Anal. Calcd. for $C_{10}H_{30}Cl_4N_4$: C, 34.49; H, 8.68; Cl, 40.73; N, 16.09. Found (dried at 100° *in vacuo*): C, 34.50; H, 8.68; Cl, 40.56; N, 16.11.

Spermine and spermidine from putrescine and acrylonitrile-1-C^{14}. In a 25-ml. flask were mixed 278 mg. of nonisotopic putrescine dihydrochloride (1.7 mmoles), 5 ml. of absolute ethanol, and 1.59 ml. of 2.17*N* sodium hydroxide solution. Into this mixture was distilled, under high vacuum at room temperature, 204 mg. (3.8 mmoles) of acrylonitrile-1-C^{14}; the flask then was sealed under vacuum.[5] After *ca.* 44 hr. the solution was refluxed and treated by the above described procedure for the preparation of radioactive spermidine and spermine from putrescine-1-C^{14}. The yields were 116 mg. (0.46 mmole) of spermidine trihydrochloride showing 0.30 μc per μ mole and 221 mg. (0.64 mmole) of spermine tetrahydrochloride showing 0.60 μc per μ mole. These compounds contained small amounts of unknown material and were purified further as described for the products obtained from putrescine-1-C^{14}.

Acknowledgement. We express our thanks to Dr. H. Tabor for the gift of the putrescine-1-C^{14}, to Dr. W. C. Alford and his associates for the microanalyses, and to Mr. William Jones and Mr. H. K. Miller for the infrared spectra.

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AND METABOLIC DISEASES
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BETHESDA 14, MD.

(5) The acrylonitrile-1-C^{14} was prepared and mixed immediately after synthesis with the putrescine solution by Dr. S. Rothschild of Tracerlab, Inc., Boston, Massachusetts. The specific activity was approximately 0.26 μc per mmole.

Steroids. CXLIV.[1] Synthesis of Some 6α,17α-Dihaloprogesterones[2]

J. S. MILLS, OCTAVIO CANDIANI, AND CARL DJERASSI

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Recent work in our laboratory[3] has demonstrated the potentiating effect upon progestational activity when a 6α-halogen atom is introduced into the progesterone molecule, notably of 17α-acetoxyprogesterone. As Engel and Jahnke[4] had observed that 17α-bromoprogesterone has about double the progestational activity of progesterone, it appeared of interest to synthesize certain progesterone analogs possessing halogen atoms at C-6 as well as C-17 and to subject them to biological assay.

For the synthesis of 6α-fluoro-17α-bromoprogesterone (VI) we selected a route patterned closely after the earlier described[5] preparation of 6α-fluoroprogesterone. 17α-Bromo-Δ^5-pregnen-3β-ol-20-one (II)[4,6] was transformed into its 5α,6α-epoxide III, which was opened to the fluorohydrin IV through the intervention of boron trifluoride.[5,7] Oxidation at C-3 by means of chromium trioxide in acetone solution[8] afforded the ketone V, whose dehydration with inversion at C-6 to 6α-fluoro-17α-bromoprogesterone (VI) was accomplished with hydrogen chloride in acetic acid.

The synthesis of 6α-chloro-17α-bromoprogesterone (XI) commenced with 17α-bromo-Δ^5-pregnen-3β-ol-20-one acetate (I),[6] which was chlorinated in carbon tetrachloride solution to the 3β-acetoxy-5α,6β-dichloride, VII. The acetoxy group was removed by exposure to hydrochloric acid and the 3β-hydroxy-5α,6β-dichloride (VIII) was oxidized[8] to 5α,6β-dichloro-17α-bromopregnane-3,20-dione (IX). Heating with ethanolic sodium acetate solution caused dehydrochlorination without inversion at C-6 to yield 6β-chloro-17α-bromoprogesterone (X), while the desired 6α-chloro-17α-bromoprogesterone (XI) was obtained by treatment of IX with hydrogen chloride in acetic acid solution.

A closely related reaction sequence was employed for 6α,17α-dichloroprogesterone (XVII). The enol diacetate XII[9] of Δ^5-pregnen-3β-ol-20-one was chlorinated to 5α,6β,17α-trichloropregnan-3β-ol-20-one acetate (XIII),[10] the 3-acetoxy group removed and the 3β-ol XIV oxidized with chromium trioxide.[8] Treatment of the resulting 5α,6β,17α-trichloropregnane-3,20-dione (XV) with sodium acetate led to 6β,17α-dichloroprogesterone (XVI), while exposure of XV to hydrogen chloride in acetic acid furnished directly the required 6α,17α-dichloroprogesterone (XVII).

Bioassays[11] in the rabbit showed that 6α-chloro-17α-bromoprogesterone (XI) and 6α,17α-dichloroprogesterone (XVII) possessed approximately 20% the oral progestational activity of Norlutin[12] (19-nor-17α-ethynyltestosterone).

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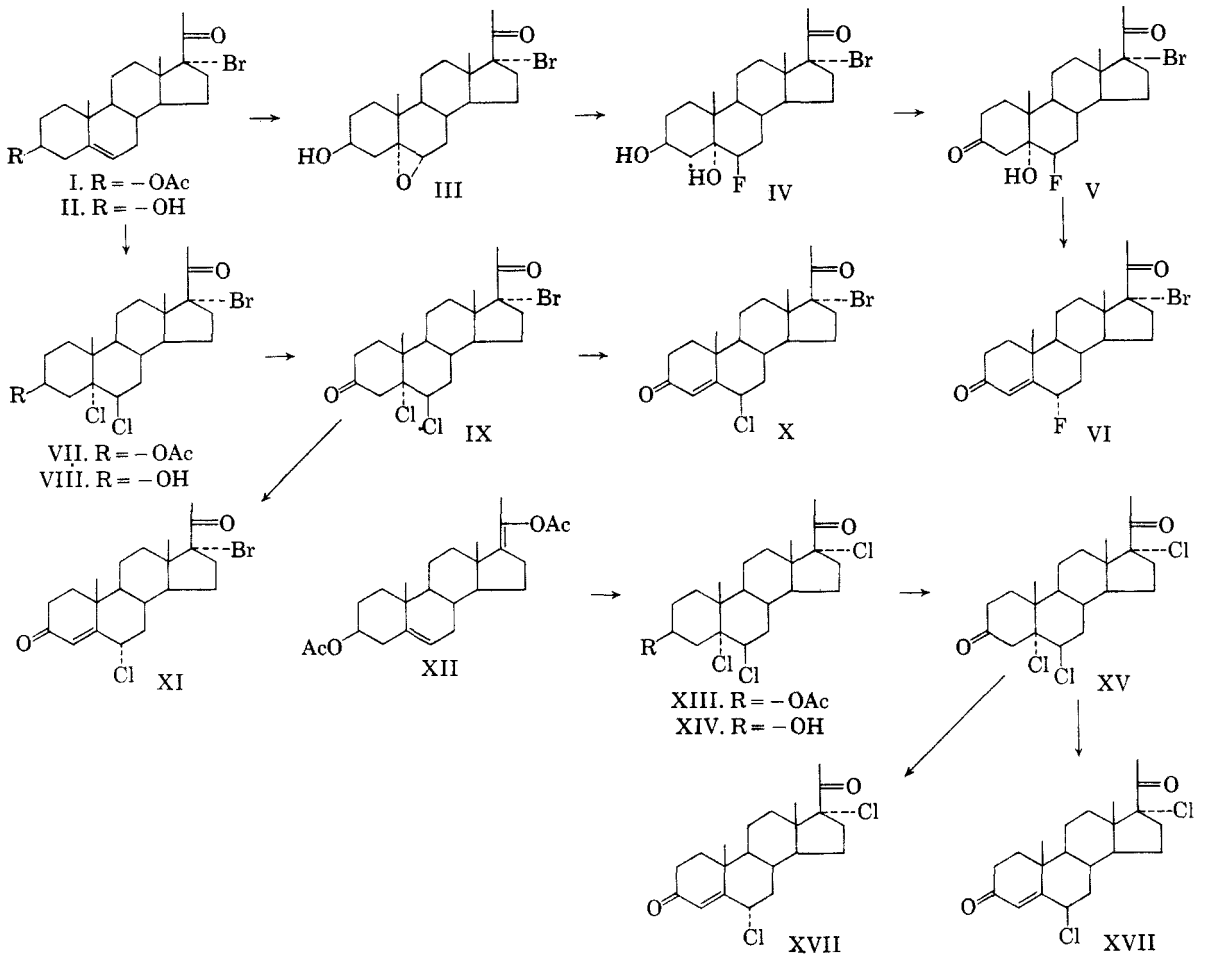

EXPERIMENTAL[13]

5α,6α-Oxido-17α-bromopregnan-3β-ol-20-one (III). 17α-Bromo-Δ⁵-pregnen-3β-ol 20-one (II)[4] (17 g.) in chloroform (140 cc.) was treated at −50° with a solution of perphthalic acid in ether (89 cc.· 1.16*N*). After 2 hr. at this temperature the mixture was kept for 16 hr. at 0°. The solution was diluted with chloroform and washed with water, aqueous sodium carbonate, and again with water, dried, and evaporated. Crystallization from acetone-hexane gave 6.3 g. of the epoxide III, m.p. 163–166°. The analytical sample melted at 170–171°, $[\alpha]_D$ −92°.

Anal. Calcd. for $C_{21}H_{31}BrO_3$: C, 61.29; H, 7.59; Br, 19.43; O, 11.66. Found: C, 61.25; H, 7.84; Br, 19.49; O, 11.75.

6β-Fluoro-17α-bromopregnane-3β,5α-diol-20-one (IV). The preceding epoxide (3 g.) in dry ether-benzene (1:1; 300 cc.) was treated with boron trifluoride etherate (3 cc.) at room temperature for 20 hr. The solution was washed with aqueous sodium carbonate solution and water, dried, and evaporated and the resulting oil chromatographed on 90 g. of alumina. Elution with ether afforded the fluorohydrin (IV) which was crystallized from acetone-hexane, m.p. 176–177° (600 mg.). The analytical sample melted at 182–183°, $[\alpha]_D$ −57°.

Anal. Calcd. for $C_{31}H_{32}BrFO_3$: C, 58.46; H, 7.47; Br, 18.52; F, 4.40. Found: C, 58.48; H, 7.55; Br, 18.68; F, 4.24.

6α-Fluoro-17α-bromoprogesterone (VI). The fluorohydrin (IV; 600 mg.) in acetone (15 cc.) was treated dropwise with a slight excess of 8*N* chromium trioxide–sulfuric acid solution[8] at 0° and the product precipitated with ice water and filtered to give 570 mg. of crude V, m.p. 186–188°. This was dissolved in glacial acetic acid (25 cc.) and the solution was saturated with dry hydrogen chloride gas at 10°. After 6 hr. at this temperature the solution was poured into aqueous sodium acetate solution and filtered to give 380 mg. of crude 6α-fluoro-17α-bromoprogesterone (VI) with $\lambda_{max}^{C_2H_5OH}$ 236 mμ, log ε 4.13. Two crystallizations from aqueous acetone afforded an analytical sample, m.p. 180–181°, $[\alpha]_D$ +12°, $\lambda_{max}^{C_2H_5OH}$ 236 mμ, log ε 4.20.

Anal. Calcd. for $C_{21}H_{28}BrFO_2$: C, 61.31; H, 6.85; Br, 19.43. Found: C, 61.61; H, 7.22; Br, 19.70.

5α,6β-Dichloro-17α-bromopregnan-3β-ol-20-one acetate (VII). To a solution of 17α-bromo-Δ⁵-pregnen-3β-ol-20-one acetate (I)[6] (3.5 g.) in carbon tetrachloride (50 ml.) and pyridine (1 ml.) cooled in Dry Ice–ethanol was added a solution of chlorine in carbon tetrachloride (10 ml.; 6.8%, 1.1 equiv.). When the color had disappeared, the solution was evaporated to dryness *in vacuo* and the resulting oil crystallized from methylene chloride–methanol to yield VII (2.5 g.), m.p. 173–178°. Recrystallization from the same solvents and from acetone-hexane afforded an analytical sample, m.p. 185–186°, $[\alpha]_D$ −79°.

Anal. Calcd. for $C_{23}H_{33}BrClO_3$: C, 54.34; H, 6.54; Br, 15.72; Cl, 13.45; O, 9.44. Found: C, 53.94; H, 6.43; Br, 16.15; Cl, 14.09; O, 9.84.

5α,6β-Dichloro-17α-bromopregnan-3β-ol-20-one (VIII). The preceding compound (3.75 g.), dissolved in dioxane-methanol (1:1; 120 ml.), was treated with concd. hydrochloric acid (4.5 ml.) and the solution allowed to stand at room

(13) Melting points are uncorrected and were determined on the Fisher Johns block. All physical measurements were performed under the direction of Dr. L. Throop. The microanalyses are due to Dr. A. Bernhardt, Mülheim, Germany. All rotations were measured in chloroform solution.

temperature for 20 hr. The product was precipitated with water, filtered, and crystallized from methanol to give (VIII) (2.6 g.), m.p. 100–115° (bubbling). The analytical sample melted at 114–116° (after drying *in vacuo*) $[\alpha]_D$ −74°.

Anal. Calcd. for $C_{21}H_{31}BrCl_2O_2$: C, 54.09; H, 6.70; Br, 17.14; Cl, 15.21. Found: C, 53.98; H, 6.76; Br, 17.91; Cl, 14.68.

5α,6β-Dichloro-17α-bromopregnane-3,20-dione (IX). The preceding compound (2.26 g.) in acetone (60 ml.) was treated at 0° with a slight excess of 8*N* chromium trioxide–sulfuric acid solution and the product precipitated by the addition of ice water. Crystallization from methanol gave the 3-ketone (IX) (1.6 g.), m.p. 158–161°. The analytical sample melted at 161–162°, $[\alpha]_D$ −85°.

Anal. Calcd. for $C_{21}H_{29}BrCl_2O_2$: C, 54.32; H, 6.29; Br, 17.21; Cl, 15.27; O, 6.89. Found: C, 54.71; H, 6.09; Br, 17.29; Cl, 15.40; O, 6.75.

6β-Chloro-17α-bromoprogesterone (X). The preceding compound (500 mg.) in absolute ethanol (40 ml.) was refluxed with fused sodium acetate (1.2 g.) for 1.5 hr. Part of the solvent was evaporated and the product precipitated with ice water. Crystallization from aqueous acetone gave 6β-chloro-17α-bromoprogesterone (X) (103 mg.), m.p. 145–148°. The analytical sample melted at 154–155°, $[\alpha]_D$ −48°, $\lambda_{max}^{C_2H_5OH}$ 240 mμ, log ε 4.12.

Anal. Calcd. for $C_{21}H_{28}BrClO_2$: C, 58.91; H, 6.59; Br, 18.66; Cl, 8.24; O, 7.48. Found: C, 58.85; H, 6.69; Br, 18.41; Cl, 8.04; O, 7.61.

6α Chloro-17α-bromoprogesterone (XI). 5α,6β-Dichloro-17α-bromopregnane-3,20-dione (IX) (400 mg.) in glacial acetic acid (25 ml.) was treated with dry hydrogen chloride gas at 10° for 2 hr. Precipitation with water and filtration gave 320 mg. of crude product, $\lambda_{max}^{C_2H_5OH}$ 236–238 mμ, log ε 4.13. Crystallization from aqueous acetone gave an analytical sample of 6α-chloro-17α-bromoprogesterone, m.p. 157–158°, $[\alpha]_D$ +14°, $\lambda_{max}^{C_2H_5OH}$ 236 mμ, log ε 4.16.

Anal. Calcd. for $C_{21}H_{28}BrClO_2$: C, 58.91; H, 6.59; Br, 18.66; Cl, 8.24; O, 7.48. Found: C, 58.65; H, 6.44; Br, 18.38; Cl, 7.81; O, 7.34.

5α,6β,17α-Trichloropregnan-3β-ol-20-one acetate (XIII). To a solution of the crude enol acetate XII[9] (3 g.) in carbon tetrachloride (15 ml.) at 0° was added a solution of chlorine in carbon tetrachloride (1%; 120 ml.) during 5 min. After a further 10 min., the solution was washed with cold 5% sodium carbonate solution and water, dried, and evaporated *in vacuo*. The resulting oil was chromatographed on 90 g. of neutral alumina. Elution with hexane-benzene (1:1) gave material which on crystallization from methylene chloride–methanol afforded 5α,6β,17α-trichloropregnan-3β-ol-20-one acetate (XIII) (711 mg.), m.p. 175–180°. Recrystallization gave an analytical sample, m.p. 194–195°, $[\alpha]_D$ −70°.

Anal. Calcd. for $C_{23}H_{33}Cl_3O_3$: C, 59.54; H, 7.17; Cl, 22.95; O, 10.34. Found: C, 58.97; H, 7.26; Cl, 23.22; O, 10.46.

5α,6β,17α-Trichloropregnan-3β-ol-20-one (XIV). The trichloroacetate XIII (2.6 g.) dissolved in dioxane-methanol (1:1; 50 ml.) was treated with concd. hydrochloric acid (4 ml.) and allowed to stand at 25°, for 24 hr. The product was precipitated with ice water, filtered, and crystallized from methylene chloride–methanol, yielding the trichloroalcohol XIV (2.15 g.), double m.p. 92° and 152–156°. The analytical sample melted at 92° and 164–165°, $[\alpha]_D$ −67°.

Anal. Calcd. for $C_{21}H_{31}Cl_3O_2$: C, 59.78; H, 7.41; Cl, 25.23. Found: C, 60.28; H, 7.47; Cl, 25.30.

5α,6β,17α-Trichloropregnane-3,20-dione (XV). The foregoing compound (1.2 g.) in acetone (30 ml.) was treated at 0° with a slight excess of 8*N* chromium trioxide–sulfuric acid. The product started to crystallize and ice water was added and the material filtered to yield the 3-ketone XV (1 g.), m.p. 161–163°. Recrystallization from aqueous acetone gave the analytical sample, m.p. 171–172°, $[\alpha]_L$ −60.5°.

Anal. Calcd. for $C_{21}H_{29}Cl_3O_2$: C, 60.08; H, 6.76; O, 7.62. Found: C, 59.90; H, 6.98; O, 7.46.

6β,17α-Dichloroprogesterone (XVI). 5α,6β,17α-Trichloropregnane-3,20-dione (500 mg.) was refluxed in absolute ethanol (40 ml.) with fused sodium acetate (1.2 g.) for 90 min. Precipitation with water and filtration gave an amorphous material with $\lambda_{max}^{C_2H_5OH}$ 240 mμ, log ε 3.90, which was chromatographed on 15 g. of neutral alumina. Elution with benzene and crystallization from aqueous acetone gave 6β,17α-dichloroprogesterone (180 mg.), m.p. 182–185°. Two further crystallizations gave material of m.p. 192–193°, $[\alpha]_D$ −30°, $\lambda_{max}^{C_2H_5OH}$ 240 mμ, log ε 4.12.

Anal. Calcd. for $C_{21}H_{28}Cl_2O_2$: C, 65.79; H, 7.36; Cl, 18.50; O, 8.35. Found, C, 65.46; H, 7.50, Cl, 18.62; O, 8.54.

6α,17α-Dichloroprogesterone (XVII). 5α,6β,17α-Trichloropregnane-3,20-dione (700 mg.) in glacial acetic acid (50 ml.) was treated at 0° with a stream of dry hydrogen chloride gas for 2 hr. The product was precipitated with ice-water and collected. Chromatography over 20 g. of alumina elution with benzene, and crystallization from aqueous acetone yielded 6α,17α-dichloroprogesterone (310 mg.), m.p. 160–162°. Recrystallization gave material of m.p. 165–166°, $[\alpha]_D$ +29°, $\lambda_{max}^{C_2H_5OH}$ 236 mμ, log ε 4.16.

Anal. Calcd. for $C_{21}H_{28}Cl_2O_2$: C, 65.79; H, 7.36; Cl, 18.50; O, 8.35. Found: C, 65.80; H, 7.46; Cl, 18.31, O, 8.26.

RESEARCH LABORATORIES
SYNTEX, S. A.
APARTADO 2679
MEXICO, D.F., MEXICO

The Preparation of 19-Nortestosterone-17-propionate

P. NARASIMHA RAO

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Among the various esters of 19-nortestosterone (I) the 17-propionate (II) has been proved to be biologically the most efficient.[1,2] It has been shown previously that attempts to prepare II with propionyl chloride or propionic anhydride gave mixtures of mono and di (enol) propionates *even at room temperature*.[3] In contrast, the preparation of II was recorded in a patent[4] by first heating a solution of I in pyridine and propionic anhydride for three hours at 75° and then for sixteen hours at room temperature. In another patent[5] the preparation of II was mentioned using propionic anhydride and pyridine without giving any physical constants of II. However, a suitable method has been worked out in these laboratories to prepare II in excellent

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