydride (20 ml.) was added to a solution of 3-methoxy-17,20;20,21-bismethylenedioxy-19-norpregna-1,3,5(10)-trien-11β-ol (Ib, 4.2 g.) in pyridine (20 ml.), and the mixture was kept at room temperature overnight. The solid obtained by dilution of the reaction mixture with water followed by filtration was washed with water and dried. Crystallization from methanol gave the product as prisms (3.7 g.), m.p. 166–168°. The analytical sample had m.p. 170–171°; $[\alpha]_D^{25}$ −45°; λ_{max} 220 (ϵ 8870), 278 (ϵ 2000), and 287 mμ (ϵ 1890); ν_{max} 1742, 1623, 1587, 1511, 1261, 1244, and 1099 cm.$^{-1}$

Anal. Calcd. for $C_{25}H_{32}O_7$ (444.51): C, 67.55; H, 7.26. Found: C, 67.57; H, 7.45.

B. 3,11β-Diacetoxy-17,20;20,21-bismethylenedioxy-19-pregna-1,3,5(10)-triene (Id, 100 mg.), anhydrous potassium carbonate (200 mg.), methyl iodide (1 g.), and absolute ethanol (4 ml.) were heated under reflux for 4 hr. The filtered reaction mixture was evaporated, and the product was collected with the aid of water. The methyl ether crystallized as prisms (80 mg.), m.p. 165–168°, from methanol and was identical to that obtained in *A*.

11β-Acetoxy-17α,21-dihydroxy-3-methoxy-19-norpregna-1,3,5(10)-trien-20-one (IVb). 11β-Acetoxy-3-methoxy-17,20;-20,21-bismethylenedioxy-19-norpregna-1,3,5(10)-triene (Ic, 2 g.), acetic acid (100 ml.), and water (50 ml.) were heated under reflux for 2 hr. The cooled reaction mixture was diluted with water, and the product was extracted in chloroform. The extract was washed with aqueous sodium bicarbonate solution, water, and dried. Solvent was evaporated, and the residue crystallized from ethyl acetate to give the product IVb as needles (900 mg.), m.p. 207–212°. The pure compound had a m.p. of 214–217°; $[\alpha]_D^{28}$ +67°; λ_{max} 221 (ϵ 9450), 279 (ϵ 2000), and 287 mμ (ϵ 1900); ν_{max} 3390, 1721, 1704, 1610, 1582, and 1504 cm.$^{-1}$ (lit.,[2] m.p. 210–215°).

Anal. Calcd. for $C_{23}H_{30}O_6$ (402.47): C, 68.63; H, 7.51. Found: C, 68.17; H, 7.52.

11β,21-Diacetoxy-20-ethylenedioxy-3-methoxy-19-norpregna-1,3,5(10)-trien-17α-ol (Vb). Ketalization[2] of 11β-acetoxy-17α-21-dihydroxy-3-methoxy-19-norpregna-1,3,5(10)-trien-20-one (IVb) gave the ketal Va. A solution of 11β-acetoxy-20-ethylendioxy-3-methoxy-19-norpregna-1,3,5(10)-triene-17α,-21-diol (Va, 2 g.) in pyridine (20 ml.) and acetic anhydride (10 ml.) was kept at room temperature overnight. The reaction mixture was diluted with water, and the gum which separated was extracted in methylene chloride. The extract was washed with aqueous sodium bicarbonate solution, water, and dried. The residual gum obtained by evaporation of solvent was crystallized from methylene chloride–isopropyl ether to give the product Vb as blades (2.1 g.), m.p. 133–135°. After being dried at 78° *in vacuo*, the compound had a m.p. of 143–144°; $[\alpha]_D^{25}$ +57°; λ_{max} 222 (ϵ 9550), 278 (ϵ 2200), and 286 mμ (ϵ 2080); ν_{max} 3546, 1733, 1616, 1582, 1504, 1252, and 1046 cm.$^{-1}$

Anal. Calcd. for $C_{27}H_{36}O_8$ (488.56): C, 66.37; H, 7.43. Found: C, 65.96; H, 7.53.

11β,21-Diacetoxy-20-ethylenedicxy-3-methoxy-19-norpregna-1,3,5(10),16-tetraene (VI). Thionyl chloride (0.2 ml.) was added dropwise to a stirred solution of 11β,21-diacetoxy-20-ethylenedioxy-3-methoxy-19-norpregna-1,3,5(10)-trien-17α-ol (Vb, 200 mg.) in pyridine (0.2 ml.), cooled to −10°. The mixture was kept at −5° for 18 hr. and was then poured into iced aqueous sodium bicarbonate solution. The mixture was extracted with methylene chloride, and the extract was washed with water and dried. Removal of solvent afforded a gum which was dissolved in the minimum amount of benzene and chromatographed on Florisil[10] (15 g.). Elution with 1–3 % acetone in petroleum ether gave an oil (120 mg.). The column was then eluted with acetone and the crystalline material obtained recrystallized from isopropyl ether to give the product as prisms (60 mg.), m.p. 145–147°. Recrystallization gave a m.p. of 147–148°; $[\alpha]_D^{25}$ +71°; λ_{max} 222 (ϵ 8700), 278 (ϵ 2000), and 287 mμ (ϵ 1880); ν_{max} 1730, 1616, 1575, 1504, 1250, and 1039 cm.$^{-1}$

Anal. Calcd. for $C_{27}H_{34}O_7$ (470.54): C, 68.92; H, 7.28. Found: C, 68.95; H, 7.65.

11β,21-Diacetoxy-20-ethylenedioxy-3-methoxy-19-norpregna-1,3,5(10)-triene-16α,17α-diol (VIIa). Osmium tetroxide (55 mg.) was added to a solution of 11β,21-diacetoxy-20-ethylenedioxy-3-methoxy-19-norpregna-1,3,5(10),16-tetraene (VI, 100 mg.) in pyridine (5 ml.), and the mixture was stirred at room temperature for 1 hr. A solution of sodium bisulfite (600 mg.) in water (10 ml.) and pyridine (6.7 ml.) was then added and stirring was continued for 15 min. The mixture was extracted with methylene chloride, and the extract was washed with water and dried. Evaporation of solvent yielded a crystalline residue which upon recrystallization from acetone–petroleum ether gave the diol VIIa as needles (90 mg.), m.p. 189–190°; $[\alpha]_D^{30}$ +74.5°; λ_{max} 222 (ϵ 9300), 278 (ϵ 2000), and 286 mμ (ϵ 1890); ν_{max} 3484, 1730, 1616, 1577, 1508, 1250, 1045, and 1028 cm.$^{-1}$

Anal. Calcd. for $C_{27}H_{36}O_9$ (504.56): C, 64.27; H, 7.19. Found: C, 64.37; H, 7.48.

20-Ethylenedioxy-3-methoxy-19-norpregna-1,3,5(10)-triene-11β,16α,17α,21-tetrol (VIIb). 11β,21-Diacetoxy-20-ethylenedioxy-3-methoxy-19-norpregna-1,3,5(10)-triene-16α,17α-diol (VIIa, 600 mg.) in benzene (60 ml.) was added to a stirred

(10) Florisil is the Floridin Co.'s registered trademark for a synthetic magnesium silicate.

suspension of lithium aluminum hydride (1.2 g.) in ether (240 ml.), and the mixture was stirred at room temperature for 1 hr. Water (30 ml.) was added dropwise and the solvent was decanted. The residue was washed thoroughly with hot chloroform. The combined solvents were evaporated, and the product VIIb was obtained as needles (449 mg.), m.p. 227–230° by crystallization from acetone–petroleum ether. The analytical sample of the same melting point had $[\alpha]_D^{25}$ + 103° (methanol:chloroform 1:1); λ_{max} 221 (ϵ 9740), 278 (ϵ 1940), and 286 mμ (ϵ 1880); ν_{max} 3497, 1612, 1580, 1504, and 1048 cm.$^{-1}$

Anal. Calcd. for $C_{23}H_{32}O_7$ (420.49): C, 65.69; H, 7.67. Found: C, 65.57; H, 8.00.

16α-Hydroxy-19-norhydrocortisone (IX). Lithium wire (300 mg.) was added in small pieces to a stirred solution of 20-ethylenedioxy-3-methoxy-19-norpregna-1,3,5(10)-triene-11β,16α,17α,21-tetrol (VIIb, 300 mg.) in liquid ammonia (90 ml.), dioxane (10 ml.), and ethanol (4.5 ml.). The blue coloration disappeared in about 15 min., and the mixture was allowed to evaporate. Water was added and the mixture was extracted with methylene chloride. The extract was washed with water and dried. Evaporation of solvent followed by crystallization of the residue from methanol–ethyl acetate gave 20-ethylenedioxy-3-methoxy-19-norpregna-2,5(10)-diene-11β,16α,17α,21-tetrol (VIII, 210 mg.) as needles, m.p. 210–225°. This compound (VIII, 200 mg.), methanol (20 ml.), and dilute sulfuric acid (2 ml.; 8% v./v.) were heated on the steam bath for 1 hr. Ethyl acetate (100 ml.) was added to the cooled solution, and the mixture was washed with aqueous sodium bicarbonate solution, water, and dried. Removal of solvent and crystallization of the residue from methanol–ethyl acetate gave 16α-hydroxy-19-norhydrocortisone as small prisms (100 mg.), m.p. 228–231° dec. The analytical sample had m.p. 229–232° dec.; $[\alpha]_D^{25}$ + 63.5° (pyridine); λ_{max} 241 mμ (ϵ 17,800); ν_{max} 3401, 1709, 1661, and 1621 cm.$^{-1}$

Anal. Calcd. for $C_{20}H_{28}O_6$ (364.42): C, 65.91; H, 7.74. Found: C, 65.84; H, 7.95.

11β,21-Dihydroxy-16α,17α-isopropylidenedioxy-19-norpregn-4-ene-3,20-dione (X). Perchloric acid (1 drop; 72%) was added to a stirred suspension of 16α-hydroxy-19-norhydrocortisone (50 mg.) in acetone (5 ml.). After 2 hr., the solution was diluted with water, and the mixture was extracted with methylene chloride. The extract was washed with aqueous sodium bicarbonate solution, water, and dried. Removal of solvent gave the acetonide X which crystallized as needles (50 mg.), m.p. 209–213°, from acetone–petroleum ether. Further crystallization gave m.p. 218–224°; $[\alpha]_D^{25}$ +133°; λ_{max} 240 mμ (ϵ 18,300); ν_{max} 3484, 1718, 1664, and 1626 cm.$^{-1}$

Anal. Calcd. for $C_{23}H_{32}O_6$ (404.49): C, 68.29; H, 7.97. Found: C, 68.53; H, 8.15.

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

16-Hydroxylated Steroids. XX.[1] Some Transformations of 16β,21-Diacetoxy-17α-hydroxypregn-4-ene-3,20-dione

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Alkaline treatment of 16β,21-diacetoxy-17α-hydroxypregn-4-ene-3,20-dione (Ia) yielded 16α,17α,21-trihydroxypregn-4-ene-3,20-dione (IIa) and two isomeric by-products tentatively formulated as 16α,17α-dihydroxy-17β-hydroxymethyl-D-homoandrost-4-ene-3,17a-dione (IIIa) and 16α,17aα-dihydroxy-17aβ-hydroxymethyl-D-homoandrost-4-ene-3,17-dione (IVa). Acidic treatment of Ia afforded 16β,17α,21-trihydroxypregn-4-ene-3,20-dione (Ib) and its C-16 monoacetate (Ic).

In view of the importance of the biological and therapeutic properties of 9α-halo-16α-hydroxycorticoids,[2] it would appear to be of considerable interest to prepare 16β-oxygenated isomers of some of these active compounds. For a thorough study of this type of compound it was desirable to study the chemistry of 16β,21-diacetoxy-17α-hydroxypregn-4-ene-3,20-dione (Ia).[3,4]

Treatment of the diacetate Ia under a variety of alkaline conditions[4] (potassium hydroxide, sodium methoxide, sodium carbonate, or sodium bicarbonate) gave in all cases an easily isolated solid which proved to be 16α,17α,21-trihydroxypregn-4-ene-3,20-dione (IIa).[5,6]

Careful partition chromatography of some of the above experiments has provided at least two more products which are isomeric with IIa and are discussed below.

The same type of retroaldol mechanism employed by Wendler and co-workers[7] to elucidate the D-homoannulation of a 16,17α-dihydroxy-20-keto steroid may be utilized to explain the epimerization at the C-16 position. Thus, a retroaldol ring opening followed by closure, as illustrated by partial structures A, B, and C, is a plausible mechanism.[8,9]

The preference for a 16α-hydroxyl conformation in

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