[CONTRIBUTION FROM THE CHEMICAL RESEARCH LABORATORIES OF SCHERING CORPORATION]

11-Oxygenated Steroids. VI. The Synthesis of Δ^4-Pregnen-11α,17α-diol-3,20-dione (11α,17α-Dihydroxyprogesterone) and Δ^4-Pregnen-11α,17α,21-triol-3,20-dione 11-Acetate (11-Epi-Compound F 11-Acetate)[1,2]

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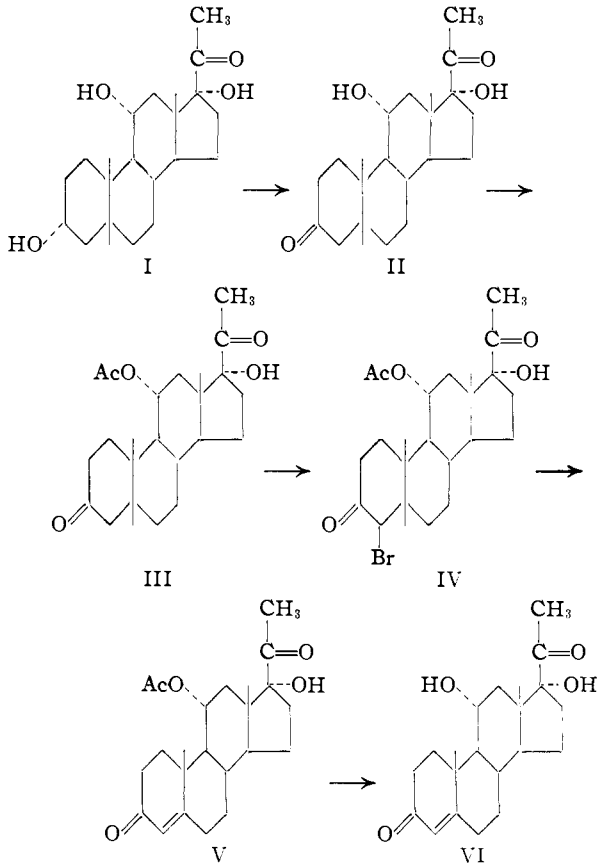
Pregnan-3α,11α,17α-triol-20-one (I), conveniently prepared *via* sodium and *n*-propyl alcohol reduction of 20-ethylene ketal of pregnan-3α,17α-diol-11,20-dione, has been converted into Δ^4-pregnen-11α,17α-diol-3,20-dione (11α,17α-dihydroxyprogesterone) and Δ^4-pregnen-11α,17α,21-triol-3,20-dione 11-acetate (11-epi-Compound F 11-acetate).

In the naturally occurring steroidal adrenal hormones which carry an hydroxyl group at C-11 (*e.g.*, corticosterone, Kendall's Compound F), this group is always found to have the β-configuration. It was of great interest, therefore, to synthesize steroids related to the known, active hormones but possessing the unnatural, or α-configuration of the hydroxyl group at C-11, and to determine the effect of this change on their biological activity.

The recent discovery[2-4] that the reduction of an 11-keto group to the 11α-hydroxyl group can be accomplished in excellent yield by means of sodium in *n*-propyl alcohol has made possible a convenient synthesis[1] of pregnan-3α,11α,17α-triol-20-one (I). This is the starting material for our synthesis of Δ^4-pregnen-11α,17α-diol-3,20-dione (VI) (11α,17α-dihydroxyprogesterone) and of Δ^4-pregnen-11α,-17α,21-triol-3,20-dione 11-acetate (XIII) (11-epi-Compound F 11-acetate).

11α,17α-Dihydroxyprogesterone has since been prepared *via* microbiological oxidation[5] of 11-desoxysteroids and from allopregnan-3α,11α,17α-triol-20-one,[6] which in turn was synthesized from diosgenin. In addition, the same investigators[5,6] prepared 11-epi-Compound F 11,21-diacetate (XII) but not the 11-monoacetate XIII.[6a]

In contrast to the 11β-hydroxyl group, which resists acetylation[7] and is easily oxidized even under mild conditions,[8] the corresponding 11α-hydroxyl group is easily acetylated, but is not oxidized easily by mild oxidizing agents. Thus, pregnan-3α,11α,-17α-triol-20-one (I) was converted into pregnan-11α,17α-diol-3,20-dione (II) in good yield by means of N-bromoacetamide in aqueous acetone. Because it was difficult to obtain the 4-bromide of II in a crystalline condition, the 11-hydroxy group was first acetylated, and then bromination at C-4 was effected by bromine in methylene chloride and *t*-butyl alcohol to yield IV. Dehydrobromination *via* the semicarbazone[9] gave Δ^4-pregnen-11α,17α-diol-3,20-dione 11-acetate (V), and 11α,17α-dihydroxyprogesterone (VI) was formed by hydrolysis of the 11-acetate by means of aqueous methanolic sodium hydroxide.



Bromination of I with bromine in chloroform solution produced 21-bromopregnan-3α,11α,17α-triol-20-one (VII). The conversion of this com-

(1) Paper V: E. P. Oliveto, H. L. Herzog and E. B. Hershberg, THIS JOURNAL, **75**, 1505 (1953).

(2) A portion of this work was reported in a preliminary communication: H. L. Herzog, E. P. Oliveto, M. A. Jevnik and E. B. Hershberg, *ibid.*, **74**, 4470 (1952).

(3) H. Heusser, R. Anliker and O. Jeger, *Helv. Chim. Acta*, **35**, 1537 (1952).

(4) H. L. Herzog, M. A. Jevnik and E. B. Hershberg, THIS JOURNAL, **75**, 269 (1953).

(5) (a) H. C. Murray and D. H. Peterson, U. S. Patent 2,602,769; (b) J. Fried, R. Thoma, J. Gerke, J. Herz, M. Donin and D. Perlman, THIS JOURNAL, **74**, 3962 (1952).

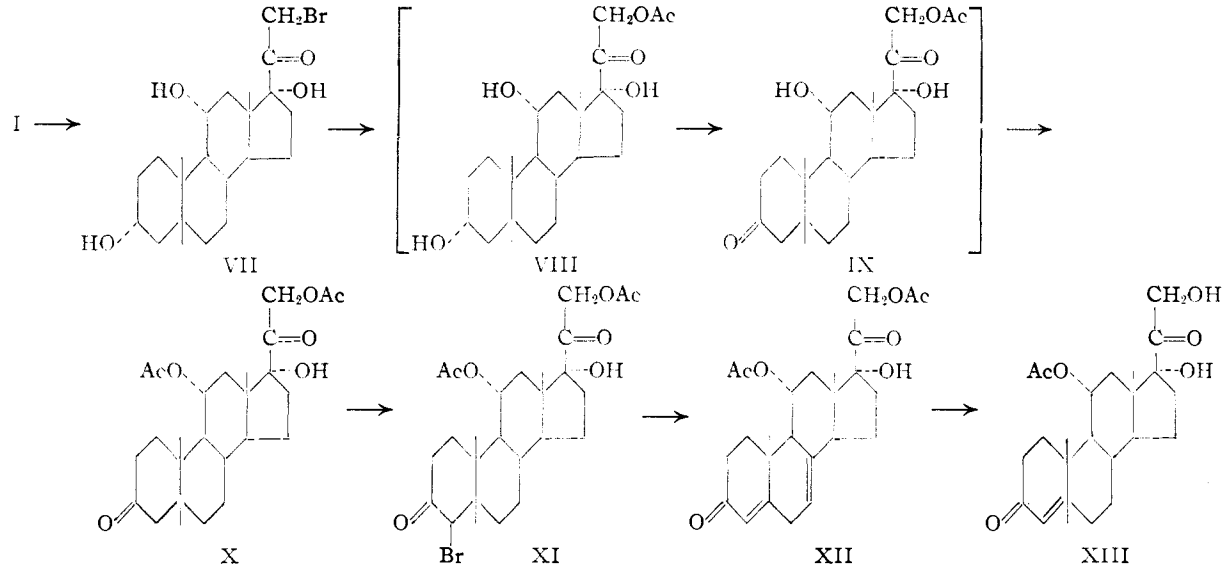
(6) J. Romo, G. Rosenkranz, F. Sondheimer and C. Djerassi, Abstracts of the 122nd meeting of the American Chemical Society, Atlantic City, N. J., Sept. 14-19, 1952, p. 61M; THIS JOURNAL, **75**, 1277 (1953).

(6a) NOTE ADDED IN PROOF.— 11-Epi-compound F 11,21-diacetate has also been prepared from sarmentogenin: A. Lardon and T. Reichstein, *Pharm. Acta. Helv.*, **27**, 287 (1952).

(7) T. F. Gallagher, *J. Biol. Chem.*, **162**, 539 (1946); L. F. Fieser and M. Fieser, "Natural Products Related to Phenanthrene," Reinhold Publ. Corp., New York, N. Y., 1949, p. 567.

(8) L. H. Sarett, M. Feurer and K. Folkers, THIS JOURNAL, **73**, 1777 (1951). These authors and others have noted, however, that the 11β-hydroxyl group is not attacked in an Oppenauer oxidation.

(9) W. F. McGuckin and E. C. Kendall, *ibid.*, **74**, 5811 (1952); V. R. Mattox and E. C. Kendall, *J. Biol. Chem.*, **188**, 287 (1951); B. Koechlin, T. Kritchevsky and T. F. Gallagher, *ibid.*, **184**, 393 (1950); E. B. Hershberg, *J. Org. Chem.*, **13**, 542 (1948).



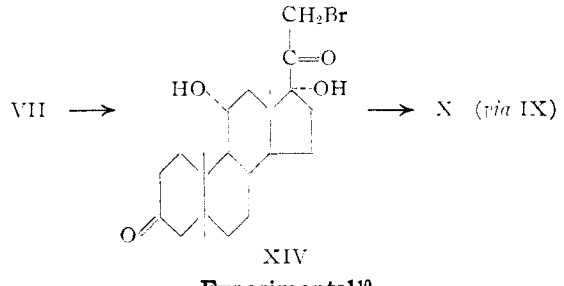
pound to 11-epi-Compound F 11-acetate (XIII) was then accomplished by two separate routes.

In one, the 21-bromide was converted into the corresponding 21-acetate VIII by refluxing with potassium acetate suspended in acetone. Pregnan-11α,17α,21-triol-3,20-dione 11,21-diacetate (X) was obtained from VIII by first oxidizing at C-3 with N-bromoacetamide in aqueous acetone and without isolation the ketone IX was acetylated at C-11 with acetic anhydride in pyridine.

Alternatively the 3-hydroxyl group in VII was oxidized by N-bromoacetamide in aqueous acetone to 21-bromopregnan-11α,17α-diol-3,20-dione (XIV). Acetoxylation at C-21 with potassium acetate, followed by acetylation at C-11 gave X.

Bromination of X at C-4 and dehydrobromination in the usual manner yielded Δ^4-pregnen-11α,17α,21-triol-3,20-dione 11,21-diacetate (XII) (11-epi-Compound F 11,21-diacetate). Acid hydrolysis removed only the 21-acetate and produced Δ^4-pregnen-11α,17α,21-triol-3,20-dione 11-acetate (XIII) (11-epi-Compound F 11-acetate).

It is interesting to note that while all of the 11α-acetates prepared in this paper were nicely crystalline compounds, many of the 11α-hydroxy compounds were not obtained crystalline (*e.g.*, VIII, IX and the 4-bromide of II) or if crystalline, formed solvates (*e.g.*, I, VII, XIV).



Experimental[10]

Pregnan-3α,11α,17α-triol-20-one (I).—This compound has been prepared previously[1] *via* the sodium and *n*-propyl alcohol reduction of pregnan-3α,17α-diol-11,20-dione 20-ethylene ketal.

Pregnan-11α,17α-diol-3,20-dione (II).—A solution of 1 g. of I in 10 ml. of acetone and 5 ml. of water was cooled to 3–5° and a solution of 1 g. of N-bromoacetamide in 5 ml. of water was added, maintaining the temperature below 5° during the addition. After two hours at 5°, the excess oxidizing agent was destroyed by the addition of 2 g. of sodium sulfite in 10 ml. of water. Further addition of water precipitated 920 mg. of II, m.p. 192–195°. The analytical sample, crystallized from aqueous acetone, melted at 192.6–194.0°, $[\alpha]_D$ +21.3° (acetone).

Anal. Calcd. for $C_{21}H_{32}O_4$: C, 72.38; H, 9.26. Found: C, 72.62; H, 9.49.

The 11-acetate III was prepared with acetic anhydride in pyridine, and after crystallization from aqueous acetone melted at 204.4–206.2°, $[\alpha]_D$ −1.4° (acetone).

Anal. Calcd. for $C_{23}H_{34}O_5$: C, 70.74; H, 8.78. Found: C, 70.95; H, 8.85.

4-Bromopregnan-11α,17α-diol-3,20-dione 11-Acetate (IV).—A solution of 2.5 g. of III in 10 ml. of methylene chloride previously saturated with hydrogen bromide and 10 ml. of *t*-butyl alcohol was cooled to 0°, and brominated by the addition of 1.1 g. of bromine in 10 ml. of methylene chloride and 10 ml. of *t*-butyl alcohol. The addition required 15 minutes and the temperature was maintained at 0° during this time. The solution was gradually warmed to room temperature and allowed to stand until the residual bromine color had discharged. The methylene chloride was removed under reduced pressure, and water added to precipitate crude IV. Recrystallization from aqueous acetone gave 2.62 g. (87%), m.p. 180–182° (dec.). The analytical sample, crystallized once more from aqueous acetone, melted at 180–181° (dec.), $[\alpha]_D$ +40.4° (acetone).

Anal. Calcd. for $C_{23}H_{33}O_5Br$: Br, 17.26. Found: Br, 17.37.

Δ^4-Pregnen-11α,17α-diol-3,20-dione 11-Acetate (V).—Compound IV was dehydrobrominated in the usual manner *via* the semicarbazone.[9] There was obtained 70% of crude V, m.p. 204–209°. The analytical sample, chromatographed over Florisil and crystallized from acetone–hexane, had m.p. 208.8–211.4°, $[\alpha]_D$ +88.2° (dioxane), ϵ_{240} 16,300 (95% ethanol).

Anal. Calcd. for $C_{23}H_{32}O_5$: C, 71.10; H, 8.30. Found: C, 70.86; H, 8.54. Lit.[5b] m.p. 205–208°, $[\alpha]_D$ +65° (chloroform); m.p.[6] 206–208°, $[\alpha]_D$ + 72° (chloroform), ϵ_{240} 17,800 (95% ethanol).

Δ^4-Pregnen-11α,17α-diol-3,20-dione (11α,17α-Dihydroxyprogesterone) (VI).—A mixture of 200 mg. of V, 100 mg. of sodium hydroxide, 8 ml. of methanol and 1 ml. of water was refluxed for 15 minutes. The excess alkali was neutralized with 1.3 ml. of acetic acid, the solution was concentrated, and water was added to precipitate crude VI. Recrystallization from aqueous methanol gave 100 mg., m.p. 219.0–220.5°, $[\alpha]_D$ +83.7° (chloroform), ϵ_{242} 14,000 ethanol).

(10) All melting points are corrected. All rotations were taken in a one-dm. tube at a concentration of about 1%. Analyses and optical data were obtained by the Microanalytical and Physical Chemistry Departments of these laboratories.

Anal. Calcd. for $C_{21}H_{30}O_4$: C, 72.80; H, 8.73. Found: C, 72.36; H, 8.90. Lit.[5a] m.p. 219–222°, $[\alpha]_D$ +87° (chloroform); m.p.[5b] 220–222°, $[\alpha]_D$ +76° (chloroform); m.p.[6] 216–218°, $[\alpha]_D$ +88° (chloroform), ϵ_{242} 15,500 (95% ethanol).

21-Bromopregnan-3α,11α,17α-triol-20-one (VII).—To remove the water of hydration, a solution of 1.0 g. of I in 50 ml. of chloroform was concentrated to a residue. The residue was dissolved in 25 ml. of C.P. chloroform, a saturated solution of hydrogen bromide in 10 ml. of C.P. chloroform was added, and the mixture was cooled to −10°. At this temperature, the solution was brominated with 480 mg. of bromine in 10 ml. of C.P. chloroform over a period of five minutes. After warming up to room temperature, the chloroform was removed under reduced pressure, the residue triturated with acetone, and the precipitated solid (900 mg.) removed by filtration. The analytical sample crystallized from acetone–water as a hydrate, m.p. 180–185° (dec.), $[\alpha]_D$ +65.8° (acetone).

Anal. Calcd. for $C_{21}H_{33}O_4Br \cdot H_2O$: Br, 17.85. Found: Br, 17.70.

21-Bromopregnan-11α,17α-diol-3,20-dione (XIV).—One gram of the 21-bromide VII was dissolved in 100 ml. of acetone and 10 ml. of water and cooled to 3–5°. One-half gram of N-bromoacetamide was added and the solution maintained at 3–5° for 1.5 hours. The excess oxidizing agent was destroyed by the addition of 1 g. of sodium sulfite, and a large excess of water was added. The mixture was extracted with chloroform, the chloroform layer washed with water, dried over sodium sulfate and concentrated to a residue under reduced pressure. The residue was crystallized from acetone–hexane to give 0.41 g. of XIV, m.p. 200–205° (dec.). The analytical sample, crystallized once more from acetone–hexane, had m.p. 207–209° (dec.), $[\alpha]_D$ +62.7° (dioxane). This material analyzed for $^1/_2$ mole of solvation, even after further crystallization.

Anal. Calcd. for $C_{21}H_{31}O_4Br \cdot {}^1/_2C_3H_6O$: Br, 17.51. Found: Br, 17.45.

Pregnan-11α,17α,21-triol-3,20-dione 11,21-Diacetate (X). (**a**).—One gram of the 21-bromide XIV was acetoxylated by refluxing for five hours with 2 g. of potassium acetate in 25 ml. of acetone. At the end of this time water was added, and the mixture was extracted with chloroform. The chloroform extract was dried over Drierite and evaporated to dryness. The residual oil was acetylated with acetic anhydride and pyridine overnight to yield 820 mg. of X, m.p. 215–223°. An analytical sample, chromatographed over Florisil and recrystallized from acetone–hexane, melted at 231.8–233.4°, $[\alpha]_D$ +43.8° (dioxane).

Anal. Calcd. for $C_{25}H_{36}O_6$: C, 66.94; H, 8.09. Found: C, 66.59; H, 8.29. Lit.[6a] m.p. 222–226°, $[\alpha]_D$ + 34.8° (acetone).

(**b**).—One gram of the 21-bromide VII was acetoxylated with potassium acetate in acetone as described above. The oily product was dissolved in a solution of 10 ml. of acetone and 1 ml. of water and after cooling to 3–5°, 0.5 g. of N-bromoacetamide was added, and the temperature was maintained for 1.5 hours afterward. Two grams of sodium sulfite was then added, the mixture was treated with water and chloroform, and the organic layer was washed with water. After drying over sodium sulfate, the organic phase was concentrated to a residue and acetylated at room temperature with acetic anhydride in pyridine overnight. Upon pouring the mixture into ice and hydrochloric acid and collecting the solids, there was obtained 875 mg. of crude X, m.p. 210–218°. The infrared spectra of the two samples of X prepared by the two different routes was identical.

4-Bromopregnan-11α,17α,21-triol-3,20-dione 11,21-Diacetate (XI).—A mixture of 2.0 g. of X in 10 ml. of methylene chloride previously saturated with hydrogen bromide and 10 ml. of *t*-butyl alcohol was cooled to 0°. At this temperature a solution of 760 mg. of bromine in 10 ml. of methylene chloride and 10 ml. of *t*-butyl alcohol was added over a 10-minute period. The solution was allowed to warm to room temperature in order to discharge the residual bromine and then concentrated under reduced pressure until solids appeared. Water was then added and the crude 4-bromide was collected with suction, dried and crystallized from aqueous acetone to give 2.03 g. (85%) of XI, m.p. 197–202° (dec.). The analytical sample, crystallized once again from aqueous acetone, melted at 203–204° (dec.), $[\alpha]_D$ +62.9° (acetone).

Anal. Calcd. for $C_{25}H_{35}O_7Br$: Br, 15.15. Found: Br, 14.91.

Δ⁴-Pregnen-11α,17α,21-triol-3,20-dione 11,21-Diacetate (11-Epi-Compound F 11,21-Diacetate) (XII).—In the usual manner[9] 1.58 g. of XI was dehydrobrominated *via* the semicarbazone to yield two crops of XII, 0.67 g., m.p. 218–223° (dec.), and 0.30 g., m.p. 214–219° (dec.) (72.5%). An analytical sample, chromatographed on Florisil and crystallized from acetone–hexane melted at 223.0–225.8° (dec.), with a phase change at 212°, $[\alpha]_D$ +116.5° (dioxane), ϵ_{240} 16,800 (ethanol).

Anal. Calcd. for $C_{25}H_{34}O_7$: C, 67.24; H, 7.68. Found: C, 67.12; H, 7.85. Lit.[5a] m.p. 198–202°, $[\alpha]_D$ +115° (chloroform); m.p.[5b] 206–208°, $[\alpha]_D$ +117° (chloroform); m.p.[6] 221–223°, $[\alpha]_D$ +120° (chloroform), ϵ_{240} 17,400 (95% ethanol); m.p.[6a] 201–206°, $[\alpha]_D$ +99.7° (acetone), ϵ_{240} 15,500 (ethanol).

Δ⁴-Pregnen-11α,17α,21-triol-3,20-dione 11-Acetate (11-Epi-Compound F 11-Acetate) (XIII).—A mixture of 2.0 g. of XII, 10 ml. of methanol, 7 ml. of water, 4.2 ml. of concentrated hydrochloric acid and 20 ml. of chloroform was allowed to stand 48 hours at 25°. Fifty ml. of water was added and the mixture was extracted with methylene chloride. The organic extracts were washed to neutrality with water, dried over magnesium sulfate and concentrated. The residue was crystallized from acetone–hexane; yield 0.85 g. of XIII, m.p. 218–223°. The analytical sample, crystallized twice more from acetone–hexane, melted at 221.0–223.0°, $[\alpha]_D$ +87.7° (dioxane), ϵ_{240} 15,300 (ethanol). The infrared spectrum confirmed the loss of one acetate group, which had been adjacent to a ketone carbonyl.

Anal. Calcd. for $C_{23}H_{32}O_6$: C, 68.29; H, 7.97. Found: C, 68.23; H, 8.24.

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