the mixture was concentrated at reduced pressure, diluted with 100 ml. of water and filtered. The white crystalline product weighed 0.44 g. (88%) after air drying (R_f 0.39, benzene–formamide papergram system).

A mixture of 0.44 g. of crude bromohydrin, 0.6 g. of potassium acetate, and 20 ml. of acetone was stirred and heated under reflux for 30 hr. It was then evaporated to dryness at reduced pressure, and the residue was extracted with methylene chloride. The extract was concentrated and poured onto a chromatographic column containing 25 g. of Florisil. The product was eluted with 10 and 12.5% acetone in Skellysolve B to yield 329 mg. (92.4%) of oxide (R_f 0.87, benzene–formamide papergram system).

To 9.5 g. of HF cooled in a solid Dry Ice–alcohol bath was added 17 ml. of cold tetrahydrofuran and a cold solution of 329 mg. of oxide dissolved in 17 ml. of methylene chloride. The mixture was swirled and then kept at 5° for 19 hr. The amber-colored solution was poured cautiously into a stirred mixture of 45 g. of Na_2CO_3 and 1 l. of water and ice. The organic phase was separated and the aqueous phase repeatedly was extracted with methylene chloride. The combined extract was dried and evaporated to a partly crystalline residue which was purified by chromatography on 25 g. of Florisil. The product was eluted with 15 and 20% acetone–Skellysolve B mixtures as crystalline plates, yield 332 mg. Recrystallization from acetone–Skellysolve B gave two crops: (a) 0.19 g. of shiny plates, m.p. 259–262° dec., λ_{max}^{alc} 239 mμ (ε 15,450); and (b) 0.06 g., m.p. 252–256° dec., total yield 72.5%.

Both crops gave but one spot on a benzene–formamide papergram (R_f 0.25).

Anal. Calcd. for $C_{24}H_{30}F_2O_6$: C, 63.70; H, 6.68; F, 8.40. Found: C, 63.40; H, 6.78; F, 8.63.

16α-Fluoro-11β,17α,21-trihydroxy-1,4-pregnadiene-3,20-dione (17).—A solution of 160 mg. of acetate **16**, 75 mg. of $KHCO_3$, 15 ml. of methanol, and 1 ml. of water was stirred for 5 hr. under nitrogen at ambient temperature. After the addition of 0.2 ml. of acetic acid and 10 ml. of water, the mixture was concentrated to a small volume. The product (130 mg.) was recovered by filtration. Recrystallization from acetone–Skellysolve B afforded 69 mg. of **17**, m.p. 245–247° dec., and 21 mg., m.p. 240–244° dec.

Anal. Calcd. for $C_{22}H_{28}F_2O_5$ (material melting at 245–247°): F, 9.26. Found: F, 8.90.

Acknowledgment.—The authors wish to thank the Physical and Analytical Chemistry Department of The Upjohn Company for analytical and spectroscopic data, and Mr. Malvin Myers, Mr. S. C. Lyster, and Mrs. F. L. Schmidt for the endocrine data.

The Synthesis of 16α-Chloro Corticoids[1]

Fred Kagan, Robert D. Birkenmeyer, and Barney J. Magerlein

The Research Laboratories, The Upjohn Company, Kalamazoo, Michigan

Received April 21, 1964

The synthesis and biological activity of a group of 16α-chloro corticoids is reported. 16α-Chloro-6α,9α-difluoroprednisolone 21-acetate is 1100 times as potent as hydrocortisone in the granuloma pouch antiinflammatory assay in rats.

In previous papers in this series[1] the synthesis and biological properties of a series of 16α-fluoro corticoids was reported. This paper records the preparation of a group of 16α-chloro-substituted prednisolone analogs and a preliminary account of their biological activity.

Although the synthesis of 16β-chlorocortisone acetate was reported in 1956, this compound showed no appreciable activity in glycogen deposition, granuloma inhibition, adrenal atrophy, thymus involution, or mineralocorticoid assays.[2] The preparation of 16α-chloro steroids bearing a fully elaborated corticoid side chain at C-17 has not been described.

Treatment of 11β-hydroxy-20β,21-oxido-1,4,16-pregnatrien-3-one (**1**) with hydrogen chloride in methylene chloride provided a mixture of 20- and 16-chloro derivatives (**2** and **3**). Purification by chromatography afforded a material identical with the 20α-chloro compound (**2**) obtained by treating 11β,16α,21-trihydroxy-1,4,17(20)-*cis*-pregnatrien-3-one 21-acetate (**13**) with thionyl chloride.[1a,b] The 16-chloro fraction, mainly **4a**, was assigned *trans*-17(20) stereochemistry by analogy with the 16-fluoro analog prepared in a like manner.[1a,b] Oxidation of crude **4a** with osmium tetroxide in the presence of N-methylmorpholine oxide–hydrogen peroxide complex[3] yielded 16α-chloroprednisolone 21-acetate (**5a**). Structure assignment was made on the basis of analytical and spectroscopic data, molecular rotation, and by analogy with 16α-fluoroprednisolone 21-acetate prepared in a similar manner.[1a,b]

Dehydration of 16α-chloroprednisolone acetate (**5a**) with N-bromoacetamide and sulfur dioxide in pyridine[4] and introduction of the 9α-fluoro substituent according to the procedure of Fried and Sabo[5] afforded 16α-chloro-9α-fluoroprednisolone 21-acetate (**9a**).

The syntheses of 6α-fluoro and 6α-methyl-16α-chloro corticoids were essentially the same as described for the 6-unsubstituted compounds with the exception that the sequences **10b** and **c** → **11b** and **c** → **12b** and **c**, were in the 3-keto-Δ^4-series in contrast to the sequence **1** → **4a** which was in the $\Delta^{1,4}$-series. Dehydrogenation of **12b** and **12c** with selenium dioxide merged the two routes at **3**.

The molecular rotation data presented in Table I for 16-halo pregnane derivatives provides the following information.

(1) The contribution to molecular rotation of a 16α-halo substituent in pregnane derivatives is consistently negative.

(2) 16β-Halo substituents generally make negative contributions to molecular rotation in pregnane derivatives; however, 16β-bromo-17α,21-dihydroxy-4-preg-

(1) (a) B. J. Magerlein, R. D. Birkenmeyer, and F. Kagan, *J. Am. Chem. Soc.*, **82**, 1252 (1960); (b) F. Kagan, B. J. Magerlein, and R. D. Birkenmeyer, *J. Org. Chem.*, **28**, 3477 (1963); (c) B. J. Magerlein, R. D. Birkenmeyer, F. H. Lincoln, and F. Kagan, *Chem. Ind.* (London), 2050 (1961).

(2) R. E. Beyler and F. Hoffman, *J. Org. Chem.*, **21**, 572 (1956).

(3) W. P. Schneider and A. R. Hanze, U. S. Patent 2,769,823 (1956).

(4) H. A. Drake, R. B. Howard, and A. E. Fonken, U. S. Patent 3,005,834 (1961).

(5) J. Fried and E. Sabo, *J. Am. Chem. Soc.*, **76**, 1455 (1954).

TABLE I

MOLECULAR ROTATION DIFFERENCES FOR 16-HALO STEROIDS

Group	Compd.	Formula	Mol. wt.	[α]D (solvent), degrees	MD	$\Delta M_D^{16\beta-16X}$	Ref.
I	Cortisol	$C_{21}H_{30}O_5$	362.5	+153 (dioxane)	+555		
	16β-Fluoro-	$C_{21}H_{29}FO_5$	380.5	+126 (dioxane)	+479	−76	*a*
II	9α-Fluorocortisol 21-acetate	$C_{23}H_{31}FO_6$	422.5	+152 (dioxane)	+642		
	16β-Fluoro-	$C_{23}H_{30}F_2O_6$	440.5	+82 (dioxane)	+361	−281	*a*
III	Prednisolone 21-acetate	$C_{23}H_{30}F_2O_6$	402.5	+114 ($CHCl_3$)	+459		
	16α-Chloro-	$C_{23}H_{29}ClO_6$	436.9	+61 ($CHCl_3$)	+267	−192	
	16α-Fluoro-	$C_{23}H_{29}FO_6$	420.5	+83 ($CHCl_3$)	+349	−110	*b*
	16β-Fluoro-	$C_{23}H_{29}FO_6$	420.5	+66 ($CHCl_3$)	+278	−181	*b*
IV	6α-Methylprednisolone 21-acetate	$C_{24}H_{32}O_6$	416.5	+95 ($CHCl_3$)	+396		
	16α-Chloro-	$C_{24}H_{31}ClO_6$	451	+49 ($CHCl_3$)	+221	−175	
	16α-Fluoro-	$C_{24}H_{31}FO_6$	434.5	+49 ($CHCl_3$)	+213	−183	*c*
V	6α-Fluoroprednisolone 21-acetate	$C_{23}H_{29}FO_6$	420.5	+102 (acetone)	+429		*d*
	16α-Chloro-	$C_{23}H_{28}ClFO_6$	455.9	+55 (acetone)	+251	−178	
	16α-Fluoro-	$C_{23}H_{28}F_2O_6$	438.5	+70 (acetone)	+307	−122	*e*
VI	6α,9α-Difluoroprednisolone 21-acetate	$C_{23}H_{28}F_2O_6$	438.5	+91 (acetone)	+399		
	16α-Chloro-	$C_{23}H_{27}ClF_2O_6$	472.9	+55 (acetone)	+260	−139	
VII	Cortisone 21-acetate	$C_{23}H_{30}O_6$	402.5	+218 ($CHCl_3$)	+877		*e*
	16β-Chloro-	$C_{23}H_{29}ClO_6$	436	+155 ($CHCl_3$)	+676	−201	*f*
	16β-Bromo-	$C_{23}H_{29}BrO_6$	481.4	+150 ($CHCl_3$)	−722	−155	*g*
VIII	4-Pregnene-3,20-dione	$C_{21}H_{30}O_2$	314.5	+192 ($CHCl_3$)	+603		*h*
	16α-Chloro-	$C_{21}H_{29}ClO_2$	349	+150 ($CHCl_3$)	+524	−79	*h*
IX	21-Hydroxy-4-pregnene-3,20-dione 21-acetate	$C_{23}H_{32}O_4$	372.5	(CHCl3)	+691		
	16α-Chloro-	$C_{23}H_{31}ClO_4$	406.9	+122 ($CHCl_3$)	+496	−195	*i*
X	17α,21-Dihydroxy-4-pregnene-3,20-dione (compound S)	$C_{21}H_{30}O_4$	346.5	+132 (dioxane)	+457		*j*
	16β-Bromo-	$C_{21}H_{29}BrO_4$	425.4	+108 (dioxane)	+459	+2	*k*
	16β-Fluoro-	$C_{21}H_{29}FO_4$	364.4	+89 (dioxane)	+324	−133	*k*
XI	17α,20,20,21-Bismethylenedioxy(20R)-4-pregnen-3-one	$C_{23}H_{32}O_4$	388.5	(dioxane)	− 74		*k*
	16β-Bromo(20R)	$C_{23}H_{31}BrO_4$	467.4	−45 (dioxane)	−210	−136	*k*
	16β-Fluoro(20R)	$C_{23}H_{31}FO_4$	406.5	+5.9 (dioxane)	+ 24	+98	*k*

[a] W. T. Moreland, R. G. Berg, D. P. Cameron, C. E. Maxwell, III, J. S. Buckley, and G. D. Laubach, *Chem. Ind.* (London), 1084 (1960). [b] *Cf.* ref. 1a and b. [c] *Cf.* ref. 1e. [d] J. A. Hogg, *et al.*, *Chem. Ind.* (London), 1002 (1958). [e] T. H. Kritchevksy, D. L. Garmaise, and T. F. Gallagher, *J. Am. Chem. Soc.*, **74**, 483 (1952). [f] R. E. Beyler and F. Hoffman, *J. Org. Chem.*, **21**, 572 (1956). [g] P. L. Julian, W. Cole, E. W. Meyer, and B. M. Regan, *J. Am. Chem. Soc.*, **77**, 4601 (1955). [h] W. Dirscherl, and F. Hanusch, *Z. Physiol. Chem.*, **252**, 49 (1938). [i] A. S. Hoffman, H. M. Kissman, and M. J. Weiss, *J. Med. Pharm. Chem.*, **5**, 962 (1962). [j] Ch. Meystre and K. Miescher, *Helv. Chim. Acta*, **34**, 2286 (1951). [k] W. T. Moreland, D. P. Cameron, R. G. Berg, and C. E. Maxwell, III, *J. Am. Chem. Soc.*, **84**, 2966 (1962).

nene-3,20-dione (group X) is an exception in which the 16β-bromo substituent appears to have little effect.

(3) The 16β-fluoro BMD derivative in group XI does not conform to the above generalizations, the contribution of the 16β-bromo substituent being strongly positive.

(4) The generalization,[6] derived for a series of 16-bromoandrostanes, which states that inversion of configuration of a 16-bromo substituent (16α → 16β) leads consistently to increased dextrorotation is not applicable to the 16-fluoro pregnanes, *e.g.*, 16-fluoroprednisolone 21-acetate showed $M_D^{16\alpha\rightarrow16\beta}$ −71° (*cf.* group III).

(5) On the basis of these observations (1 to 4) it would appear that the effect on molecular rotation of a 16-halogen substituent in steroids is very sensitive to the substituents present at C-17 thus limiting generalizations to particular series, *e.g.*, androstanes, pregnanes, BMD's., etc.

Biological Evaluation.—The introduction of a 16α-chloro group into the 21-acetates of prednisolone, 6α-methylprednisolone, and 6α-fluoroprednisolone as well as their 9α-fluoro analogs produced a marked potentiation in antiinflammatory and liver glycogen deposition activity (*cf.* Table II). The greatest effect was observed in corticoids which contained a 9α-fluoro substituent (*cf.* Table II). The most potent compound, 16α-chloro-6α,9α-difluoroprednisolone 21-acetate (**9a**), was 1100 times as potent as hydrocortisone as an antiinflammatory agent and approximately as potent in the liver glycogen deposition assay. This is one of the most potent corticoids ever reported.

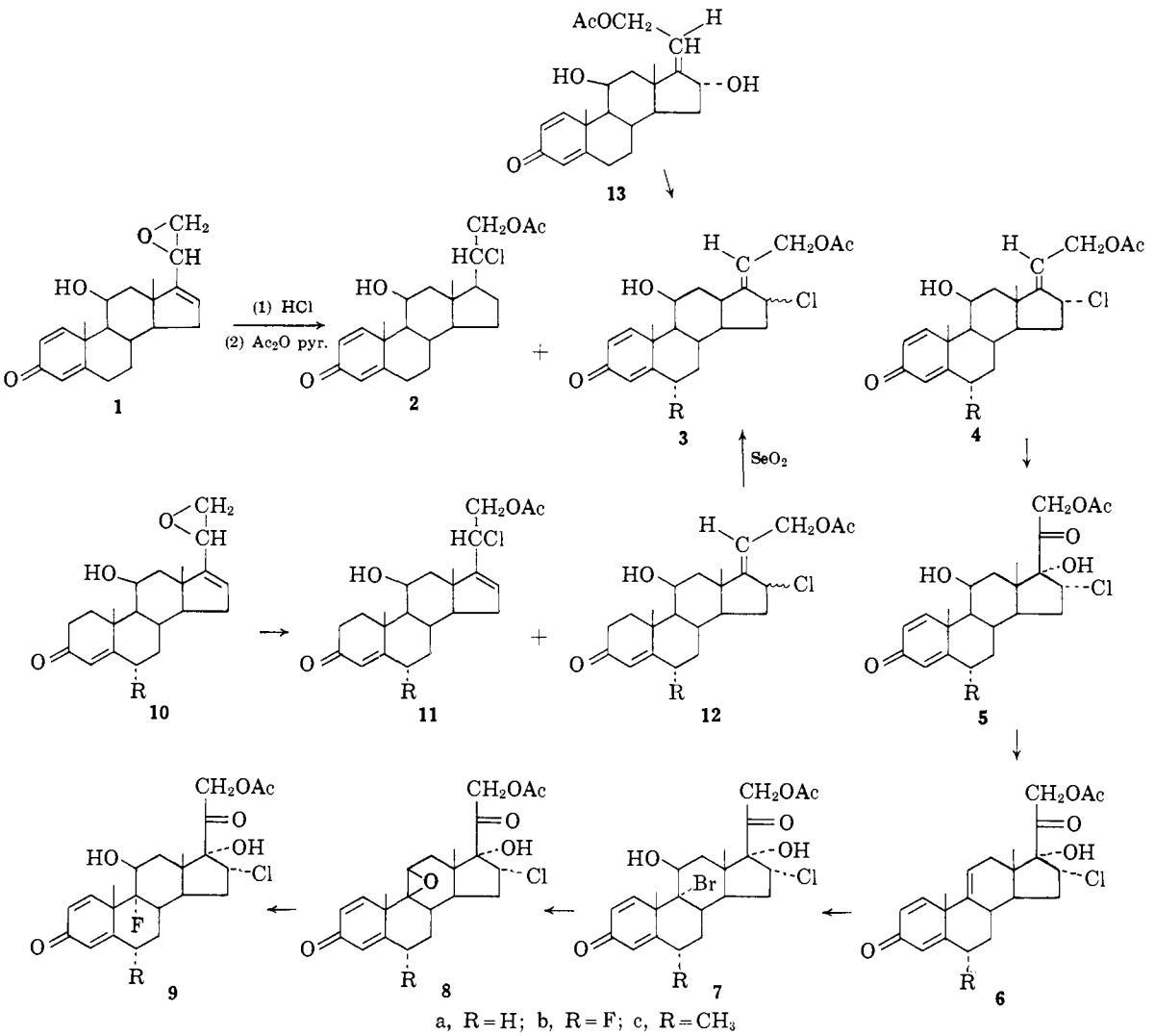
Experimental[7]

20α-Chloro-11β,21-dihydroxy-1,4,16-pregnatrien-3-one 21-Acetate (2) and 16α-Chloro-11β,21-dihydroxy-1,4,17(20)-*trans*-pregnatrien-3-one 21-Acetate (4a).—In a dry flask were placed 40 g. (0.555 mole) of tetrahydrofuran and 500 ml. of dry methylene chloride. This solution was cooled to 5°, saturated with HCl, and a solution of 6.52 g. (0.02 mole) of 11β-hydroxy-20β,21-oxido-1,4,16-pregnatrien-3-one (**1**)[16b] in 100 ml. of dry methylene chloride was added. The reaction mixture was stored at 5° for 18 hr. The solvents and excess HCl were removed under reduced pressure and the residue was acetylated with pyridine–acetic anhydride. After the usual work-up[1] the mixture of crude acetates was placed on a Florisil[8] column, eluted with 12% ace-

(6) C. W. Shoppee, R. H. Jenkins, and G. H. Summers, *J. Chem. Soc.*, 3052 (1958).

(7) Melting points were taken in capillary tubes on a Hoover melting point apparatus (Arthur H. Thomas and Co. "Uni-Melt"), calibrated against a series of standard samples. Rotations were measured in chloroform.

(8) A synthetic magnesia–silica gel, Floridin Co., Warren, Pa.



a, R = H; b, R = F; c, R = CH_3

TABLE II

EFFECT OF 16α-CHLORINATION ON BIOLOGICAL ACTIVITY

Compd. (21-acetates)	Anti-inflammatory (× hydrocortisone)	Liver glycogen deposition[c] (× hydrocortisone)
Prednisolone	3[a]	4[a]
16α-Chloro-(**5a**)	8[b]	9
16α-Chloro-9α-fluoro-(**9a**)	313[b]	360
6α-Methylprednisolone	10	15
16α-Chloro-(**5c**)	19[d]	15
6α-Fluoroprednisolone	25	100
16α-Chloro-(**5b**)	58[b]	100
16α-Chloro-9α-fluoro-(**9b**)	1100[b]	1030

[a] W. E. Dulin, L. E. Barnes, E. M. Glenn, S. C. Lyster, and E. J. Collins, *Metab. Clin. Exptl.*, **7**, 398 (1958). Note: these data are for the 21-alcohol. [b] Subcutaneous multiple dose assay [*cf.* A. Robert and J. E. Nezamis, *Acta Endocrinol*, **25**, 105 (1957)]. [c] R. Stafford, L. Barnes, B. Bowman, and M. Meinzinger, *Proc. Soc. Exptl. Biol. Med.*, **89**, 371 (1955). [d] Subcutaneous single dose assay.

tone–88% Skellysolve B[9] (v./v.), and all fractions were papergrammed on the Bush B-3 system at about 25° on Whatman No. 2 paper. Two major products were present. The least polar of these, the 20-chloro isomer (2.0 g., 24% column yield) was recrystallized from acetone–Skellysolve B to a melting point of 162–164°, $[\alpha]_D$ +63°, λ_{max}^{EtOH} 242 mμ (ε 15,250). The infrared spectrum, $[\alpha]_D$, melting point, and papergram behavior indicated that this material was identical with 20α-chloro-11β,21-dihydroxy-1,4,16-pregnatrien-3-one 21-acetate (**2**) obtained by treating 11β,16α,21-trihydroxy-1,4,17(20)-*cis*-pregnatrien-3-one 21-acetate (**13**)[1b] with thionyl chloride.

Anal. Calcd. for $C_{23}H_{29}ClO_4$: C, 68.22; H, 7.22; Cl, 8.76. Found: C, 68.24; H, 7.44; Cl, 8.85.

The more polar fraction, the 16-chloro product (0.8 g., 10% column yield), was recrystallized from acetone and used in the preparation of 16α-chloroprednisolone acetate without further purification. Recovery from the latter reaction of unchanged starting material afforded a purified sample of **4a**. An analytical sample, recrystallized from acetone, melted at 187–189°, $[\alpha]_D$ −37°, λ_{max}^{EtOH} 241.5 mμ (ε 16,550).

Anal. Calcd. for $C_{23}H_{29}ClO_4$: C, 68.22; H, 7.22; Cl, 8.76. Found: C, 67.81; H, 7.07; Cl, 8.75.

16α-Chloro-11β,17α,21-trihydroxy-1,4-pregnadiene-3,20-dione 21-Acetate or 16α-Chloroprednisolone Acetate (5a).—In a 100-ml. flask were placed 445 mg. (1.1 mmoles) of **4a**, 10 mg. of osmium tetroxide, 30 ml. of *t*-butyl alcohol, 0.75 ml. of pyridine, and 1.35 ml. of a 2 *N* solution of N-methylmorpholine oxide–hydrogen peroxide.[3] This mixture was stirred at about 25° for 5 hr. About 25 ml. of a freshly prepared solution of 1% sodium hydrosulfite was then added and stirred for 5 min., and the reaction mixture was filtered through a Magnesol[10] mat. The *t*-butyl alcohol was evaporated from the filtrate under vacuum at a bath temperature of about 35°. The residue was taken up in about 100 ml. of methylene chloride, washed with two 50-ml. portions of dilute HCl, then twice with 50-ml. portions of water, filtered, and evaporated under vacuum, yielding 400 mg. of crude product. This material was dissolved in about 20 ml.

(9) A saturated hydrocarbon fraction, b.p. 60–71°, Skelly Oil Company, Kansas City, Mo.

(10) Synthetic magnesium silicate, Waverly Chemical Co., Matuaronek, N. Y.

of methylene chloride and placed on a column of 50 g. of Florisil and eluted with 12% acetone–88% Skellysolve B (v./v.). The progress of the purification was monitored by paper chromatography (FBF system).[11] Judicious combination of fractions and recrystallization from ethyl acetate afforded material melting at 240–242°. This material gave positive Beilstein and Tollens tests and its infrared absorption spectrum was consistent with the proposed structure. A subsequent preparation gave larger amounts of product, whose melting point and infrared spectrum were identical with that of the compound described above; this latter preparation had $[\alpha]D$ +61°, λ_{max}^{EtOH} 243 mμ (ε 15,160).

Anal. Calcd. for $C_{23}H_{29}ClO_5$: C, 63.22; H, 6.69; Cl, 8.15. Found: C, 63.02; H, 6.56; Cl, 8.06.

16α-Chloro-17α,21-dihydroxy-1,4,9(11)-pregnatriene-3,20-dione 21-Acetate (6a).—To a stirred solution of 590 mg. of **5a** in 8 ml. of pyridine was added 316 mg. of N-bromoacetamide. The solution was stirred at about 25° for 20 min. and then cooled to 10° and maintained at this temperature while saturating with SO_2 by passing a stream of the gas over the surface of the stirred reaction mixture. Water (100 ml.) was added and the solid precipitate was collected on a filter, washed with water, and dried. This crude product was purified *via* chromatography on 50 g. of Florisil. The purified product, 474 mg., was eluted with 12% acetone–88% Skellysolve B (v./v.) and was used in the next step without further purification.

16α-Chloro-9α-bromo-11β,17α,21-trihydroxy-1,4-pregnadiene-3,20-dione 21-Acetate (7a).—To a stirred solution of 474 mg. of **6a** in 32 ml. of *t*-butyl alcohol and 8 ml. of methylene chloride was added a mixture of 1.45 ml. of 70% perchloric acid in 10 ml. of water and a solution of 186 mg. of N-bromoacetamide in 6 ml. of *t*-butyl alcohol. After stirring for 15 min. at about 25°, a solution of 266 mg. of sodium sulfite in 15 ml. of water was added, the mixture was concentrated under reduced pressure to about 20 ml., diluted with 100 ml. of water, and filtered. The dried, white precipitate weighed 594 mg. This material was used in the next step without further purification.

16α-Chloro-9β,11β-oxido-17α,21-dihydroxy-1,4-pregnadiene-3,20-dione 21-Acetate (8a).—A mixture of 594 mg. of crude bromohydrin (**7a**), 750 mg. of potassium acetate, and 50 ml. of acetone was stirred and heated at reflux for 20 hr. The mixture was evaporated to dryness under reduced pressure and the residue was extracted with methylene chloride. The extract was concentrated to about 20 ml., poured onto a chromatographic column made up of 60 g. of Florisil, and the product was eluted with 12% acetone–88% Skellysolve B (v./v.) to yield 368 mg. of the desired oxide.

16α-Chloro-9α-fluoro-11β,17α,21-trihydroxy-1,4-pregnadiene-3,20-dione 21-Acetate (9a).—To 11.9 g. of HF contained in a polyethylene bottle and cooled in a Dry Ice–alcohol bath was added 21 ml. of cold tetrahydrofuran and then a cold solution of 368 mg. of **8a** in 20 ml. of methylene chloride. The mixture was stirred at about 5° for 20 hr. and then poured cautiously into an ice-cold solution of 57 g. of Na_2CO_3 in 1 l. of water. The aqueous solution was extracted with four 100-ml. portions of methylene chloride, and the combined extracts were dried and evaporated to about 20 ml. This crude solution was poured onto a chromatographic column containing 50 g. of Florisil and the product was eluted with 15% acetone–85% Skellysolve B (v./v.). The major chromatographic fractions were combined and recrystallized from ethyl acetate to yield 201 mg. [32.8% yield from 16α-chloroprednisolone acetate (**5a**)]. The product melted at 246–247° and had $[\alpha]D$ +61°, λ_{max}^{EtOH} 238 mμ (ε 15,750).

Anal. Calcd. for $C_{23}H_{28}ClFO_6$: C, 60.72; H, 6.20; Cl, 7.79; F, 4.18. Found: C, 60.46; H, 6.15; Cl, 7.75; F, 4.18.

16ξ-Chloro-6α-fluoro-11β,21-dihydroxy-4,17(20)-*trans*-pregnadien-3-one 21-Acetate (12b) and 20α-Chloro-6α-fluoro-11β,21-dihydroxy-4,16-pregnadien-3-one 21-Acetate (11b).—The reaction of 6α-fluoro-11β-hydroxy-20β,21-oxido-4,16-pregnadien-3-one (**10b**)[11b] with HCl was carried out in the same manner as described for the preparation of **2** and **3**. Two main products were again obtained after chromatography, the least polar (34% column yield) being the 20-chloro isomer and the more polar (23% column yield) being the 16-chloro isomer. A portion of this latter material was recrystallized from acetone to m.p. 164–166°, $[\alpha]D$ −5°, λ_{max}^{EtOH} 235 mμ (ε 16,650) and 216 mμ (sh) (ε 13,200).

Anal. Calcd. for $C_{23}H_{30}ClFO_4$: C, 65.01; H, 7.12; Cl, 8.34; F, 4.47. Found: C, 65.37; H, 7.17; Cl, 8.88; F, 4.51.

16α-Chloro-6α-fluoro-11β,21-dihydroxy-1,4,17(20)-*trans*-pregnatrien-3-one 21-Acetate (4b).—A mixture of 9.5 g. of **12b**, 4.3 g. of selenium dioxide, 1.45 ml. of pyridine, and 265 ml. of *t*-butyl alcohol was heated at reflux for 18 hr. After evaporation to dryness under vacuum, the residue was dissolved in methylene chloride, washed with dilute HCl and water, and chromatographed over Florisil, eluting with 12% acetone–88% Skellysolve B. An 88% yield of column fractions was obtained which was used in the preparation of 16α-chloro-6α-fluoroprednisolone 21-acetate (**5b**). From this latter reaction a purified sample of **4b** was recovered. An analytical sample recrystallized from ethyl acetate melted at 175–178°, $[\alpha]D$ −37°, λ_{max}^{EtOH} 242 mμ (ε 17,250).

Anal. Calcd. for $C_{23}H_{28}ClFO_4$: C, 65.32; H, 6.67; Cl, 8.38; F, 4.49. Found: C, 65.36; H, 6.55; Cl, 8.43; F, 4.29.

16α-Chloro-6α-fluoro-11β,17α,21-trihydroxy-1,4,pregnadiene-3,20-dione 21-Acetate (5b).—This reaction was carried out in the same manner as described for the preparation of 16α-chloroprednisolone acetate (**5a**). A 12% column yield of product was obtained which after recrystallization from ethyl acetate, melted at 286° $[\alpha]D$ (acetone) +55°, λ_{max}^{EtOH} 241 mμ (ε 16,750).

Anal. Calcd. for $C_{23}H_{28}ClFO_6$: C, 60.72; H, 6.20; Cl, 7.79; F, 4.18. Found: C, 60.45; H, 6.04; Cl, 7.87; F, 3.90.

16α-Chloro-6α,9α-difluoro-11β,17α,21-trihydroxy-1,4-pregnadiene-3,20-dione 21-Acetate (9b).—The sequence of reactions **5b → 6b → 7b → 8b → 9b** was carried out in the same manner as in the 6-unsubstituted series which yielded 16α-chloro-9α-fluoroprednisolone 21-acetate (**9a**). A 27% over-all yield for the four steps to **9b** was obtained. The column fractions after recrystallization from ethyl acetate melted at 291°, $[\alpha]D$ +55° (acetone), λ_{max}^{EtOH} 238 (ε 17,000).

Anal. Calcd. for $C_{23}H_{27}ClF_2O_6$: C, 58.41; H, 5.76; Cl, 7.50; F, 8.04. Found: C, 58.49; H, 5.90; Cl, 7.55; F, 7.73.

16ξ-Chloro-6α-methyl-11β,21-dihydroxy-4,17(20)-*trans*-pregnadien-3-one 21-Acetate (12c) and 20α-Chloro-6α-methyl-11β,21-dihydroxy-4,16-pregnadien-3-one 21-Acetate (11c).—This reaction was carried out in the same manner as described for the preparation of **2** and **3**. Two main products were again obtained after chromatography, the least polar (30% column yield) being the 20-chloro isomer. The more polar material (15% column yield), the 16-chloro fraction, was used in the preparation of **4c** with no further purification.

16α-Chloro-6α-methyl-11β,21-dihydroxy-1,4-17(20)-*trans*-pregnatrien-3-one 21-Acetate (4c).—This reaction was carried out in the same manner as described for the preparation of "16α-chloro-6α-fluorotrienediol 21-acetate" (**4b**). The crude product was not chromatographed, but used without further purification in the preparation of 16α-chloro-6α-methylprednisolone 21-acetate (**5c**). A purified sample of the starting material (**4c**) was recovered from this reaction. An analytical sample recrystallized from ethyl acetate melted at 191–192°, $[\alpha]D$ −45°, λ_{max}^{EtOH} 242 mμ (ε 15,600).

Anal. Calcd. for $C_{24}H_{31}ClO_4$: C, 68.80; H, 7.46; Cl, 8.46. Found: C, 68.57; H, 7.38; Cl, 8.58.

16α-Chloro-6α-methyl-11β,17α,21-trihydroxy-1,4-pregnadiene-3,20-dione 21-Acetate (5c).—This reaction was carried out in the same manner as described for the preparation of 16α-chloroprednisolone acetate (**5a**). A small amount of product was obtained which could not be crystallized. Evaporation of an ethyl acetate solution gave an amorphous material softening at 227–230°, $[\alpha]D$ +49°, λ_{max}^{EtOH} 243 mμ (ε 14,100).

Anal. Calcd. for $C_{24}H_{31}ClO_6$: C, 63.92; H, 6.93; Cl, 7.86. Found: C, 64.41; H, 7.04; Cl, 7.15.

Acknowledgment.—The authors wish to thank the Physical and Analytical Chemistry Department of The Upjohn Company for analytical and spectroscopic data, and Mr. Malvin Myers, Mr. S. C. Lyster, and Mrs. F. L. Schmidt for the endocrine data.

(11) A. Zaffaroni, R. B. Burton, and E. H. Keutmann, *Science*, **111**, 6 (1950).