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THE SYNTHESIS OF 17α-METHYLPROGESTERONE DERIVATIVES

A NEW CLASS OF ORALLY ACTIVE GESTAGENS

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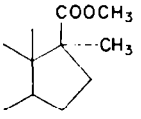
Abstract—The preparation of a new series of derivatives of 17α-methylprogesterone through a sterically hindered Grignard reaction is reported.

PROGESTERONE is devoid of appreciable oral activity but substituents, particularly at positions 6 and 17 of metabolic importance, are known to impart oral activity to the molecule.[2]

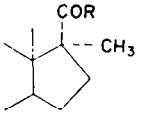
This paper deals with the preparation of 6 and 21 substituted 17α-methylprogesterones, a class of substances which we synthesized following the observation that 17α-methylprogesterone,[3] contrary to previous reports,[4] possessed oral activity (cf. Table 1).

17α-Methyl-20-ketopregnanes were first prepared by Marker[5] by ozonolysis or drastic oxidative cleavage of the corresponding 20-methylene compounds.

Two alternative methods were employed by Plattner[3] and by Heusser[6]; namely, by hydrolysis of an etianic ester (I) to the corresponding acid (IIa) and conversion of the latter to the methyl ketone (IIe) via the acid chloride (IIb), the diazoketone (IIc) and the chloroketone (IId)[3] or, more directly by the transformation of IIb to IIe with dimethyl cadmium.[6]



I



IIa (R = OH)
IIb (R = Cl)
IIc (R = CHN_2)
IId (R = CH_2Cl)
IIe (R = CH_3)
IIf (R = C_2H_5)
IIg (R = C_3H_7)

An ester of the type I can be easily obtained,[7] e.g. by alkaline treatment of a 17α-bromo-20-ketopregnane (Favorski rearrangement), in very good yield.

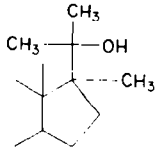
[1] Presented at the *International Congress on Hormonal Steroids* Milan, May (1962).
[2] L. Fieser and M. Fieser, *Steroids* pp. 564–566, Reinhold, New York (1959).
[3] Pl. A. Plattner, H. Heusser, P. Th. Herzig, *Helv. Chim. Acta* **32**, 270 (1949).
[4] Ch. R. Engel, Dissertation, ETH, Zurich (1951); cf. also *Acta Endocrin* Suppl., **51**, 913 (1960).
[5] R. E. Marker and R. B. Wagner, *J. Amer. Chem. Soc.* **64**, 1273 (1942).
[6] Hs. H. Günthard, E. Bergier, Ch. R. Engel and H. Heusser, *Helv. Chim. Acta* **35**, 2437 (1952).
[7] R. E. Marker and R. B. Wagner, *J. Amer. Chem. Soc.* **64**, 216 (1942).

The procedures of Marker and of the Swiss authors were not practical for our purposes and accordingly, we studied the reaction of the Favorski ester (I) with methyl-magnesium bromide under different conditions of temperature, time and solvent, aiming at a sterically controlled Grignard reaction[8] which would stop at the methyl-ketone (IIe) stage.

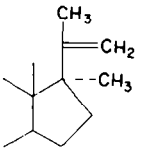
The 17α-methyl group hinders sufficiently the vicinal 20-ketone to allow a recovery of the latter in high yield when the Grignard reaction is carried out at the refluxing temperature of benzene for 3 hours or of anisole for one hour.

Excess of the Grignard reagent at room temperature does not affect the hindered carbomethoxy group which is recovered unchanged even after 20 hours.

Higher temperatures and longer periods of time, however, result in the formation of the carbinol (III), easily dehydrated by acids to the corresponding methylene compound (IV).[5]



III



IV

Substituted Favorski esters of the type V or VI can undergo a double Grignard reaction, with the concomitant introduction of a methyl group in position 6.

The selectivity of the Grignard reaction was demonstrated by the opening of the epoxide (Va) with excess Grignard reagent, at room temperature, without affecting the ester function (cf. Experimental) or of the epoxide (XIa) without extensively affecting the fluoroketone function. The latter stereoselective reaction allowed the preparation in good yield, of 6,17-dimethyl-21-fluoroprogesterones, starting from fluorinated intermediates of the type XII.

Lengthening of the progesterone side chain is possible if the ester (I) is treated with a suitable Grignard reagent such as ethyl or propylmagnesium halide. The alkyl ketones (IIf and IIg) were obtained this way; the biological activity of the corresponding progesterones, however, was predictably[9] diminished.

Introduction of a 21-fluoro substituent was conveniently achieved by condensing the crude ketone (VII) of the Grignard reaction (always accompanied by small quantities of the carbinol (III) and of the starting material (I), depending on the conditions) with ethyloxalate, (the alkaline salts of the oxalyl enolate (VIII) being water soluble, this presented a convenient method of separation of the ketone (VII) from the by-products[10]), followed by treatment of the oxalyl derivative with perchloryl fluoride[11] to give the fluoroketone (XIIa).

Introduction of a halogen function at position 6 was conventionally achieved by opening of a 5α,6α-epoxide with hydrogen halide (XI → X) or of a 6α,7α-epoxide (XV) with concomitant dehydration to the dienone (XIV).[12]

[8] R. Deghenghi and R. Gaudry, *J. Amer. Chem. Soc.* **83**, 4668 (1961).

[9] A. Wettstein, *Helv. Chim. Acta* **23**, 1371 (1940).

[10] Ketones of the type VII are too hindered to allow formation of water soluble Girard derivatives.

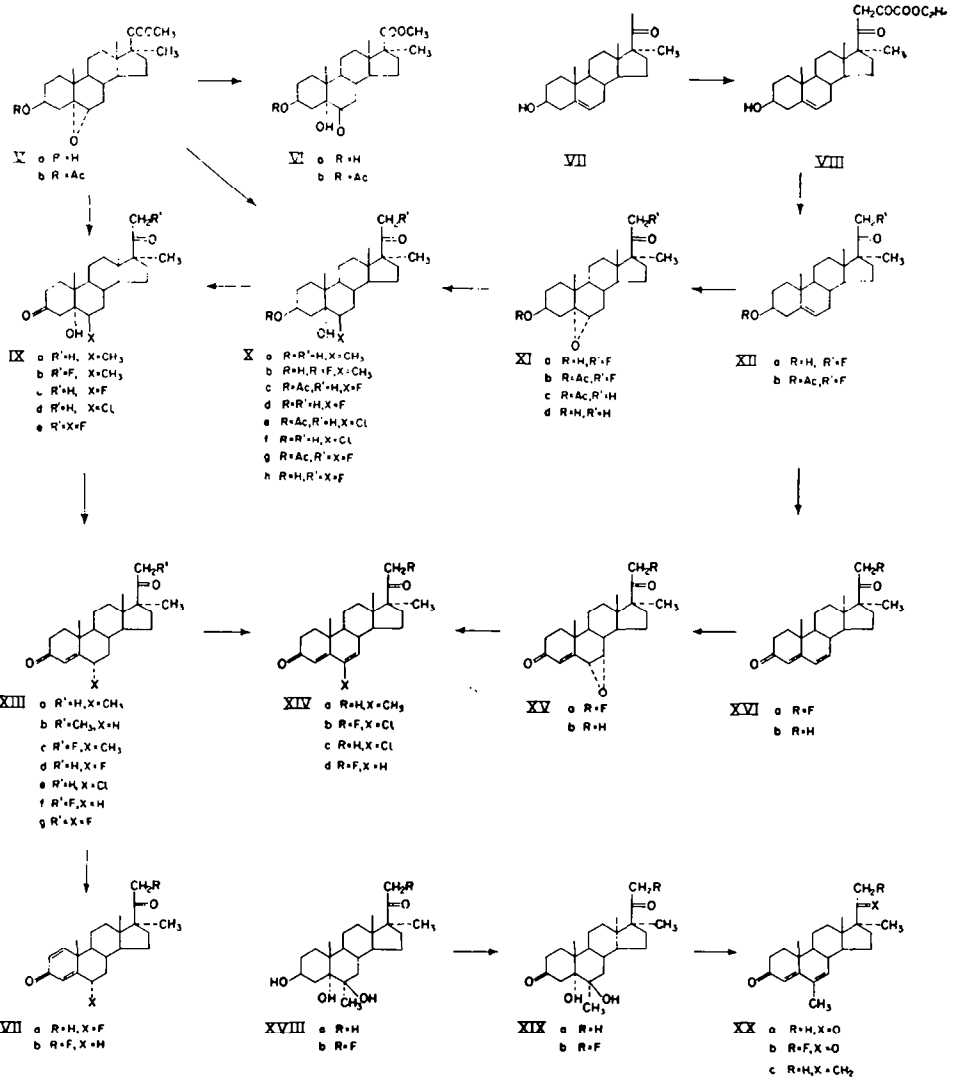
[11] C. E. Inman, R. E. Oesterling and E. A. Tyczkowski, *J. Amer. Chem. Soc.* **80**, 6533 (1958).

[12] L. H. Knox, J. A. Zderic, J. P. Ruelas, C. Djerassi and H. J. Ringold, *J. Amer. Chem. Soc.* **82**, 1230 (1960).

Elaboration of the Δ^4-3-keto moiety as in XIII was achieved, in the usual way, through hydrolysis and oxidation[13] of the oxygen function in position 3 (X → IX) and dehydration with epimerization at C_6 under acid or alkaline conditions (IX → XIII).

Double bonds at C_1-C_2 or at C_6-C_7 were introduced by quinone dehydrogenation[14,15] of the corresponding enone (XIII → XIV, XIII → XVII).

Another route to $\Delta^{4,6}$-3-ketones was made possible by dehydration of a carbinolic function as in XIX which was obtained by oxidation of the triol (XVIII) afforded by the reaction of the keto ester (VIa) with Grignard reagent.



[13] H. Kiliani and B. Merk, *Ber. Dtsch. Chem. Ges* **34**, 3562 (1901).
[14] D. Burn, D. N. Kirk and V. Petrow, *Proc. Chem. Soc.* 14 (1960).
[15] E. J. Agnello and G. D. Laubach, *J. Amer. Chem. Soc.* **79**, 1257 (1957).

Table 1 shows the progestational activity of our series as measured by the Clauberg test.[16]

TABLE 1

	Compound	Clauberg test–relative potency	
		s.c. progesterone = 1	oral norethindrone = 1
A.	17α-Methylprogesterone (17-MP)	2	1/20
B.	6α-Chloro-17-MP	<5	—
C.	6-Chloro-6-dehydro-17-MP	5–8	20
D.	6α-Fluoro-17-MP	>5	<½
E.	6α-Fluoro-1-dehydro-17-MP	<5	½
F.	6α-Methyl-17-MP	5	1
G.	6-Methyl-6-dehydro-17-MP	5	10
H.	21-Fluoro-17-MP	>10	<1/10
I.	21-Fluoro-1-dehydro-17-MP	<5	<1
J.	21-Fluoro-6-chloro-6-dehydro-17-MP	5	10
K.	6α,21-Difluoro-17-MP	10	<10
L.	21-Fluoro-6α-methyl-17-MP	10	<1
M.	21-Fluoro-6-methyl-6-dehydro-17-MP	10	<10

Compounds C, G and J are powerful oral gestagens devoid of any androgenic, masculinizing or adrenal depressant activity.

EXPERIMENTAL

Rotations were taken in 1% chloroform solution at 23 ± 2°. M.p.s. were not corrected. UV spectra were taken in ethanol.

17-Methyl-5-pregnen-3β-ol-20-one (VII)[8]. To 3β-hydroxy-17α-methyl-5-etienic acid methyl ester[8] (0·50 g) dissolved in dry benzene (30 ml) was added a 3M solution (10 ml) of CH_3MgBr in ether. Solvent was distilled until the temperature of the liquid reached 70°, then the reaction mixture was refluxed with stirring in an atmosphere of nitrogen for 3·5 hr. A saturated solution of ammonium chloride was added to stop the reaction and the mixture was subsequently extracted with ether, washed with dilute HCl and NaOH solutions, then with water to give, after drying and removal of the solvent, a crystalline solid (0·41 g), m.p. 172–176°, representing a mixture of 17-methyl-pregnenolone[8] and 3β,20-dihydroxy-Δ^5-bisnorcholane. 17-Methylpregnenolone was purified by crystallization, chromatography or through the corresponding acetate, $[\alpha]_D$ −54° (reported[8] $[\alpha]_D$ −32°), and isolated in 60–70% yield, m.p. 189–192° (reported[8] 185–187°).

When the Grignard reaction was performed in refluxing anisole, the reaction time was 1 hr. In most cases the crude product was used without purification.

3β-Hydroxy-17α-methyl-5α,6α-epoxyetianic acid methyl ester (Va). A solution of 3β-hydroxy-17α-methyl-5-etienic acid methyl ester[8] (10 g) in chloroform (20 ml) was added slowly, with stirring, while the temperature was being held between −2° and +2°, to a mixture of anhydrous sodium acetate (1·0 g) and a 40% solution of peracetic acid (10 ml). The reaction mixture was stirred for 2·5 hr at 0°, then extracted with chloroform, washed to neutrality, and the solvent evaporated to give a residue (10·8 g). Crystallization of this residue from methanol gave material (6·0 g) with m.p. 167–171°. An analytical sample had m.p. 170–171°, $[\alpha]_D$ −67·2°. (Found: C, 72·26; H, 9·43. $C_{22}H_{34}O_4$ requires: C, 72·89; H, 9·45%).

3β-Acetoxy-17α-methyl-5α,6α-epoxyetianic acid methyl ester (Vb). The title compound was prepared as above by epoxidation of the corresponding acetate or by acetylation of Va with acetic anhydride in pyridine. It was crystallized from methanol, m.p. 201–202°, $[\alpha]_D$ −56°. (Found: C, 73·94; H, 9·18. $C_{24}H_{36}O_4$ requires: C, 74·19; H, 9·34%).

3β,5α-Dihydroxy-6β,17α-dimethyletianic acid methyl ester. Epoxy ester (Va, 2·0 g) in dry benzene (120 ml) was stirred at room temp for 17 hr with a 3M solution of CH_3MgBr in ether (45 ml). The

[16] C. Revesz *et al.*, to be published.

usual working up gave 1·98 g of crystalline product, m.p. 191–193°. An analytical sample had m.p. 195–197° (CH_2Cl_2-hexane), $[\alpha]_D$ −25·2°. (Found : C, 72·95; H, 10·29. $C_{23}H_{38}O_4$ requires: C, 72·97; H, 10·12%).

3β,5α-Dihydroxy-6β,17α-dimethylpregnan-20-one (Xa). To a solution of epoxy ester (Va, 2·0 g) in dry benzene (120 ml) was added a 3M solution (45 ml) of CH_3MgBr in ether. The mixture was allowed to react at 65° for 3·5 hr as described for the preparation of VII. Working up in the same way gave a crystalline product (1·95 g), m.p. 188–192°, representing crude Xa, which was directly oxidized to IXa.

5α-Hydroxy-6β,17-dimethylpregnane-3,20-dione (IXa). To a solution of crude Xa (840 mg, m.p. 188–192°) in acetone (45 ml) was added, while stirring at 0°, a solution of 8N chromic acid in dil sulfuric acid (2·5 ml).[18] Stirring was continued for 3 min, the mixture was diluted with water, extracted with ether, the combined extracts washed to neutrality and the solvent evaporated to give 800 mg of a crystalline product, m.p. 230–233°, representing crude IXa which was directly dehydrated to XIIIa.

6α,17-Dimethylprogesterone (XIIIa). To a suspension of crude IXa (770 mg) in methanol (50 ml) was added a 5% aqueous NaOH solution (2·5 ml). The solution was refluxed in an atmosphere of nitrogen for 1 hr, acidified with acetic acid and evaporated to dryness. The residue was taken up in ether and washed to neutrality with dil aqueous $NaHCO_3$ solution and water. The dried solution was evaporated leaving an oil (746 mg) which was chromatographed on neutral alumina (Woelm, III). Pet ether–benzene (4:1) eluted crystalline fractions of 6α,17-dimethylprogesterone, m.p. 137–140° (ether); λ_{max} 241 mμ, ε 16,000; $[\alpha]_D$ +90·5°. (Found: C, 80·78; H, 10·09. $C_{23}H_{36}O_2$ requires: C, 80·65; H, 10·01%).

Further eluates contained the by-product *6α,17,20-trimethyl-20-hydroxy-4-pregnen-3-one*, m.p. 175–178° (acetone); λ_{max} 241 mμ, ε 14,500; $[\alpha]_D$ +53·2°. (Found: 80·97; H, 10·47. $C_{24}H_{38}O_2$ requires: C, 80·39; H, 10·68%).

6,17-Dimethyl-4,6-pregnadiene-3,20-dione (XIVa). Chloranil (1·6 g)[15] was added to a solution of XIIIa (2·0 g) in isobutanol (60 ml). The resulting suspensions was refluxed for 10 hr, extracted with ether and the combined extracts washed with 10% aqueous NaOH solution and water. The dried solution was evaporated to dryness and the oily residue (1·8 g) crystallized upon addition of ether, m.p. 138–140°. An analytical sample had m.p. 144–146°; λ_{max} 288 mμ, ε 25,000; $[\alpha]_D$ +79°. (Found: C, 81·06; H, 9·52. $C_{23}H_{32}O_2$ requires: C, 81·13; H, 9·47%).

17,21-Dimethylprogesterone (XIIIb). A Grignard solution was made in the usual way from Mg shavings (7·5 g), ethyl bromide (0·3 mole) and ether (80 ml). This solution (20 ml) was added to a solution of 3β-hydroxy-17α-methyl-5-etienic acid methyl ester (1·0 g)[8] in anisole (60 ml). The ether was distilled and the reaction mixture was stirred and refluxed in an atmosphere of nitrogen for 1 hr. Working up in the usual way gave a yellow oil (1·06 g) which crystallized from ether–hexane to give crude 17,21-dimethylpregnenolone, m.p. 134–140°. One more crystallization from methanol–water gave a sample (0·420 g) with m.p. 143–148°.

The pregnenolone (393 mg) prepared as above was dissolved in toluene (15 ml) and some solvent (4 ml) was distilled. Cyclohexanone (4 ml) and a solution of aluminum isopropoxide (250 mg) in toluene (4 ml) were added and the reaction mixture was refluxed for 1 hr. Rochelle salt solution was added to the reaction mixture which was then extracted with ether and steam distilled. Working up in the usual way gave an oil (400 mg) which crystallized as needles (280 mg), m.p. 154–156°, from ether–hexane. An analytical sample had m.p. 157–159°, $[\alpha]_D$ +107·7°. (Found: C, 80·71; H, 10·04. $C_{23}H_{36}O_2$ requires: C, 80·65; H, 10·01%).

6α,17-Dimethyl-21-fluoroprogesterone (XIIIc). 3β-Acetoxy-5α,6α-epoxy-17-methyl-21-fluoropregnan-20-one (XIb, 1·73 g) was dissolved in dry benzene (120 ml). To the cooled solution, a 3M solution of CH_3MgBr in ether (36 ml), was added and the reaction mixture was stirred at room temp for 17 hr. Working up in the usual way gave crude *3β,5α-dihydroxy-6β,17-dimethyl-21-fluoropregnan-20-one* (Xb) as an amorphous product. This was dissolved in acetone (100 ml) and oxidized at 0° with an 8N solutions (3 ml) of chromic acid. The usual working up gave *5α-hydroxy-6β,17-dimethyl 21-fluoropregnane-3,20-dione* (IXb, 1·42 g) as a white solid, m.p. 190–193°.

Diketone (IXb, 1·75 g) prepared as described above was dissolved in 5% methanolic NaOH solution (40 ml) and refluxed 1 hr in an atmosphere of nitrogen. The usual working up gave crude XIIIc (1·616 g) which was chromatographed over neutral alumina (Woelm, III, 40 g). Elution with pet ether–benzene (1:1) gave 0·70 g of product. One crystallization from acetone–hexane–ether gave an analytical sample m.p. 177–179°, $[\alpha]_D$ +79·4°. (Found: C, 77·02; H, 9·18; F 5·24. $C_{22}H_{33}FO_2$: C, 76·63; H, 9·33; F, 5·27%).

6,17-*Dimethyl-6-dehydro-21-fluoroprogesterone* (XXb). The title compound was prepared by chloranil dehydrogenation[15] of 6α,17-dimethyl-21-fluoroprogesterone (XIIIc) as described for XIVa. An analytical sample had m.p. 161–163° (ether–hexane); λ_{max} 290 mμ, ε 21,300; $[\alpha]_D$ +57·8°. (Found: C, 76·91; H, 9·00. $C_{23}H_{31}FO_3$ requires: C, 77·05; H, 8·72%).

3β-*Acetoxy*-5α,6α-epoxy-17-*methylpregnan*-20-*one* (XIc). A solution of 17-methylpregnenolone acetate[3] (3·92 g) in chloroform (17 ml) was slowly added to a cooled mixture (temp between −2° and +2°) of sodium acetate (400 mg) and peracetic acid (4 ml). The reaction mixture was stirred for 2 hr at a temp of 0–5°. The chloroform solution was washed with aqueous sodium bicarbonate solution and water, dried and evaporated. The residue was crystallized from methanol giving a first crop (1·78 g), m.p. 198–200° and a second crop (363 mg). An analytical sample had m.p. 198–200°, $[\alpha]_D$ −56·3°. (Found: C, 73·94; H, 9·18. $C_{24}H_{36}O_4$ requires: C, 74·19; H, 9·34%).

3β-*Hydroxy*-5α,6α-*epoxy*-17-*methylpregnan*-20-*one* (XId). The epoxidation of crude 17-methylpregnenolone (VII, 33·0 g) was carried out under the same conditions described for the preparation of XIc. Crystallization of the crude product from methanol gave a first crop (9·15 g) of the epoxide (XId), m.p. 219–221° and a second crop (2·75 g), m.p. 218–220°. An analytical sample had m.p. 223–224°, $[\alpha]_D$ −67·1°. (Found: C, 76·35; H, 9·81. $C_{22}H_{34}O_3$ requires: C, 76·28; H, 9·86%).

Acetylation of this compound with acetic anhydride and pyridine afforded a product identical with the acetate (XIc) prepared above.

3β-*Acetoxy*-5α-*hydroxy*-6β-*fluoro*-17-*methylpregnan*-20-*one* (Xc). To a solution of anhydrous HF (6·1 g) in tetrahydrofuran (13·2 g) and chloroform (6 ml) at −60° was added a solution of epoxide (XIc, 6·1 g) in chloroform (45 ml). The temp was held at −10° for 2 hr and the mixture was then poured into cold aqueous sodium bicarbonate solution. The organic layer was decanted and washed with bicarbonate solution and water to neutrality. The residue (6·36 g), after removal of solvents, crystallized from methanol to give the fluorohydrin (Xc, 3·6 g), m.p. 222° (dec), $[\alpha]_D$ −32·9°. (Found: C, 70·50; H, 8·90; F, 4·98. $C_{24}H_{37}FO_4$ requires: C, 70·55; H, 9·13; F, 4·65%).

3β,5α-*Dihydroxy*-6β-*fluoro*-17-*methylpregnan*-20-*one* (Xd). A solution of 3β-acetoxy-5α-hydroxy-6β-fluoro-17-methylpregnan-20-one (Xc, 10 g) in methanol (450 ml) containing perchloric acid (70%, 10 ml) was heated to reflux until all the solid had dissolved. The solution was then kept at room temp overnight. Water was added and the solid (8·66 g), m.p. 214°, was collected by filtration. Crystallization from acetone–hexane gave a product with decomposition range 193° to 206° depending on the rate of heating. An analytical sample had m.p. 197° (dec), $[\alpha]_D$ −17°. (Found: C, 71·76; H, 9·30; F, 5·14. $C_{22}H_{35}FO_3$ requires: C, 72·09; H, 9·63; F, 5·18%).

5α-*Hydroxy*-6β-*fluoro*-17-*methylpregnane*-3,20-*dione* (IXc). To a solution of 3β,5α-dihydroxy-6β-fluoro-17-methylpregnan-20-one (Xd, 8·0 g) in acetone (500 ml) was added (at a temp of 10–15°) an 8N chromic acid solution (20 ml).[18] Stirring was continued for 2 min and the mixture then poured into ice-water and extracted with methylene chloride. The organic layer was washed to neutrality and evaporated giving a crystalline product (6·4 g), m.p. 244° (dec). The m.p. was not raised by recrystallization from acetone–hexane. $[\alpha]_D$ +10·6°. (Found: C, 72·38; H, 9·00; F, 5·27. $C_{22}H_{33}FO_3$ requires: C, 72·49; H, 9·12; F, 5·21%).

6α-*Fluoro*-17-*methylprogesterone* (XIIId). Dry HCl was bubbled through a solution of 5α-hydroxy-6β-fluoro-17-methylpregnane-3,20-dione (IXc, 3·4 g) in chloroform (71 ml) during 1 hr at 0°. The solution was then kept an additional hour at 0°, washed to neutrality, evaporated and the residue crystallized from ether giving a substance (1·90 g) with m.p. 181–183°. An analytical sample had m.p. 188–189° (acetone–hexane); λ_{max} 236 mμ, ε 18,000; $[\alpha]_D$ +95·4°. (Found: C, 76·50; H, 8·95; F, 5·19. $C_{22}H_{31}FO_2$ requires: C, 76·26; H, 9·02; F, 5·48%). The sign of the rotation indicates a 6α-fluorine[17] substituent.

6α-*Fluoro*-17-*methyl*-1,4-*pregnadiene*-3,20-*dione* (XVIIa). A mixture of XIIId (1·32 g), 2,3-dichloro-5,6-dicyanoquinone (0·86 g) and *p*-toluenesulfonic acid (33 mg) in benzene (66 ml) was refluxed for 18 hr. The cooled solution was filtered to separate the hydroquinone and the filtrate was washed with aqueous bicarbonate solution and water. The dried solution was evaporated and the residue crystallized from acetone–hexane to give XVIIa, m.p. 215–217° (dec); λ_{max} 244 mμ, ε 19,100; $[\alpha]_D$ +57·8°. (Found: C, 76·57; H, 8·43; F, 5·47. $C_{22}H_{29}FO_2$ requires: C, 76·71; H, 8·48; F, 5·51%).

3β-*Acetoxy*-5α-*hydroxy*-6β-*chloro*-17-*methylpregnan*-20-*one* (Xe). Dry HCl was passed through a solution of 5α,6α-epoxide (XIc, 7·5 g) in chloroform (60 ml) for 1 hr at room temp. The reaction

[17] Ch. R. Engel and R. Deghenghi, *Canad. J. Chem.* **38**, 452 (1960).

solution was left at room temp for an addition hr; the chloroform solution was then washed to neutrality with water, aqueous bicarbonate solution and water. The residue after removal of the solvent was crystallized from methylene chloride–methanol yielding a first crop (4·62 g) of material, m.p. 211° (dec) and a second crop, m.p. 209–210° (dec). An analytical sample had m.p. 214–215° (dec), $[\alpha]_D$ −49·7°. (Found: C, 68·17; H, 8·65; Cl, 8·30. $C_{24}H_{37}ClO_4$ requires: C, 67·81; H, 8·77; Cl, 8·35%).

3β,5α-Dihydroxy-6β-chloro-17-methylpregnan-20-one (Xf). A mixture of Xe (4·88 g) and methanol (125 ml) containing 70% perchloric acid (3 ml) was boiled until the solid dissolved and the resulting solution was kept at room temp overnight. Water was added and the solid collected by filtration, washed and dried, m.p. 181–182° (dec). Crystallization from acetone–hexane gave pure material (2·95 g), m.p. 182–183°, $[\alpha]_D$ −25·7°. (Found: C, 69·28; H, 9·20; Cl, 9·05. $C_{22}H_{35}ClO_3$ requires: C, 68·99; H, 9·21; Cl, 9·27%).

5α-Hydroxy-6β-chloro-17-methylpregnane-3,20-dione (IXd). To a solution of 3β,5α-dihydroxy-6β-chloro-17-methylpregnan-20-one (Xf, 2·95 g) in acetone (150 ml) was added an 8N solution (7·5 ml) of chromic acid[18] at a temp between 10° and 15°. Stirring was continued for 2 min and the mixture poured into water. The solid which precipitated was collected by filtration and crystallized from ether giving a substance (2·21 g) with m.p. 221° (dec) Crystallization from acetone–hexane gave material with a decomposition range 207–219°, $[\alpha]_D$ −19·8°. (Found: C, 69·05; H, 8·61; Cl, 9·28. $C_{22}H_{33}ClO_3$ requires: C, 69·32; H, 8·73; Cl, 9·30%).

6α-Chloro-17-methylprogesterone (XIIIe). Dry HCl was passed through an ice-cold solution of 5α-hydroxy-6β-chloro-17-methylpregnane-3,20-dione (IXd, 2·13 g) in chloroform (60 ml) for 1 hr. The solution was kept at 0° for an additional hr, then washed to neutrality with aqueous bicarbonate solution and water. The residue (1·85 g), after removal of the solvent, was purified by crystallization from acetone–hexane giving a substance with m.p. 190° (dec); λ_{max} 236 mμ, ε 14,600; $[\alpha]_D$ −57·9°. (Found: C, 72·71; H, 8·90; Cl, 9·82. $C_{22}H_{31}ClO_2$ requires: C, 72·79; H, 8·61; Cl, 9·78%).

17-Methyl-4,6-pregnadiene-3,20-dione (XVIb). 17-Methylpregnenolone[3] (VII, 1·0 g) was dissolved in dry toluene (30 ml) and to this solution was added cyclohexanone (10 ml), aluminum isopropoxide (1·0 g) and chloranil (0·50 g). The reaction mixture was refluxed for 1 hr, cooled, diluted with water and extracted with ether. The combined extracts were washed with dil aqueous NaOH solution and water and then steam distilled. Working up in the usual way afforded a yellowish residue (0·995 g) which was purified by chromatography over neutral alumina (Woelm, III) and crystallization from hexane, m.p.148–150°; λ_{max} 287 mμ, ε 27,800; $[\alpha]_D$ +82·4°. (Found: C, 80·52; H, 9·22. $C_{22}H_{30}O_2$ requires: C, 80·93; H, 9·26%).

Alternatively, this compound could be obtained by chloranil dehydrogenation[15] of 17-methylprogesterone.[3]

6α,7α-Epoxy-17-methylprogesterone (XVb). To a solution of dienone (XVIb, 5·19 g) in methylene chloride (540 ml) was added a 0·429 N solution (360 ml) of monoperphthalic acid in ether. The reaction solution was left at room temp for 3 days.[12] The solution was then washed with aqueous bicarbonate solution and water, dried and evaporated to give a residue (4·5 g) which was purified by chromatography over neutral alumina (Woelm, III) and crystallization from hexane. The pure material (1·46 g) had m.p. 172–173°; λ_{max} 241 mμ, ε 15,800; $[\alpha]_D$ +61·8°. (Found: C, 77·45; H, 9·08. $C_{22}H_{30}O_3$ requires: C, 77·15; H, 8·83%).

6-Chloro-17-methyl-4,6-pregnadiene-3,20-dione (XIVc). A solution of 6α,7α-epoxide (XVb, 1·26 g) in glacial acetic acid (50 ml) was saturated with HCl (anhydrous). The reaction mixture was kept at room temp for 4 hr, poured into ice-water and the precipitated solid collected by filtration and washed free of acid. Chromatography on neutral alumina (Woelm, III) gave an oil (647 mg) which crystallized from methanol, m.p. 125–126°. An analytical sample had m.p. 125–126° (hexane); λ_{max} 286 mμ, ε 23,000; $[\alpha]_D$ −53·5°. (Found: C, 73·48; H, 8·10; Cl, 9·79. $C_{22}H_{29}ClO_2$ requires: C, 73·20; H, 8·09; Cl, 9·83%).

17-Methyl-21-fluoropregnenolone acetate (XIIb). To a solution of sodium (5·46 g) in dry ethanol (500 ml) was added crude 17-methylpregnenolone (VII, 57·5 g, obtained from the Grignard reaction in anisole) and a solution of diethyl oxalate (81·6 g) in dry ethanol (60 ml). The reaction mixture was refluxed for 6 hr. The sodium enolate which formed was collected by filtration and subsequently washed with ethanol and then with anhydrous ether. This solid was then suspended in methylene chloride to which enough 10% HCl solution was added to dissolve the compound. The organic layer was washed free of acid and evaporated to give the ethoxalyl derivative (VIII, 31·0 g). A solution of this substance in dry methanol (750 ml) and ether (1000 ml) was added to a solution of sodium (5·67 g)

in methanol (450 ml). After stirring for 2 hr the enolate (25·2 g) was collected by filtration and washed with ether.

A stream of perchloryl fluoride was passed through a suspension of the enolate in dry methanol, cooled to −15°. The cooling bath was then removed and the addition of perchloryl fluoride continued until the solution was neutral and clear. Two thirds of the solvent of the solution were removed under red press; potassium acetate (50·4 g) and methanol (250 ml) were added, the reaction mixture was refluxed for 6 hr and then left at room temp overnight. Dilution with water afforded crude *17-methyl-21-fluoropregnenolone* (XIIa, 19·2 g), m.p. 197–203°.

Crude XIIa (2·0 g) was acetylated in the usual manner with acetic anhydride and pyridine and the product was purified by chromatography on Florisil. The pure compound (1·2 g) had m.p. 196–198° (methylene chloride–hexane), $[\alpha]_D$ −63·6°. (Found: C, 73·52; H, 9·00; F, 4·72. $C_{24}H_{35}FO_3$ requires: C, 73·81; H, 9·03; F, 4·06%).

17-Methyl-21-fluoropregnenolone (XIIa). The acetate (XIIb, 250 mg) prepared above was hydrolysed by treatment with 70% perchloric acid (0·2 ml) in methanol (20 ml) at room temp overnight. Working up in the usual way gave crystalline material (178 mg), m.p. 210–216°. Crystallization from acetone–hexane afforded an analytical sample, m.p. 212–217°, $[\alpha]_D$ +63·4°. (Found: C, 75·63; H, 9·25; F, 5·55. $C_{22}H_{33}FO_2$ requires: C, 75·82; H, 9·54; F, 5·45%).

17-Methyl-21-fluoroprogesterone (XIIIf). From a solution of crude 17-methyl-21-fluoropregnenolone (XIIa, 24·23 g) in toluene (1300 ml) and cyclohexanone (260 ml), 200 ml of solvent were distilled. Then aluminum isopropoxide (13·2 g) was added and the reaction mixture was refluxed for 1 hr. Hydrochloric acid solution (10%, 130 ml) was added to the cooled reaction mixture which was subsequently steam distilled. Extraction with methylene chloride and working up in the usual way left a residue which was only partially soluble in ether. The insoluble portion (15·94 g) proved to be the desired product, m.p. 168–175°. Crystallization from acetone–hexane gave pure material, m.p. 180–182°; λ_{max} 242 mμ, ϵ 19,150; $[\alpha]_D$ +95·9°. (Found: C, 76·38; H, 8·88; F, 5·38. $C_{22}H_{31}FO_2$ requires: C, 76·26; H, 9·02; F, 5·48%).

17-Methyl-21-fluoro-1,4-pregnadiene-3,20-dione (XVIIb). To a solution 17-methyl-21-fluoroprogesterone (XIIIf, 347 mg) in dioxane (12 ml) was added *p*-toluenesulfonic acid (19 mg) and 2,3-dichloro-5,6-dicyanoquinone (250 mg) and the reaction solution was heated on a steam bath for 3·5 hr. After cooling, the hydroquinone was removed by filtration and the filtrate diluted with ether, washed to neutrality and evaporated to give a residue (338 mg) which crystallized from acetone. The product was purified by chromatography through silica gel and crystallization from acetone-hexane to give a substance with m.p. 162–164°; λ_{max} 246, ϵ 15,800; $[\alpha]_D$ +23·2°. (Found: C, 76·67; H, 8·35; F, 5·73. $C_{22}H_{29}FO_2$ requires: C, 76·72; H, 8·49; F, 5·52%).

3β-Acetoxy-5α,6α-epoxy-17-methyl-21-fluoropregnan-20-one (XIb). A solution of XIIb (21·6 g) in chloroform (330 ml) was slowly added to a stirred suspension of sodium acetate (2·16 g) in peracetic acid (21·6 ml) at a temp of −2° to −2°. Stirring was continued for 2 hr at this temp. The chloroform layer was washed to neutrality and evaporated; the residue crystallized from methanol to give the 5α,6α-epoxide, m.p. 212–215°, $[\alpha]_D$ −61·9°. (Found: C, 70·60; H, 8·76; F, 4·44. $C_{22}H_{35}FO_4$ requires: C, 70·90; H, 8·68; F, 4·67%).

3β,5α-Dihydroxy-6β,21-difluoro-17-methylpregnan-20-one (Xh). A solution of 5α,6α-epoxide (XIb, 6·8 g) in chloroform (50 ml) was added to a solution of anhydrous HF in tetrahydrofuran (15 ml) and chloroform (6·8 ml) at −60°. The solution was kept at −10° for 2 hr, then poured into ice-cold bicarbonate solution; the organic layer was washed to neutrality, dried, and evaporated. The residue crystallized from methylene chloride–methanol to give *3β-acetoxy-5α-hydroxy-6β,21-difluoro-17-methylpregnan-20-one* (Xg, 3·4 g), m.p. 229–230° (dec). This acetate was hydrolysed in the usual manner with perchloric acid in methanol to give Xh, m.p. 198–204°, $[\alpha]_D$ −24·8°. (Found: C, 68·45; H, 8·75; F, 9·83. $C_{22}H_{34}F_2O_3$ requires: C, 68·72; H, 8·91; F, 9·88%).

5α-Hydroxy-6β,21-difluoro-17-methylpregnane-3,20-dione (IXe). To a solution of 3β,5α-dihydroxy-6β,21-difluoro-17-methylpregnan-20-one (Xh, 1·6 g) in acetone (100 ml) was added an 8 N solution (4·03 ml) of chromic acid[13] at a temp between 10° to 15°. Stirring was continued for 2 min, the reaction mixture was poured into water and extracted with methylene chloride. The organic solution was washed to neutrality and evaporated to give the product, m.p. 245° (dec), $[\alpha]_D$ = 0°. (Found: C, 69·26; H, 8·64; F, 9·27; $C_{22}H_{32}F_2O_3$ requires: C, 69·10; H, 8·43; F, 9·93%).

6α,21-Difluoro-17-methylprogesterone (XIIIg). Dry HCl was bubbled through a suspension of 5α-hydroxy-6β,21-difluoro-17-methylpregnane-3,20-dione (IXe, 1·0 g) in chloroform (21 ml) at a

emp of 0° for 1 hr. The reaction solution was kept an additional hour at 0°, washed free of acid, dried and evaporated. The residue crystallized from acetone–hexane, m.p. 165° (dec); λ_{max} 236 mμ, ε 17,400; $[\alpha]_D$ +82·4°. (Found: C, 72·26; H, 8·13; F, 9·80. $C_{22}H_{30}F_2O_2$ requires: C, 72·49; H, 8·29; F, 10·48%).

17-Methyl-21-fluoro-4,6-pregnadiene-3,20-dione (XIVd). A solution of 17-methyl-21-fluoroprogesterone (XIIIf, 7·81 g) in glacial acetic acid (8 ml) and t-butanol (200 ml) was refluxed with chloranil (7·8 g) under nitrogen for 16 hr. After removal of the solvents the residue was taken up in ether and filtered. The filtrate was washed with aqueous 50% KOH solution, water, aqueous sodium hydrosulfite solution, aqueous KOH solution and water. Evaporation of the dried ether solution afforded a residue, m.p. 165–167°, which was purified by chromatography on neutral alumina (Woelm, III), m.p. 166–168° (acetone–hexane); λ_{max} 286 mμ, ε 27,700; $[\alpha]_D$ +60·7°. (Found: C, 77·02; H, 8·41; F, 5·49. $C_{22}H_{29}FO_2$ requires: C, 76·71; H, 8·49; F, 5·51%).

6α,7α-Epoxy-17-methyl-21-fluoroprogesterone (XVa). A solution of 17-methyl-21-fluoro-4,6-pregnadiene-3,20-dione (XIVd or XVIa, 3·93 g) in methylene chloride (350 ml) and a 0·429 N ethereal solution (300 ml) of monoperphthalic acid was kept at room temp for 90 hr. The organic layer, after dilution with water, was washed to neutrality and the solvent removed. A yellow residue was obtained and subsequently chromatographed on neutral alumina (Woelm, III). The purified product (1·17 g) crystallized from methylene chloride–hexane, m.p. 201–203°, λ_{max} 241 mμ, ε 15,300; $[\alpha]_D$ +47·9°. (Found: 73·70; H, 8·12; F, 5·19. $C_{22}H_{29}FO_3$ requires: C, 73·30; H, 8·11; F, 5·27%).

6-Chloro-17-methyl-21-fluoro-4,6-pregnadiene-3,20-dione (XIVb). Dry HCl was bubbled through a solution of 6α,7α-epoxide (XVa, 900 mg) in acetic acid (40 ml) during 5 min and the reaction solution was kept at room temp for 6 hr. The usual working up gave a residue which was chromatographed on neutral alumina (Woelm, III) and crystallized from acetone–hexane to give the pure product, m.p. 182–184°; λ_{max} 286 mμ, ε 21,100; $[\alpha]_D$ +38·5°. (Found: C, 69·95; H, 7·41; Cl, 9·13; F, 5·25. $C_{22}H_{28}ClFO_2$ requires: C, 69·73; H, 7·45; Cl, 9·37; F, 5·01%).

3β,5α,6β-Trihydroxy-17α-methyletianic acid methyl ester. 3β-Hydroxy-17αmethyletienic acid methyl ester[8] (10·0 g) was dissolved in 88% formic acid (100 ml) and heated on a steam bath for 10 min.[18] To the cooled solution was slowly added 30% H_2O_2 solution (10 ml) and the reaction solution was kept at room temp for 3 hr. Dilution with water precipitated a solid which was separated by filtration. This solid was dissolved in methanol (150 ml) and enough 10% methanolic KOH solution was added to maintain a pH of 10 for 10 min while heating on a steam bath. The reaction solution was then poured into water and the solid (10 g, m.p. 245–255°) which separated was collected by filtration. One crystallization from acetone gave an analytical sample, m.p. 262–265°, $[\alpha]_D$ −2·1°. (Found: C, 69·28; H, 9·26. $C_{22}H_{36}O_5$ requires: C, 69·44; H, 9·54%).

This compound could also be obtained in good yield by acid catalyzed opening of the 5α,6α-epoxide (Va).

3β,5α-Dihydroxy-6-oxo-17α-methyletianic acid methyl ester (VIa). To a solution of 3β,5α,6β-trihydroxy-17α-methyletianic acid methyl ester (18·4 g) in methanol (180 ml), ether (180 ml) and water (190 ml)[19] was added N-bromosuccinimide (19·0 g) with stirring. The reaction solution was kept at 0° for 2 hr and then enough saturated aqueous $NaHCO_3$ solution was added to decolorize the solution. Ether was removed from the solution under red press at room temp, water was added and the solid which precipitated was collected by filtration. Crystallization form methanol–ethyl acetate gave a first crop (6·7 g), m.p. 276–280° and concentration of the mother liquors gave 3·6 g of the same material. An analytical sample had m.p. 277–285° (dec), $[\alpha]_D$ −59·5°. (Found: C, 69·55; H, 8·85; $C_{22}H_{34}O_5$ requires: C, 69·81; H, 9·05%).

The acetate (VIb) had m.p. 241–243° (ethanol–water).

3β,5α,6β-Trihydroxy-6α,17-dimethylpregnan-20-one (XVIIIa). To a solution of 3β,5α-dihydroxy-6-oxo-17α-methyletianic acid methyl ester (VIa, 25·0 g) in dry tetrahydrofuran (1250 ml) and dry benzene (2000 ml) was added, during 10 min with stirring, a 3 M solution (750 ml) of CH_3MgBr in ether. The reaction mixture was stirred at room temp overnight, more Grignard solution (375 ml) was added and then 1250 ml of solvent were distilled. Heating at the reflux temp with stirring was continued for 5 hr.

To the ice-cooled reaction mixture, aqueous saturated ammonium chloride solution (500 ml) was cautiously added while stirring. The organic layer was separated and the aqueous phase was extracted

[18] L. F. Fieser and S. Rajagopalan, *J. Amer. Chem.* **71**, 3938 (1949).

[19] L. F. Fieser and M. Fieser, *Steroids* pp. 189–190, Reinhold, New York (1959).

with ethyl acetate. The combined organic extracts were washed with aqueous ammonium chloride solution and water, dried and evaporated to give a white solid (25·2 g), m.p. 209–218°. The analytical sample crystallized from aqueous methanol as the monohydrate, m.p. 234–237°, $[\alpha]_D$ −7·5°. (Found: C, 69·90; H, 10·15. $C_{23}H_{38}O_4 \cdot H_2O$ requires: C, 69·66; H, 10·17%).

6α,17-*Dimethylpregnane*-5α,6β-*diol*-3,20-*dione* (XIXa). Crude 3β,5α,6β-trihydroxy-6α,17-dimethylpregnan-20-one (XVIIIa, 25·2 g) was dissolved in acetone and oxidized at 15° by adding an 8 N chromic acid solution[13] (75 ml) while stirring for a period of 6 min. The reaction mixture was poured into water, extracted with ethyl acetate and the combined extracts were washed until neutral. Evaporation of the solvent gave the crude product (23·3 g), m.p. 206–215° (dec). An analytical sample (acetone) had m.p. 243–245° (dec), $[\alpha]_D$ −16·9°. (Found: C, 73·23; H, 9·65. $C_{23}H_{36}O_4$ requires: C, 73·36; H, 9·64%).

6,17-*Dimethyl*-4,6-*pregnadiene*-3,20-*dione* (XXa). Crude 6α,17-dimethylpregnane-5α,6β-diol-3,20-dione (XIXa, 70·0 g) was dissolved in absolute ethanol (1400 ml) containing concentrated HCl (4 ml). The reaction solution was refluxed for 1 hr, cooled, diluted with water and extracted with ether. The combined extracts were washed to neutrality, dried and evaporated. The residue which was obtained was a mixture of the diketone (XXa) and to the *methylene compound* (XXc) and weighed 61·5 g. One crystallization from ether afforded XXa (19·5 g), m.p. 138–140°. The mother liquors were chromatographed on neutral alumina (Woelm, III, 1300 g). Elution with hexane–benzene(4:1) gave crude XXc (13·04 g); further elution with hexane–benzene (3:2) and benzene afforded XXa (26·17 g) which was combined with the material obtained by direct crystallization above and crystallized from ether–hexane to give pure 6,17-dimethyl-4,6-pregnadiene-3,20-dione (XXa, 28·0 g), m.p. 139–141°; λ_{max} 289 mμ, ε 24,900; $[\alpha]_D$ +73·9. (Identical with product XIVa).

The crude methylene compound (XXc) obtained above was rechromatographed on alumina (Woelm, III, 500 g) and elution with hexane–benzene (4:1) gave crystalline material (6·90 g). Recrystallization from aqueous acetone and then from acetone gave clusters of needles (2·09 g), m.p. 145–147°; λ_{max} 289 mμ, ε 23,500; $[\alpha]_D$ +25°. (Found: C, 84·87; H, 10·30. $C_{21}H_{34}O$ requires: C, 85·15; H, 10·12%).

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