17α-HALOGENATED PROGESTERONES: ORALLY-ACTIVE PROGESTINS[1]

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ABSTRACT

17α-Chloroprogesterone, 6α-fluoro-17α-bromoprogesterone, 1-dehydro-6α-fluoro-17α-bromoprogesterone, and 6α-chloro-17α-bromoprogesterone have been synthesized. These compounds have been found to be orally-active progestins without androgenic properties.

In recent years, considerable effort has been devoted to the search for orally-active progestational agents to substitute for the natural hormone, progesterone. The newer synthetic progestogens which have acquired prominence because of their oral activity fall into two classes: 19-norsteroids such as 19-norprogesterone (1) and 17α-ethynyl-19-nortestosterone (2) and its $\Delta^{5(10)}$-isomer (3), and derivatives of progesterone containing a 17α-acetoxy substituent (4–7).

It has been shown recently that 17α-bromoprogesterone (8) is an orally-active progestogen (9), indicating that substituents other than acetoxyl at C-17 can enhance the very weak oral activity of progesterone. It was clearly of interest to prepare other 17α-halogenated progesterones, and to determine whether modifications in structure which enhance the activity of 17α-acetoxyprogesterone, such as the introduction of a 6α-halo substituent and a Δ^1-double bond (4, 5), would have a similar effect on the comparatively weak oral activity of 17α-bromoprogesterone.

In this paper, we record the synthesis and preliminary biological evaluation of 17α-chloroprogesterone and of the 6α-fluoro-, 1-dehydro-6α-fluoro-, and 6α-chloro-derivatives of 17α-bromoprogesterone.

17α-Chloroprogesterone

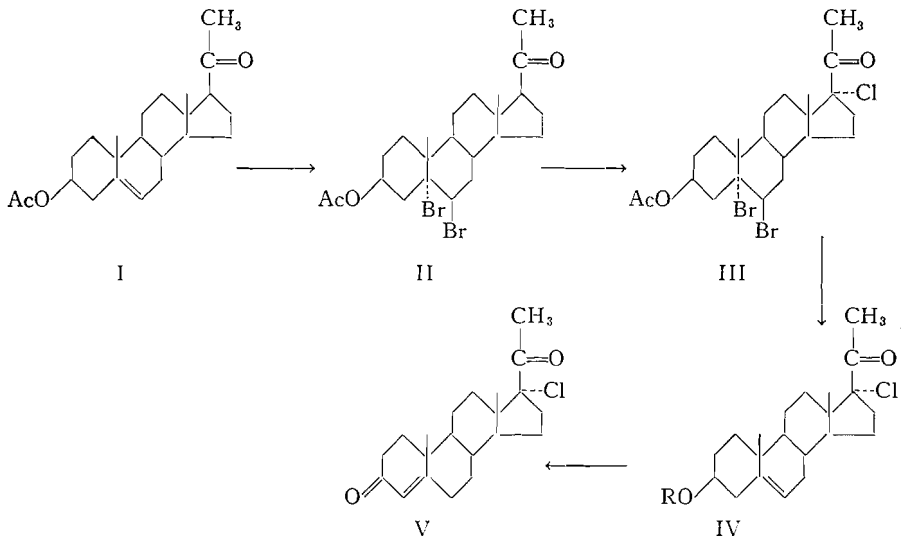
Pregnenolone acetate (I) was brominated at a low temperature, and the 5,6-dibromide II was allowed to react with chlorine in acetic acid. The resulting mixture of 17- and 21-chloro derivatives (III) was treated with sodium iodide in acetone which regenerated the 5,6-double bond and replaced chlorine at C-21 with iodine. Finally, the iodine at C-21 was removed by reduction with aqueous sodium bisulphite solution (10) and 17α-chloropregnenolone acetate (IV, R = Ac) was isolated after chromatographic purification. The α-configuration of the chlorine was inferred from the general preference for "back-side" attack and from the fact that bromination of 20-ketones has been clearly shown to result in the formation of 17α-bromo derivatives (11).

Acid-catalyzed hydrolysis of IV (R = Ac) yielded 17α-chloropregnenolone (IV, R = H), which, without purification, was oxidized with chromic acid in acetone (12). The shift of the double bond into conjugation with the carbonyl group to yield 17α-chloroprogesterone (V) was completed by treatment of the crude oxidation product with oxalic acid (13).

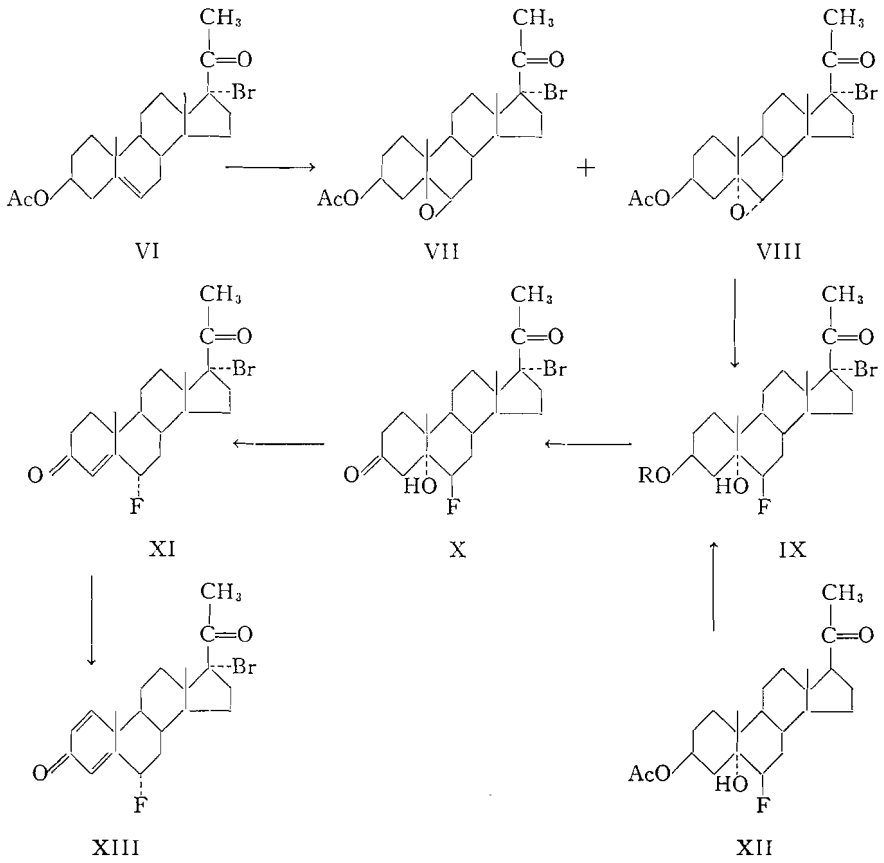
6α-Halo-17α-bromoprogesterones[2]

17α-Bromopregnenolone acetate (VI) (8, 10) was converted to a 6-fluoro derivative by conventional means (14). Epoxidation of VI with monoperphthalic acid gave a mixture of 5β,6β- and 5α,6α-epoxides, VII and VIII. The epoxides were separated by chromatog-

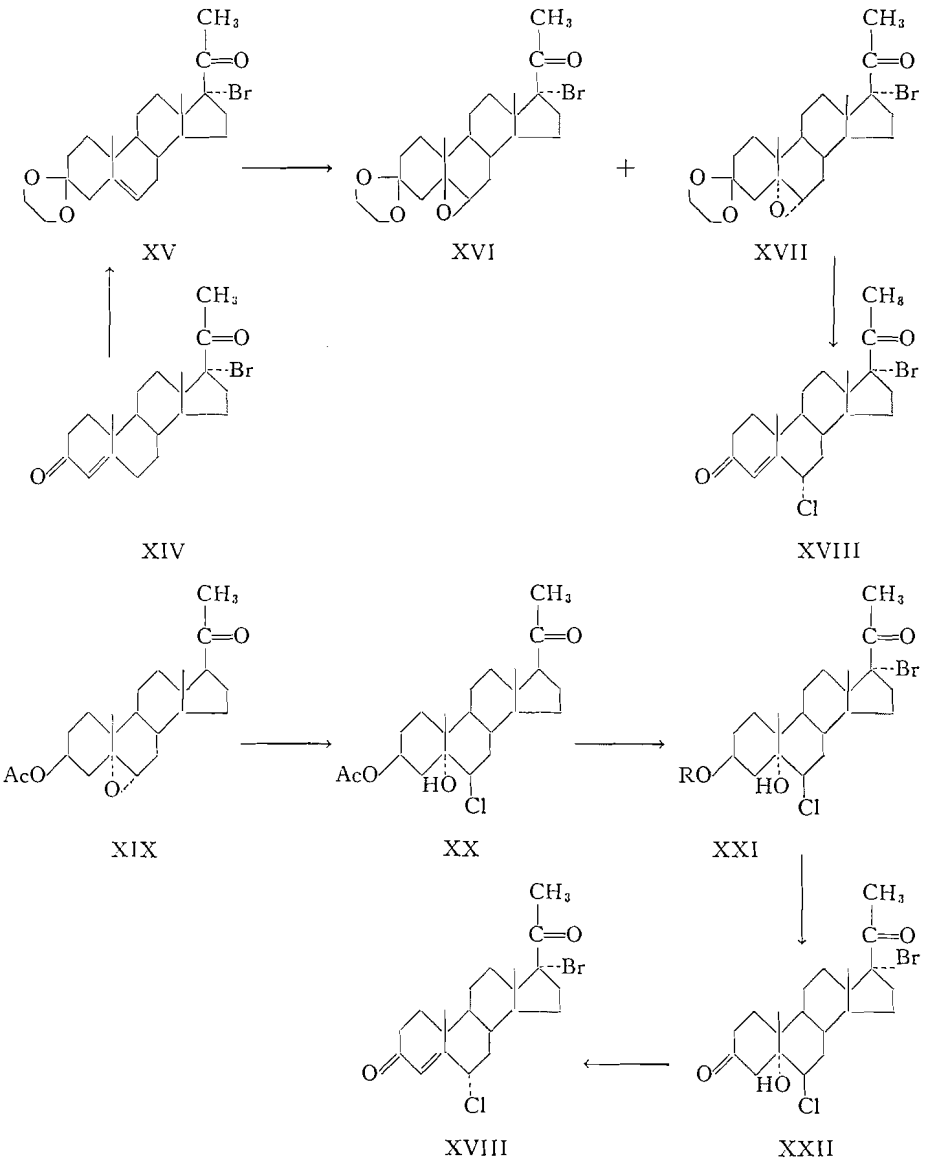
[1]*Manuscript received May 9, 1960.*
Contribution from the Ayerst Research Laboratories, P.O. Box 6115, Montreal, Que.
[2]*While this article was in manuscript, the synthesis of 6α-fluoro-17α-bromoprogesterone was reported by Ch. R. Engel and R. Deghenghi, Can. J. Chem.* **38**, *452 (1960).*



raphy on Florisil, and the more strongly adsorbed and more levorotatory isomer was assigned the α-structure by analogy with other pairs of epimeric 5,6-epoxides (15). Cleavage of the epoxide ring of VIII with anhydrous hydrogen fluoride (14, 16) gave the



5α-hydroxy-6β-fluoro derivative IX (R = Ac) in good yield. The alternative method of forming the fluorohydrin, reaction of the epoxide with boron trifluoride etherate (6, 15, 17–20), gave much less satisfactory results. The fluorohydrin acetate IX (R = Ac) was hydrolyzed with perchloric acid in methanol to the diol IX (R = H). Oxidation of the diol with sodium dichromate in acetic acid and dehydration of the resulting diketone X with anhydrous hydrogen chloride in chloroform gave 6α-fluoro-17α-bromoprogesterone (XI), λ_{max} 237 mμ, ε 17,800. The stability of XI to further treatment with acid and the value of the extinction coefficient (6β-fluoro-Δ^4-3-ketones have extinction coefficients of 10,000–13,000 (18)) served to establish that the expected inversion of C-6 had occurred, and that the fluorine was in the equatorial (6α) configuration.



The fluorohydrin IX (R = Ac) was also obtained, in good yield, by bromination of 3β-acetoxy-5α-hydroxy-6β-fluoropregnan-20-one (XII) (16, 17) with N-bromosuccinimide (21).

Dehydrogenation of XI with 2,3-dichloro-5,6-dicyanoquinone (22) yielded the 1-dehydro analogue XIII, which was also obtained, in lower yield, by reaction of XI with selenium dioxide.

For the synthesis of 6α-chloro-17α-bromoprogesterone, 17α-bromoprogesterone (XIV) was converted to the corresponding 3-monoethylene ketal XV by reaction with ethylene glycol and *p*-toluenesulphonic acid in refluxing toluene. Epoxidation of the ketal with monoperphthalic acid gave a mixture of 5β,6β- and 5α,6α-epoxides XVI and XVII, separated by chromatography on Florisil. The configurations of the epoxides were assigned on the basis of their relative behavior during chromatography and a comparison of optical rotations, since it is known (15) that in any pair of epimeric 3-ketal-5,6-epoxides, the α-epoxide is more polar toward adsorbents and is more levorotatory than the β-epimer.

Treatment of the α-epoxide XVII with anhydrous hydrogen chloride in chloroform resulted in cleavage of the epoxide linkage to form the 5α-hydroxy-6β-chloro derivative, hydrolysis of the ketal group, dehydration to the α,β-unsaturated ketone, and inversion of configuration at C-6, and 6α-chloro-17α-bromoprogesterone (XVIII) was isolated in 80% yield. The structure of XVIII was established by elemental analysis, by infrared and ultraviolet spectral data, and by the stability of the compound to acid.

In a second synthesis of XVIII, 3β-acetoxy-5α,6α-epoxypregnan-20-one (XIX) (16, 17) was allowed to react with hydrogen chloride in chloroform, and the resulting 5α-hydroxy-6β-chloro derivative XX was brominated at C-17 with N-bromosuccinimide to give XXI (R = Ac). Acid-catalyzed hydrolysis to the diol XXI (R = H), oxidation to the diketone XXII, and dehydration-inversion with hydrogen chloride then led to XVIII.

A crystalline product could not be obtained from attempted dehydrogenations of XVIII with selenium dioxide or 2,3-dichloro-5,6-dicyanoquinone.

Biological Activity

The progestational activity of the 17α-halogenated progesterones relative to progesterone (subcutaneous) and to 17α-ethynyl-19-nortestosterone (oral), as determined in the Clauberg assay, is summarized in Table I. It will be seen that chlorine has a smaller

TABLE I

Relative progestational activity (Clauberg assay)

	Subcutaneous	Oral
Progesterone	1.0	
17α-Ethynyl-19-nortestosterone		1.0
17α-Bromoprogesterone (XIV)	2.0	0.04
17α-Chloroprogesterone (V)	1.0	<0.04
6α-Fluoro-17α-bromoprogesterone (XI)	4.0	0.3
6α-Chloro-17α-bromoprogesterone (XVIII)	2.0	0.3

potentiating effect on the progestational activity than does bromine at C-17α of progesterone. But fluorine and chlorine at C-6α enhance the activity of 17α-bromoprogesterone to about the same extent as they enhance the activity of 17α-acetoxyprogesterone (6, 7). Preliminary assays indicated that the 1-dehydro derivative XIII was more active than XI.

There have been a number of reports recently that the administration of some synthetic progestins to rats (23) and to humans (24) during gestation can induce masculinization of female fetuses. For example, it has been found (23) that when pregnant rats are treated with relatively low doses of 17α-ethynyl-19-nortestosterone or 6α-methyl-17α-acetoxyprogesterone (5), serious masculinization occurs in the female offspring. It was therefore of interest to test some of the compounds made in this investigation for androgenic activity. The 17α-bromoprogesterones did not show androgenic properties in castrated male rats, nor was there any indication of masculinization in female offspring of pregnant rats which had been treated with high doses of XI or XIV.

The detailed results of the biological assays of these compounds will be published elsewhere (25).

EXPERIMENTAL

Melting points are uncorrected. Rotations were determined in chloroform solution at a concentration of about 1%, and ultraviolet spectra were taken in solution in 95% ethanol. The alumina used for chromatography was Merck chromatographic grade alumina which had been neutralized by being allowed to stand overnight in ethyl acetate and reactivated by heating *in vacuo* at 145° for 18 hours. Microanalyses were carried out in our analytical laboratory by Mr. W. J. Turnbull and associates.

17α-CHLOROPROGESTERONE

17α-Chloropregnenolone Acetate (IV, R = Ac*)*

To a stirred solution of 50.0 g of 3β-acetoxy-5-pregnen-20-one in 930 ml of chloroform cooled to −60° was added over a period of 2 hours 467 ml of a 0.3 *M* solution of bromine in carbon tetrachloride. After the solution was warmed to room temperature, the volume was reduced to about 100 ml *in vacuo* and the 5α,6β-dibromide II was precipitated by the addition of 350 ml of methanol. The yield was 60.4 g, m.p. 143–146° decomp.

To a solution of 14.0 g of II in 125 ml of acetic acid containing 0.1 ml of concentrated hydrochloric acid was added 78.4 g of a solution of chlorine in acetic acid (2.46 g chlorine per 100 g of solution) over a period of 1 hour. After 250 ml of water was added, the mixture was refrigerated overnight and the colorless solid was filtered and washed with water. Crystallization from methylene chloride – methanol yielded 10.3 g of a mixture of 17- and 21-chlorodibromides (III), m.p. 129–137° decomp. This product was dissolved in 100 ml of boiling acetone and a solution of 10 g of sodium iodide in 60 ml of acetone was added. After it was heated under reflux for 1 hour, under nitrogen, the mixture was cooled in ice and the iodine was reduced by the slow addition of 362 ml of 0.1 *N* sodium thiosulphate solution. The precipitated product was dissolved in 70 ml of ether, 10 ml of 10% sodium bisulphite solution was added, and the mixture was shaken intermittently for 30 minutes, after which no further iodine color developed on standing. The ether solution was washed with an additional portion of bisulphite solution and with water and was dried and concentrated to dryness. The resulting solid (6.8 g) could not be readily purified by crystallization.

A 1.87 g portion of this product was chromatographed on 65 g of alumina. Elution with 650 ml of benzene–petroleum ether 1:3 yielded 1.45 g of 3β-acetoxy-17α-chloro-5-pregnen-20-one (IV, R = Ac), m.p. 145–148°. Crystallization from methylene chloride – methanol gave an analytical sample, m.p. 147–149°, $[\alpha]_D$ −84.9°. Anal. Calc. for $C_{23}H_{33}ClO_3$: C, 70.30; H, 8.46; Cl, 9.02. Found: C, 70.41; H, 8.67; Cl, 9.18.

17α-Chloroprogesterone (V)

A mixture of 4.65 g of the acetate IV (R = Ac), 130 ml of methanol, and 4.65 ml of 70% perchloric acid was heated at the boiling point until the solid had dissolved and was then left at room temperature for 24 hours. Water (140 ml) precipitated 3.80 g of 17α-chloropregnenolone (IV, R = H), m.p. 120°, resolidifying and remelting at 156–161°, which was not further purified.

To a stirred solution of 3.48 g of 17α-chloropregnenolone in 140 ml of acetone cooled to 5° under nitrogen was added 2.78 ml of a chromic acid solution (26.72 g of chromium trioxide in 23 ml of sulphuric acid diluted to 100 ml with water). After the solution had been stirred for 5 minutes, 420 ml of water was added and the precipitated solid was filtered and dried (3.25 g). This product was dissolved in 43 ml of ethanol, 1.6 g of oxalic acid was added, and the solution was heated under reflux under nitrogen for 45 minutes. Water was added and the product was extracted with ether. The ether solution was washed with 5% sodium bicarbonate solution and with water, and the brown gum remaining after drying and evaporation of the solvent was adsorbed on 150 g of alumina in benzene – petroleum ether 1:1. Elution with 600 ml of benzene gave 1.14 g of colorless solid which was crystallized from aqueous methanol yielding 1.00 g of 17α-chloroprogesterone (V), m.p. 166–168°. Recrystallization from aqueous methanol gave an analytical sample, m.p. 168.5–170°, $[\alpha]_D$ +51.0°, λ_{max} 240 mμ (ε 17,900). Anal. Calc. for $C_{21}H_{29}ClO_2$: C, 72.31; H, 8.38; Cl, 10.12. Found: C, 72.63; H, 8.39; Cl, 10.31.

6α-FLUORO-17α-BROMOPROGESTERONE

Epoxidation of 17α-Bromopregnenolone Acetate

To a stirred, ice-cooled solution of 5.00 g of 3β-acetoxy-17α-bromo-5-pregnen-20-one in 75 ml of chloroform was added, over a period of 15 minutes, 102 ml of a 0.342 *M* solution of monoperphthalic acid in ether. After storage at 10° for 4 days, the mixture was filtered, and the filtrate was washed with 10% sodium bicarbonate solution and with water and dried over magnesium sulphate. The crude product obtained after evaporation of the solvent was dissolved in benzene and chromatographed on 150 g of Florisil. Two liters of benzene containing 1% ethyl acetate eluted 1.12 g of the *5β,6β-epoxide* VII, which was recrystallized from ethyl acetate, m.p. 158–160.5°, $[\alpha]_D$ −57.6°. Anal. Calc. for $C_{23}H_{33}BrO_4$: C, 60.92; H, 7.34; Br, 17.62. Found: C, 61.15; H, 7.22; Br, 17.57.

Elution of the column with 2 liters of benzene containing 5% ethyl acetate gave 2.82 g of the *5α,6α-epoxide* VIII, which, after recrystallization from ethyl acetate had a melting point of 192–193°, $[\alpha]_D$ −102.4°. Anal. Calc. for $C_{23}H_{33}BrO_4$: C, 60.92; H, 7.34; Br, 17.62. Found: C, 60.64; H, 7.12; Br, 17.31.

3β-Acetoxy-5α-hydroxy-6β-fluoro-17α-bromopregnan-20-one (IX)

A. From the Epoxide VIII

To 51.1 g of anhydrous hydrogen fluoride in a polyethylene bottle in a Dry Ice–acetone bath at −60° was added slowly, in turn, 102 g of dry tetrahydrofuran, 50 ml of chloroform, and a solution of 51.1 g of the epoxide VIII in 325 ml of chloroform. The solution was kept at −10° for 2 hours and was then poured, with stirring, into a mixture containing 200 g of potassium carbonate, 600 ml of water, ice, and 100 ml of chloroform. The chloroform solution was washed with sodium bicarbonate solution and with water, dried over magnesium sulphate, and evaporated to dryness *in vacuo*. Crystallization from methylene chloride – methanol yielded 34.7 g of the fluorohydrin IX, m.p. 170–171° decomp. The analytical sample, obtained by crystallization from the same solvent

mixture had a melting point of 173° decomp., $[\alpha]_D$ −78.3°. Anal. Calc. for $C_{23}H_{34}BrFO_4$: C, 58.34; H, 7.24; Br, 16.88; F, 4.01. Found: C, 58.32; H, 7.26; Br, 16.85; F, 3.89.

B. From 3β-Acetoxy-5α-hydroxy-6β-fluoropregnan-20-one (XII)

A mixture of 20.0 g of the fluorohydrin XII, 15.0 g of N-bromosuccinimide, and 500 ml of carbon tetrachloride was heated under reflux on the steam bath. When the solvent was boiling vigorously, the flask was irradiated with a 250-watt infrared lamp and refluxing was continued for 10 minutes. The flask was then cooled in an ice bath, the mixture was filtered, and the filtrate was washed with dilute sodium bisulphite solution and with water. The dried (Na_2SO_4) solution was evaporated to dryness *in vacuo* and 40 ml of methanol was added to the amorphous residue. The mixture was brought rapidly to the boiling point, cooled in ice, and the crystalline product was filtered and washed with methanol. The yield of 17α-bromo derivative IX was 15.1 g, m.p. 171.5° decomp., identical (mixed m.p. and infrared spectrum) with the product obtained in *A*.

In larger runs it was found desirable to have a small amount of pyridine present to inhibit the ionic bromination which sometimes occurred. Thus, a mixture of 100 g of IX, 75 g of N-bromosuccinimide, 2.5 liters of carbon tetrachloride, 24 g of pyridine, and 6 g of benzoyl peroxide heated under reflux for 15 minutes followed by working up as above, yielded 80 g of VI, m.p. 174° decomp.[3]

3β,5α-Dihydroxy-6β-fluoro-17α-bromopregnan-20-one (IX, R = H)

A mixture of 34.7 g of the acetate IX (R = Ac), 500 ml of methanol, and 12 ml of 70% perchloric acid was boiled until the steroid had dissolved (about 10 minutes) and was then left at room temperature for 17 hours. The solid obtained by the addition of 500 ml of water was crystallized from methanol, yielding 25.8 g of the diol IX (R = H), m.p. 174° decomp. Recrystallization from aqueous methanol gave the analytical sample, m.p. 176° decomp., $[\alpha]_D$ −65.2°. Anal. Calc. for $C_{21}H_{32}BrFO_3$: C, 58.46; H, 7.48; Br, 18.52; F, 4.40. Found: C, 58.22; H, 7.71; Br, 18.44; F, 4.56.

5α-Hydroxy-6β-fluoro-17α-bromopregnane-3,20-dione (X)

To a solution of 25.8 g of the diol IX (R = H) in 250 ml of acetic acid cooled to 15° was added with stirring a solution of 25.8 g of sodium dichromate dihydrate in 520 ml of acetic acid. After the mixture had been allowed to stand at room temperature for 16 hours, 50 ml of methanol was added, followed by 1300 ml of water. The finely divided solid was filtered and washed well with water. The wet product, which was difficult to dry, was dissolved in methylene chloride (in which it was only moderately soluble), and the solution was dried over sodium sulphate and concentrated. Crystallization from methylene chloride – methanol yielded 16.4 g of the diketone X, m.p. 174° decomp., and 2.8 g, m.p. 173° decomp. The analytical sample, m.p. 173.5–174.5° decomp., $[\alpha]_D$ −42.1°, was obtained by crystallization from *i*-propanol. Anal. Calc. for $C_{21}H_{30}BrFO_3$: C, 58.75; H, 7.04; Br, 18.61; F, 4.93. Found: C, 58.71; H, 6.91; Br, 18.90; F, 4.49.

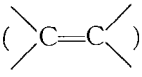
6α-Fluoro-17α-bromoprogesterone (XI)

Anhydrous hydrogen chloride was passed for 1 hour through an ice-cooled suspension of 10.8 g of the diketone X in 200 ml of chloroform. The solid went rapidly into solution. After standing an additional hour in the ice bath, the orange solution was washed with water, 10% sodium bicarbonate solution, and again with water. Drying over sodium sulphate and evaporation of the solvent gave a solid which was crystallized from methylene chloride – methanol, yielding 6.5 g of 6α-fluoro-17α-bromo-4-pregnene-3,20-dione

[3]*We are indebted to Dr. Gordon Myers for carrying out this experiment.*

(XI) as colorless needles, m.p. 173–175.5° decomp. From the mother liquors, an additional 0.5 g of product was obtained, m.p. 171–173° decomp. Recrystallization from methylene chloride – methanol yielded an analytical sample, m.p. 176–177.5° decomp., $[\alpha]_D$ +17.0°, λ_{max} 236 mμ (ε 17,800). Anal. Calc. for $C_{21}H_{28}BrFO_2$: C, 61.34; H, 6.86; Br, 19.43; F, 4.62. Found: C, 61.51; H, 7.06; Br, 19.28; F, 4.42.

1-Dehydro-6α-fluoro-17α-bromoprogesterone (XIII)

A solution of 1.00 g of XI, 0.64 g of 2,3-dichloro-5,6-dicyanoquinone (22), and 26 mg of *p*-toluenesulphonic acid in 40 ml of benzene was heated under reflux for 18 hours. The cooled mixture was filtered, and the filtrate was diluted with 20 ml of ethyl acetate and washed (initially without shaking to avoid emulsions) with 10% sodium bicarbonate solution and with water. After drying over magnesium sulphate, the solvent was removed *in vacuo*, and the solid residue was chromatographed in benzene on 10 g of Florisil. Elution with 250 ml of benzene containing 5–10% ethyl acetate yielded 656 mg of pale yellow solid. Crystallization from methylene chloride – methanol (charcoal) gave 0.51 g of XIII as colorless plates, m.p. 181–182° decomp. The analytical sample was obtained by recrystallization from acetone–hexane and melted at 181–183° decomp., $[\alpha]_D$ −20.5°, λ_{max} 241 mμ (ε 18,200), $\nu_{max}^{CS_2}$ 1711 cm^{-1} (20-ketone), 1675 cm^{-1} (3-ketone), 1637 cm^{-1} (), 904 cm^{-1}. Anal. Calc. for $C_{21}H_{26}BrFO_2$: C, 61.63; H, 6.40; Br, 19.53; F, 4.64. Found: C, 61.52; H, 6.31; Br, 19.38; F, 4.78.

6α-CHLORO-17α-BROMOPROGESTERONE

3,3-Ethylenedioxy-17α-bromo-5-pregnen-20-one (XV)

A mixture of 10.0 g of 17α-bromoprogesterone, 310 ml of toluene, 80 ml of ethylene glycol, and 0.30 g of *p*-toluenesulphonic acid was heated under reflux under a water separator for 6 hours. After it was cooled in ice, the mixture was washed with 10% sodium bicarbonate solution and with water, and the solvent was removed *in vacuo*. Crystallization from methanol containing a few drops of pyridine yielded 5.0 g of the 3-ketal XV, m.p. 128–130°. The analytical sample was obtained by crystallization from methanol, m.p. 131–132°, $[\alpha]_D$ −84.0°. The infrared spectrum (CS_2) showed a single carbonyl band at 1705 cm^{-1}. Anal. Calc. for $C_{23}H_{33}BrO_3$: C, 63.16; H, 7.60; Br, 18.27. Found: C, 63.40; H, 7.60; Br, 18.56.

Epoxidation of XV

To a solution of 2.00 g of the bromoketal XV in 40 ml of chloroform cooled to −60° was added 47 ml of a 0.192 *M* solution of monoperphthalic acid in ether over a period of 20 minutes. After it had been stirred at −60° for 2 hours, the mixture was kept overnight at 0°, washed with 5% sodium carbonate solution and with water, dried over magnesium sulphate, and the solvent was removed. The crude product was chromatographed in benzene on 60 g of Florisil. Elution with benzene containing 2% ether gave the *5β,6β-epoxide* XVI, which was crystallized from methanol, yielding 0.70 g, m.p. 119–120°. Recrystallization from methanol gave an analytical sample, m.p. 120–121°, $[\alpha]_D$ −38.4°. Anal. Calc. for $C_{23}H_{33}BrO_4$: C, 60.92; H, 7.33; Br, 17.63. Found: C, 60.69; H, 7.23; Br, 17.74.

The *5α,6α-epoxide* XVII was obtained by elution of the column with benzene containing 10% ether. Crystallization from methanol gave 0.69 g of XVII, m.p. 180–182°. The analytical sample, obtained by recrystallization from methanol, had m.p. 182–183°,

$[\alpha]_D$ −88.4°. Anal. Calc. for $C_{23}H_{33}BrO_4$: C, 60.92; H, 7.33; Br, 17.63. Found: C, 60.72; H, 7.25; Br; 17.62.

3β-Acetoxy-5α-hydroxy-6β-chloropregnan-20-one (XX)

Hydrogen chloride was passed for 1 hour through a solution of 122 g of 3β-acetoxy-5α,6α-epoxypregnan-20-one (XIX) (18, 19) in 1 liter of chloroform. After an additional hour at room temperature, the solution was washed with water, 10% sodium bicarbonate solution, and water again, and dried over sodium sulphate. Removal of the solvent and crystallization from methylene chloride – methanol yielded two crops of XVI totalling 101 g, m.p. 230–233° decomp. Recrystallization from the same solvent combination raised the m.p. to 232–234° decomp., $[\alpha]_D$ +8.1°. Anal. Calc. for $C_{23}H_{35}ClO_4$: C, 67.22; H, 8.58; Cl, 8.63. Found: C, 67.41; H, 8.49; Cl, 8.67.

3β-Acetoxy-5α-hydroxy-6β-chloro-17α-bromopregnan-20-one (XXI, R = Ac)

A suspension of 101 g of the chlorohydrin XX and 101 g of N-bromosuccinimide in 2.6 liters of carbon tetrachloride was heated to the boiling point and irradiated with two 250-watt heat lamps for 15 minutes. The mixture was then cooled in ice and filtered, and the filtrate was washed with 5% sodium bisulphite solution, 10% sodium bicarbonate solution, and water. Drying over sodium sulphate and evaporation of the solvent *in vacuo* gave a crude product, which, on crystallization from aqueous methanol, yielded 80 g of XXI (R = Ac), m.p. 188–190° decomp. The analytical sample, m.p. 190–191° decomp., $[\alpha]_D$ −66.1, was obtained by recrystallization from aqueous methanol. Anal. Calc. for $C_{23}H_{34}BrClO_4$: C, 56.39; H, 7.00. Found: C, 56.10; H, 6.92.

3β,5α-Dihydroxy-6β-chloro-17α-bromopregnan-20-one (XXI, R = H)

Eighty grams of the acetate XXI (R = Ac) was dissolved in 2 l. of methanol by warming and 50 ml of 70% perchloric acid was added. The solution was left overnight at room temperature and the product was then precipitated by the addition of 1 liter of water. The yield of diol XXI (R = H) was 54 g, m.p. 175° decomp. After recrystallization from acetone–hexane, the diol melted at 175.5° decomp., $[\alpha]_D$ −70.7°, but it did not give a satisfactory analysis. Anal. Calc. for $C_{21}H_{32}BrClO_3$: C, 56.31; H, 7.20. Found: C, 56.94; H, 7.00.

5α-Hydroxy-6β-chloro-17α-bromopregnane-3,20-dione (XXII)

To a solution of 51.5 g of diol XXI (R = H) in 515 ml of acetic acid was added a solution of 25.75 g of sodium dichromate in 515 ml of acetic acid. The mixture was left for 4 hours at room temperature, 2 liters of water was added, and the precipitated solid was filtered and washed with water. The yield of diketone XXII was 42 g, m.p. 188–190° decomp. The analytical sample, m.p. 190° decomp., $[\alpha]_D$ −62.2°, was obtained by recrystallization from *i*-propanol. Anal. Calc. for $C_{21}H_{30}BrClO_3$: C, 56.57; H, 6.78. Found: C, 56.58; H, 6.75.

6α-Chloro-17α-bromoprogesterone (XVIII)

A. From the Epoxyketal XVII

Hydrogen chloride was passed for 1 hour through a solution of 1.3 g of XVII in 30 ml of chloroform. After it had been allowed to stand an additional hour, the solution was washed with water, with 5% sodium carbonate solution, and with water again and dried over magnesium sulphate. The product obtained on evaporation of the solvent was crystallized from acetone–hexane, yielding 0.98 g of 6α-chloro-17α-bromo-4-pregnene-3,20-dione (XVIII), m.p. 156–157°. Recrystallization from the same solvent mixture gave

an analytical sample, m.p. 157–158°, $[\alpha]_D$ +6.5°, λ_{max} 237 mμ (ε 16,200). Anal. Calc. for $C_{21}H_{28}BrClO_2$: C, 58.96; H, 6.60. Found: C, 59.02; H, 6.40.

B. From the Hydroxyketone XXII

An ice-cooled suspension of 3.0 g of XXII in 75 ml of chloroform was treated with hydrogen chloride for 1 hour, and, after an additional hour, the product was isolated as in *A*. Crystallization from acetone–hexane yielded 2.3 g of XVIII, m.p. 152–153°, identical by mixed m.p. and infrared spectrum with the product obtained in *A*.

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