Disubstituted Progesterones. The 6,16-Chloro and Methyl Series

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The syntheses of 6α- and β-chloro-16α-methyl, 6α- and β-chloro-16α-chloro and 6α-methyl-16α-chloroprogesterones are described.

The ability of various steroids to inhibit the uterotrophic action of estrogens is well documented.[1] In the main, the majority of compounds have been testosterone analogs, while some estrogens and corticoids are also active. These active compounds are useful in the treatment of clinical conditions associated with abnormal estrogen metabolism or exaggerated end organ effect.

We have been interested in the progestin steroids as antagonists to estrogen action since the initial finding that substituted progesterones are potent and also orally effective.[2] It was of interest to prepare other derivatives in the 6,16-disubstituted series, and now we wish to report the synthesis of 6α- and 6β-chloro-16α-methyl-, 6α- and 6β-chloro-16α-chloro-, and 6α-methyl-16α-chloroprogesterones, and some preliminary biological data.[3]

The addition of chlorine to 16α-methylpregnenolone acetate (Ia) by the procedure of Cutler, *et al.*,[4] furnished 5α,6β-dichloro-16α-methylpregnan-3β-ol-20-one acetate (IIa). Hydrolysis of the 3-acetoxy group and oxidation at C-3 gave the corresponding ketone derivative (IVa). Heating with methanolic sodium acetate solution caused dehydrochlorination without inversion at C-6 to yield the desired compound, 6β-chloro-16α-methylprogesterone (Va). Epimerization to the 6α-compound (VIa) was effected by hydrogen chloride in acetic

(1) (a) S. Roberts and C. Szego, *Phys. Rev.*, **33**, 593 (1953); (b) R. A. Edgren, D. Calhoun, R. Elton and F. Colton, *Endocrinology*, **65**, 265 (1959); (c) V. A. Drill, "Biological Activities of Steroids in Relation to Cancer," G. Pincus and E. P. Vollmer, ed., Adacemic Press, 1960, p. 25; (d) R. I. Dorfman, F. A. Kincl and H. J. Ringold, *Endocrinology*, **68**, 17, 43 (1961).

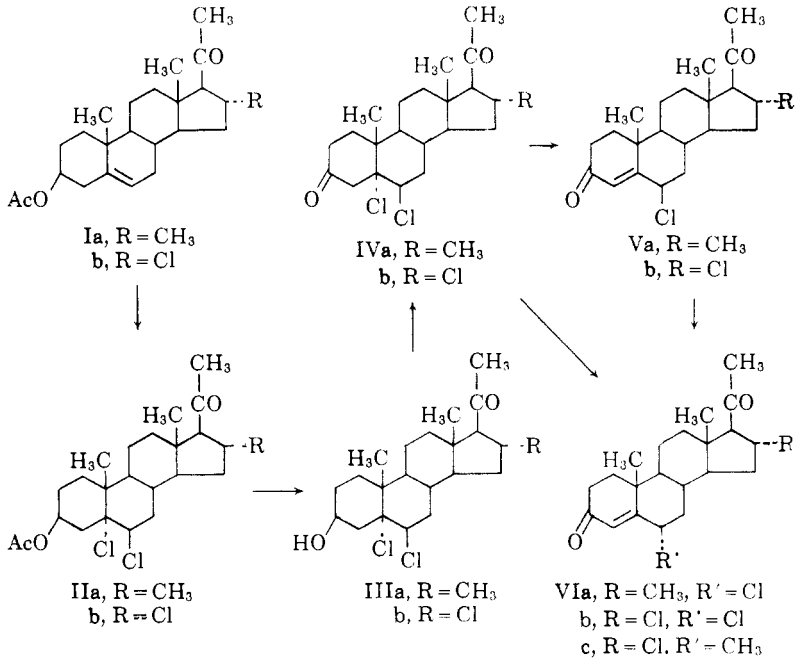
(2) R. J. Kraay and R. T. Rapala, paper submitted for presentation at the Endocrine Meeting, Chicago, Illinois, June, 1962.

(3) Antiestrogenic activity as measured in the immature mouse is expressed as the minimum effective dose of test compound administered subcutaneously or by gavage needed to produce a significant inhibition of the uterine hypertrophy induced by 0.3 μg. of subcutaneously administered estrone.[1b,d] Complete data on biological activities carried out in the Eli Lilly Research Laboratories will be reported in another journal.

(4) F. A. Cutler, Jr., L. Mandell, D. Shew, J. F. Fischer, and J. M. Chemerda, *J. Org. Chem.*, **24**, 1621 (1959).

acid solution. Alternatively, the 3-keto derivative IVa on treatment with dry hydrogen chloride in acetic acid[5] yielded the 6α-chloro-16α-methylprogesterone (VIa), directly.

A closely related reaction sequence was employed for the 6β,16α- and 6α,16α-dichloroprogesterones. The conjugate addition of hydrogen chloride to 3β-acetoxy-5,16-pregnadien-20-one gave the 16α-chloro derivative (Ib).[6] Chlorine addition to this resulted in the formation of 5α,6β,16α-trichloropregnan-3β-ol-20-one acetate (IIb). Hydrolysis using methanolic potassium bicarbonate as above removed the acetoxy group at C-3 but also eliminated one mole of hydrogen chloride from the molecule giving 5α,6β-dichloro-16-pregnen-3β-ol-20-one. However, using the perchloric acid–methanol conditions of Fried and Sabo,[7] the desired trichloro compound IIIb was obtained. Oxidation of IIIb furnished the 3-keto derivative (IVb), which upon treatment with sodium acetate in methanol gave in good yield the 6β,16α-dichloroprogesterone compound (Vb). Exposure of Vb to hydrogen chloride in acetic acid[8] yielded the desired 6α,16α-dichloroprogesterone (VIb).



(5) J. S. Mills, O. Candiani, and C. Djerassi, *J. Org. Chem*, **25**, 1056 (1960).
(6) R. M. Dodson and P. B. Sollman, U.S. Patent 2,708,201 (May 10, 1955).
(7) J. Fried and E. F. Sabo, *J. Am. Chem. Soc.*, **79**, 1130 (1957).
(8) J. A. Edwards, H. J. Ringold, and C. Djerassi, *ibid.*, **82**, 2318 (1960).

The synthesis of 6α-methyl-16α-chloroprogesterone (VIc) was accomplished by the conjugate addition of hydrogen chloride to 6α-methyl-4,16-pregnadiene-3,20-dione.[9]

Biological assays[8] in the immature mouse showed that compounds Va, Vb, VIa, b, and c were active as antiestrogens. Parenteral activity was demonstrated by each of these compounds at a dose level of 10–100 μg., a level at which progesterone is inactive. The oral effectiveness increases in the following order: Vb, Va, VIb, VIc, and VIa. The most potent compound, VIa, 6α-chloro-16α-methylprogesterone, at an oral or subcutaneous dose of 10 μg. causes a significant suppression in the estrone induced uterine hypertrophy. Parenteral and oral progestational activity as studied in the Clauberg assay of these five compounds is considerably less than that of progesterone. It would then appear that the progestational activity does not parallel the interesting antiestrogen effects.

Experimental[10]

5α,6β-Dichloro-16α-methylpregnan-3β-ol-20-one Acetate (IIa).—A solution of 10 g. of 16α-methylpregnenolone acetate[11] and 0.35 ml. of pyridine in 60 ml. of anhydrous benzene was added to a stirred yellow solution of chlorine gas dissolved in 60 ml. of anhydrous benzene containing 0.35 ml. of pyridine. The procedure and work-up were carried out as described previously.[4] Evaporation of the solvent and crystallization of the residue from methanol yielded crystalline material (7.6 g.), m.p. 196–200°. A sample for analysis was recrystallized from methanol, m.p. 195–197°.

Anal. Calcd. for $C_{24}H_{36}Cl_2O_3$: C, 65.01; H, 8.19. Found: C, 64.77; H, 8.01.

5α,6β-Dichloro-16α-methylpregnan-3β-ol-20-one (IIIa).—To 300 mg. of IIa in 15 ml. of methanol was added a solution of 225 mg. of potassium bicarbonate in 1 ml. of water. The solution was then refluxed for 1 hr., concentrated to a small volume by evaporation *in vacuo*, and then diluted with 15 ml. of water. After cooling, the precipitate was collected, washed and dried. The material weighed 220 mg. and melted at 145–152°. For analysis the sample was recrystallized from ether–petroleum ether and melted at 175–178°.

Anal. Calcd. for $C_{22}H_{34}Cl_2O_2$: C, 65.82; H, 8.54. Found: C, 65.59; H, 8.80.

5α,6β-Dichloro-16α-methylpregnan-3,20-dione (IVa).—To 220 mg. of IIIa, dissolved in 18 ml. of acetone at 0° was added 0.18 ml. of a 6 *N* chromium trioxide in sulfuric acid solution.[5] The resulting mixture was stirred for 5 min. and then poured into an ice–water mixture. The crystals that were collected, washed and dried weighed 200 mg. and had melting point 170–179°. Recrystallization was

(9) B. Loken and H. Flores, U. S. Patent 2,880,213 (March 31, 1959).

(10) All melting points are uncorrected. All rotations were done in chloroform. We gratefully acknowledge valuable assistance by: Messrs. G. M. Maciak, H. L. Hunter, W. L. Brown, A. Brown, elemental analyses; Messrs. L. Howard, T. Psarras, J. Klemm, and Miss M. Hofmann, physicochemical measurements.

(11) S. Bernstein, E. W. Cantrall, and J. P. Dusza, *J. Org. Chem.*, **26**, 269 (1961).

not successful as elimination of hydrogen chloride took place rapidly in several solvents.

Anal. Calcd. for $C_{22}H_{32}Cl_2O_2$: C, 66.16; H, 8.08. Found: C, 66.26; H, 8.19.

6β-Chloro-16α-methylprogesterone (Va).—A mixture of 200 mg. of IVa, 750 mg. sodium acetate and 15 ml. of methanol was heated at reflux for 2.5 hr. The solvent was evaporated partially under vacuum and 15 ml. of water added to precipitate a white solid, weight 100 mg., m.p. 154–158°, λ_{max}^{EtOH} 239 (ε 13,350). Several recrystallizations from ether furnished an analytical sample, m.p. 165–167°, λ_{max}^{EtOH} 239 mμ (ε 14,150), $[\alpha]_D$ +65.9°.

Calcd. for $C_{22}H_{31}ClO_2$: C, 72.82; H, 8.61. Found: C, 72.88; H, 8.55.

6α-Chloro-16α-methylprogesterone (VIa). (a) From IVa.—5α,6β-Dichloro-16α-methylpregnan-3,20-dione (200 mg.) was dissolved in 12 ml. of glacial acetic acid. Dry hydrogen chloride gas was bubbled for 2 hr. through this solution, while stirring and maintaining the solution at 0°. The reaction mixture then was poured into 75 g. of ice-water and the resulting precipitate collected, washed and dried. Recrystallization from ether gave VIa, m.p. 189–192°, λ_{max}^{EtOH} 235 mμ (ε 14,500), $[\alpha]_D$ +120.6°.

Anal. Calcd. for $C_{22}H_{31}ClO_2$: C, 72.82; H, 8.61. Found: C, 72.81; H, 8.51.

(b) From Va.—The 6β-chloro derivative (Va) (100 mg.), was dissolved in 8 ml. of glacial acetic acid, and a slow current of hydrogen chloride gas was passed through the solution for 1.5 hr. The reaction mixture was cooled to 25° and then left at this temperature for 4 hr. After dilution with 50 ml. of water, the precipitate was collected, washed and dried. Crystallization from methanol furnished 35 mg., m.p. 179–183°, of the 6α-chloro isomer, identical in all respects with that prepared above in (a).

6α-Methyl-16α-chloroprogesterone (VIc).—A solution of 3 g. of 6α-methyl-16-dehydroprogesterone[9] in 125 ml. of anhydrous chloroform was cooled to 0° and dry hydrogen chloride gas was passed through the solution for 8 min. The reaction mixture then was blanketed with nitrogen gas and cooled in an ice-bath for 2.5 hr. Evaporation of the solvent produced a semicrystalline mass which upon recrystallization from ether yielded 2.49 g. of material, m.p. 160–165°, λ_{max}^{EtOH} 240 mμ (ε 16,000), $[\alpha]_D$ +138.0°. Further recrystallization from ether gave an analytical sample, m.p. 168–171°.

Anal. Calcd. for $C_{22}H_{31}ClO_2$: C, 72.82; H, 8.61. Found: C, 72.77; H, 8.60.

16α-Chloro-5-pregnen-3β-ol-20-one Acetate (Ib).—Dry hydrogen chloride was passed for about 10 min. into a stirred solution of 500 mg. of 5,16-pregnadiene-3β-ol-20-one acetate in 21 ml. of anhydrous chloroform, and the reaction mixture was allowed to remain in an ice-bath for 2 hr. The solution was evaporated *in vacuo* and the product recrystallized twice from ether, m.p. 185–187°; yield, 270 mg., $[\alpha]_D$ −8.2°.

Anal. Calcd. for $C_{23}H_{33}ClO_3$: C, 70.30; H, 8.46. Found: C, 70.56; H, 8.61.

5α,6β,16α-Trichloropregnan-3β-ol-20-one Acetate (IIb).—The chlorination of Ib was carried out by the same procedure used to prepare IIa. From 500 mg. of Ib there was obtained 240 mg. of IIb. Recrystallization from methanol and then acetone gave crystals melting at 218–221°.

Anal. Calcd. for $C_{23}H_{33}Cl_3O_3$: C, 59.55; H, 7.17. Found: C, 60.02; H 7.55.

5α,6β,16α-Trichloropregnan-3β-ol-20-one (IIIb).—A solution of 352 mg. of

IIb in 160 ml. of methanol was treated with 0.35 ml. of 70% perchloric acid and the reaction stirred 18 hr. at room temperature.[7] The solution was neutralized with potassium bicarbonate, and 150 ml. of water was added to precipitate the product. Upon cooling, the precipitate was collected, washed and dried; weight, 285 mg., m.p. 148–155°. The analytical specimen was prepared by recrystallization from ether–petroleum ether, m.p. 175–179°.

Anal. Calcd. for $C_{21}H_{31}Cl_3O_2$: C, 59.79; H, 7.41. Found: C, 60.20; H, 7.51.

5α,6β-Dichloro-16-pregnen-3β-ol-20-one.—The hydrolysis of IIb was carried out essentially by the same procedure as for IIa. From 320 mg. of IIb and 320 mg. of potassium bicarbonate in 35 ml. of methanol after a 1 hr. reflux period there was obtained 303 mg. of crude product, m.p. 184–193°, λ_{max}^{EtOH} 238 mμ (ε 8,020). Recrystallization from aqueous methanol furnished the analytical sample, m.p. 189–203, λ_{max}^{MeOH} 238 mμ (ε 9,500).

Anal. Calcd. for $C_{21}H_{30}Cl_2O_2$: C, 65.43; H, 7.85. Found: C, 65.85; H, 7.98.

5α,6β,16α-Trichloropregnane-3,20-dione (IVb).—The oxidation of the trichloro derivative IIIb was performed with the 6 *N* chromium trioxide in sulfuric acid–acetone solution as described in the preparation of IVa. From 100 mg. of IIIb there was obtained 65 mg. of IVb, m.p. 184–196°. The crystalline powder was washed and dried rapidly and analyzed immediately.

Anal. Calcd. for $C_{21}H_{29}Cl_3O_2$: C, 60.08; H, 6.96. Found: C, 60.23; H, 6.93.

6β,16α-Dichloroprogesterone (Vb).—A mixture of 200 mg. of IVb, 750 mg. of sodium acetate and 15 ml. of methanol was refluxed for 2.5 hr. The work-up and isolation was identical with that in the preparation of Va. The dichloro compound thus obtained had m.p. 175–185°, λ_{max}^{EtOH} 239 mμ (ε 11,780). Recrystallization from ether–petroleum ether raised the m.p. to 187–190°, $[\alpha]D$ +60.8°, λ_{max}^{EtOH} 239 mμ (ε 15,100).

Anal. Calcd. for $C_{21}H_{28}Cl_2O_2$: C, 65.81; H, 7.36. Found: C, 65.72; H, 7.50.

6α,16α-Dichloroprogesterone (VIb). (a) **From Vb.**—The epimerization was carried out by dissolving 100 mg. of Vb in 8 ml. of acetic acid and passing anhydrous hydrogen chloride through the solution for 80 min. After 4 additional hours, the solution was diluted with water and the product collected. After recrystallization from ether–petroleum ether there was obtained 35 mg. of crystals, m.p. 178–184°. The infrared and ultraviolet absorption spectra were identical with those of the compound as prepared in (b) below.

(b) **From IVb.**—Using identical conditions as employed in the preparation of VIa from IVa, 200 mg. of IVb yielded 175 mg. of VIb, m.p. 181–187°. The analytical sample was recrystallized twice from ether–petroleum ether, m.p. 187–191°, λ_{max}^{EtOH} 236 mμ (ε 14,850), $[\alpha]D$ +98.8°.

Anal. Calcd. for $C_{21}H_{28}Cl_2O_2$: C, 65.81; H, 7.36. Found: C, 65.40; H, 7.27.