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STEROIDS—CXXI[1] SYNTHESIS OF HALOGENATED STEROID HORMONES

6α-FLUORO CORTICAL HORMONES A NEW CLASS OF POWERFUL CORTICOIDS[2]

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Abstract—Incubation of 6α-fluoro Reichstein's Compound "S" (I) and its Δ^1-analog (IV) with bovine adrenals followed by acetylation led to 6α-fluorohydrocortisone acetate (II) and 6α-fluoroprednisolone acetate (III) respectively. Selenium dioxide oxidation of II also afforded III. Chromium trioxide oxidation of II and III gave 6α-fluorocortisone acetate (VIIa) and 6α-fluoroprednisone acetate (VIIIa) respectively. An alternate, all-chemical synthesis of 6α-fluorocortisone acetate (VIIa) from cortisone acetate (V) is described.

Dehydration of 6α-fluorohydrocortisone acetate gave 6α-fluoro-$\Delta^{9(11)}$-dehydro-Compound "S" (XIV). Formation of the corresponding 9β,11β-epoxide (XV) and reaction with hydrogen fluoride then gave 6α,9α-difluorohydrocortisone acetate (XVI) which afforded the prednisolone analog (XVII) upon oxidation with selenium dioxide.

IN 1954 Fried and Sabo[3] reported the synthesis of the first fluorinated steroid hormone, 9α-fluorohydrocortisone. This compound was remarkable in that it exhibited approximately ten times the liver glycogen activity of hydrocortisone in the adrenalectomized rat and approximately twenty times the glucocorticoid activity of hydrocortisone in man.[4] In addition it had mineralocorticoid activity equal to that of aldosterone.[4]

These findings stimulated a considerable interest in fluorinated steroid hormones which was increased when some 12α-fluoro-[5] and 21-fluoro steroid hormones[6] were shown to exhibit more favorable biological activities as compared to the non-fluorinated parent compounds.

In view of these remarkable biological findings it seemed desirable to investigate the synthesis of steroid cortical hormone analogs with fluorine substituents in positions other than C-9, C-12 and C-21.

Recently we described the synthesis of several 6α- and 6β-fluoro steroid hormones[1,7] and in this paper we wish to report an extension of this work to the synthesis of a series of 6α-fluoro-[2] and 6α,9α-difluoro-cortical hormones. These compounds represent a new class of highly active cortical hormones.

[1] Part CXX: A. Bowers, L. C. Ibáñez and H. J. Ringold, *Tetrahedron* **7**, 138 (1959).
[2] A preliminary announcement of part of this work has been published: A. Bowers and H. J. Ringold, *J. Amer. Chem. Soc.* **80**, 4423 (1958). This work was also presented in part by A. B. at the Steroids and Natural Products Section of the Gordon Research Conference, August 1958.
[3] J. Fried and E. F. Sabo, *J. Amer. Chem. Soc.* **76**, 1455 (1954); *Ibid.* **79**, 1130 (1957).
[4] For a full discussion of the biological and clinical effects of a 9α-fluorine atom cf. J. Fried and A. Borman, *Vitamins and Hormones* **16**, 303 (1958).
[5a] J. E. Herz, J. Fried and E. F. Sabo, *J. Amer. Chem Soc.* **78**, 2017 (1956); [b] D. Taub, R. D. Hoffsommer and N. L. Wendler, *Ibid.* **78**, 2912 (1956).
[6a] P. Tannhauser, R. J. Pratt and E. V. Jensen, *J. Amer. Chem. Soc.* **78**, 2658 (1956); [b] J. E. Herz, J. Fried, P. Grabowich and E. F. Sabo, *Ibid* **78**, 4812 (1956).
[7] A. Bowers and H. J. Ringold, *Tetrahedron* **3**, 14 (1958).

10A—(4 pp.)

In view of the availability of 6α-fluoro Reichstein's Compound "S" (6α-fluoro-Δ^4-pregnen-17α,21-diol-3,20-dione)[1] (I) and the reported transformation of Compound "S" into hydrocortisone by biochemical methods,[8,9] a plausible route to 6α-fluorohydrocortisone appeared to be by 11β-hydroxylation of 6α-fluoro-Compound "S" (I). It was considered unlikely that the fluorine atom at C-6 would interfere markedly with enzymatic hydroxylation at C-11.

Indeed, incubation of 6α-fluoro-Compound "S" (I) with bovine adrenals[9,10] from freshly killed animals led in 65 per cent yield to 6α-fluorohydrocortisone, isolated as the C-21-monoacetate (II).[11] These two conversions are the first instances of adrenal incubation of compounds containing halogen substituents.

Selenium dioxide[12] oxidation of II smoothly afforded 6α-fluoroprednisolone acetate (III). The latter compound was also prepared by the adrenal incubation of Δ^1-dehydro-6α-fluoro-Compound "S"[1] (IV) followed by acetylation.

A rigorous proof that compounds II and III have the assigned structures is presented in the sequel.

6α-Fluorocortisone acetate (Va) and 6α-fluoroprednisone acetate (VIa) were then obtained by the respective oxidations of II and III with 8 N chromic acid in acetone solution.[13]

An alternate, completely chemical route to 6α-fluorocortisone acetate was then investigated. Previous work[1] has shown that 6-fluoro-Δ^4-3-ketones can be prepared from the parent Δ^4-3-ketones by boron trifluoride etherate cleavage of their derived 3-cycloethylene ketal 5α,6α-epoxides followed by treatment with anhydrous hydrogen chloride.

However in view of the known instability of 17α-hydroxy-20-ketones (with or without a C-21-hydroxyl group) to some types of Lewis acids, for example, aluminum isopropoxide[14a,b] or boron trifluoride in acetic acid[14b,15a–c] readily induce D-homo rearrangement, it was necessary to establish the stability of this ketol system to an excess of boron trifluoride in an ether–benzene mixture for 3 hr at room

[8] Several groups have utilized an 11β-hydroxylating micro-organism, cf. [a] D. R. Collingsworth, M. P. Brunner and W. J. Haines, *J. Amer. Chem. Soc.* **74**, 2381 (1952); [b] P. W. O'Connel, K. M. Mann, E. D. Neilson and F. R. Hanson, *J. Appl. Microbiol.* **3**, 16 (1955); [c] G. M. Shull and D. A. Kita, *J. Amer. Chem. Soc.* **77**, 763 (1955).

[9] An alternative approach to 11β-hydroxylation has been via incubation with bovine adrenals: A. Zaffaroni, H. J. Ringold, G. Rosenkranz, F. Sondheimer, G. H. Thomas and C. Djerassi, *J. Amer. Chem. Soc.* **80**, 6110 (1958).

[10] The formation of 6α-chlorohydrocortisone by the adrenal incubation of 6α-chloro-Compound "S" has been reported recently, cf. H. J. Ringold, O. Mancero, C. Djerassi, A. Bowers, E. Batres, H. Martinez, E. Necoechea, J. Edwards, M. Velasco, C. C. Campillo and R. I. Dorfman, *J. Amer. Chem. Soc.* **80**, 6464 (1958).

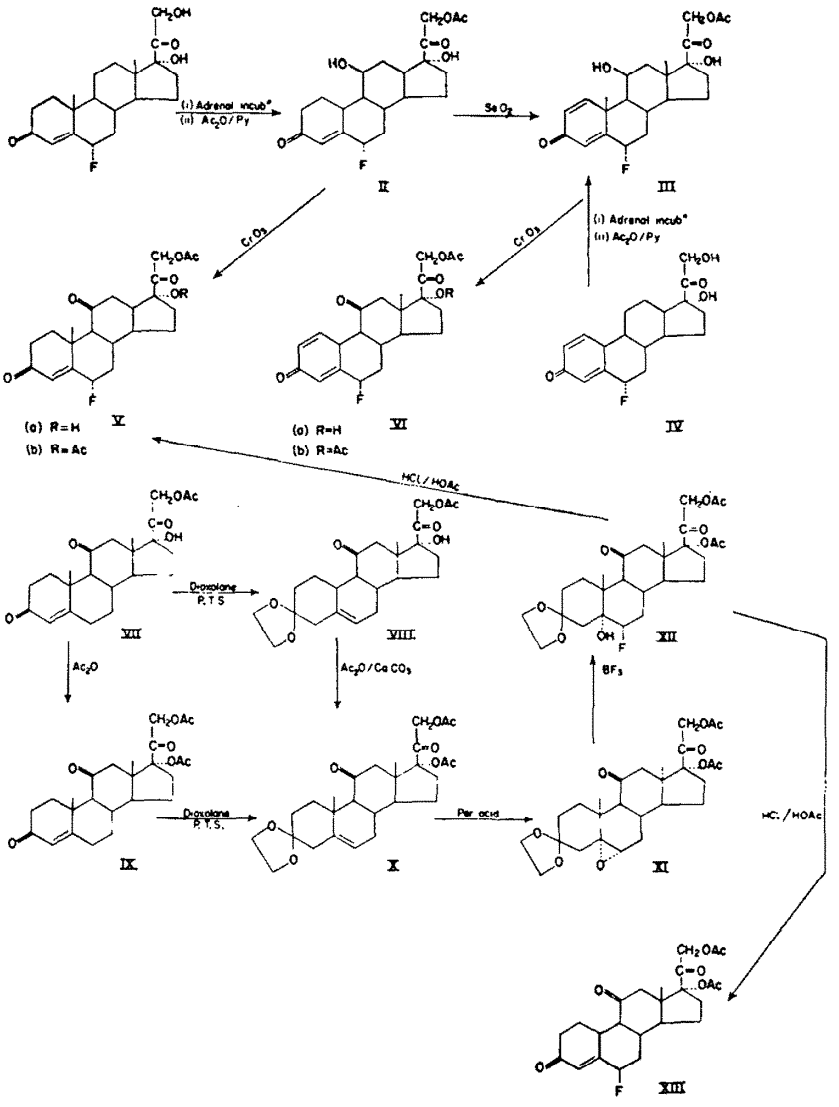
[11] Simultaneous with our earlier communication[9] a preliminary announcement from the Upjohn Laboratories reported the synthesis of a series of 6α-fluoro- and 6α,9α-difluorocortical hormones by an independent method; J. A. Hogg, G. B. Spero, J. L. Thompson, B. J. Magerlein, W. P. Schneider, D. H. Peterson, O. K. Sebek, H. C. Murray, J. C. Babcock, R. L. Pederson and J. A. Campbell, *Chem. & Ind.* 1002 (1958).

[12a] H. J. Ringold, G. Rosenkranz and F. Sondheimer, *J. Org. Chem.* **21**, 239 (1956); [b] Ch. Meystre, H. Frey, W. Voser and A. Wettstein, *Helv. Chim. Acta* **39**, 734 (1956); [c] S. A. Szpilfogel, T. A. P. Posthumus, M. S. De Winter and D. A. van Dorp, *Rec. Trav. Chim.* **75**, 457 (1956); [d] K. Florey and A. R. Restivo, *J. Org. Chem.* **22**, 406 (1957).

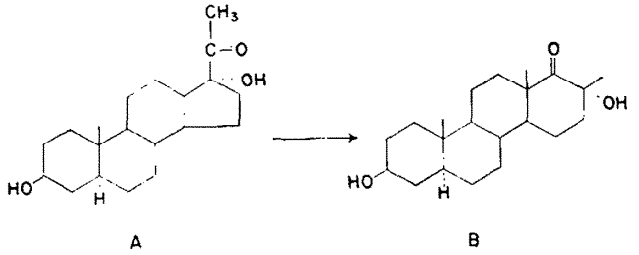
[13a] K. Bowden, I. M. Heilbron, E. R. H. Jones and B. C. L. Weedon, *J. Chem. Soc.* **39**, (1946); [b] A. Bowers, T. G. Halsall, E. R. H. Jones and A. J. Lemin, *Ibid.* 2548 (1953).

[14a] H. E. Stavely, *J. Amer. Chem. Soc.* **63**, 3127 (1941); [b] D. K. Fukushima, S. Dobriner, M. S. Heffler, T. H. Kritchevsky, F. Herling and G. Roberts, *Ibid.* **77**, 6585 (1955).

[15a] C. W. Shoppee and D. A. Prins, *Helv. Chim. Acta* **26**, 201 (1943); [b] N. L. Wendler and D. Taub, *Chem. & Ind.* 505 (1955); [c] N. L. Wendler, D. Taub, D. K. Fukushima and S. Dobriner, *Ibid.* 1259 (1955).



temperature. Although these conditions are much milder than any reported previously[14,15] D-homo rearrangement does occur.



Compound L (allopregnane-3β,17α-diol-20-one) (A) for example, afforded 3β,17α-dihydroxy-17β-methyl-D-homoandrostane-17a-one (B)[14b] in 51 per cent yield, together with a by-product m.p. 196–197°, $[\alpha]_D$ + 118° in 16 per cent yield. The by-product exhibited bands in the infrared at 339 cm^{-1}, 1700 cm^{-1} and 1683 cm^{-1}.

However, 17α-acetoxy-20-ketones are known to be stable to Lewis acids.[16] Thus a desirable precursor for the preparation of 6α-fluorocortisone acetate appeared to be the ketal-epoxide diacetate (XI) and two alternate routes to XI from cortisone acetate (VII) were investigated.

The room temperature acetylation of cortisone acetate with acetic anhydride and acetic acid in the presence of *p*-toluene-sulfonic acid is known to afford cortisone diacetate[16a,17] but we were not able to obtain better than a 38 per cent yield of the diacetate (IX) by this method. A similar yield was obtained by acetylating cortisone acetate with acetic anhydride under reflux for 24 hr in a nitrogen atmosphere.[18] However ketalization of IX by the dioxolane method[19] did lead to the corresponding 3-cycloethylene ketal (X), albeit in only 53 per cent yield. A superior approach to X was then developed via cortisone acetate-3-cycloethylene ketal (VIII).[20] This compound has been prepared from cortisone acetate (VII) in 94 per cent yield[20b,21] by the dioxolane method[19] and it remained only to acetylate at C-17 with preservation of the acid labile ketal system. This was carried out by heating a solution of the ketal monoacetate (VIII) in acetic anhydride under reflux for 24 hr in a nitrogen atmosphere in the presence of finely divided calcium carbonate. Under these conditions a 55 per cent yield of the ketal diacetate (X) was obtained. Epoxidation of X with monoperphthalic acid then led in high yield to the α-epoxide (XI), which underwent fission with boron trifluoride[1,7,22] in anhydrous benzene–ether solution to afford the 6β-fluoro-5α-hydroxy fluorohydrin (XII). Anhydrous hydrogen chloride treatment of XII for 25 min[1] gave 6β-fluorocortisone diacetate (XIII). Prolongation of the reaction time to 24 hr afforded 6α-fluorocortisone diacetate (Vb). The molecular rotations and ultraviolet light absorption properties of XIII and Vb were in full accord with their assigned structures.[23] It is noteworthy that the time for complete inversion of the 6β-fluorine atom in the presence of the 11-keto group is greater than that of an 11-desoxy-6β-fluoro-Δ^4-3-ketone.[24]

Selenium dioxide oxidation[12] of 6α-fluorocortisone diacetate (Vb) smoothly afforded 6α-fluoroprednisone diacetate (VIb). Mild alkaline hydrolysis of Vb in a nitrogen atmosphere followed by room temperature acetylation with acetic anhydride and pyridine led to 6α-fluorocortisone acetate (Va) identical in every respect with the product obtained by the chromic acid oxidation of 6α-fluorohydrocortisone acetate

[16a] R. B. Turner, *J. Amer. Chem. Soc.* **75**, 3489 (1953); [b] H. J. Ringold, B. Loken, G. Rosenkranz and F. Sondheimer, *Ibid.* **78**, 816 (1956).

[17] In the absence of acetic acid the major product from this reaction is $\Delta^{3,5}$-pregnadiene-3,17α,21-triol-11,20-dione triacetate, cf. A. Bowers, L. C. Ibáñez and H. J. Ringold, *J. Amer. Chem. Soc.* **81**, 3707 (1959).

[18] Huang-Minlon, E. Wilson, N. L. Wendler and M. Tishler, *J. Amer. Chem. Soc.* **74**, 5394 (1952).

[19] H. Dauben, B. Loken and H. J. Ringold, *J. Amer. Chem. Soc.* **76**, 1359 (1954).

[20a] R. Antonucci, S. Bernstein, M. Heller, R. Lenhard, R. Littell and J. H. Williams, *J. Org. Chem.* **18**, 70 (1953); [b] F. Sondheimer, O. Mancera and G. Rosenkranz, *J. Amer. Chem. Soc.* **76**, 5020 (1954).

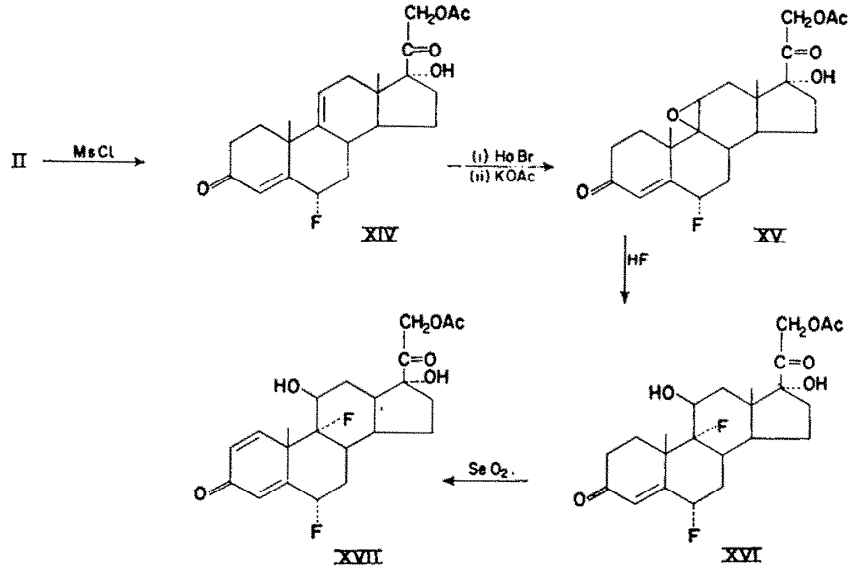
[21] The excellent yield in this reaction may be due to the highly insoluble nature of VIII, the ketal precipitating as the reaction proceeds. The ketal diacetate (X), however, is soluble in the reaction mixture and it could only be isolated in 53% yield from IX.

[22] H. B. Henbest and T. I. Wrigley, *J. Chem. Soc.* 4765 (1957).

[23] For a discussion of the characteristic differences of the ultraviolet light absorption spectra and molecular rotations between epimeric C-6-fluoro-Δ^4-3-ketones.[1]

[24] The reported epimerizations of 6β-fluoroprogesterone[7] and 6β-fluoro-Compound "S" diacetate.[1]

(II). This reaction sequence affords unambiguous proof that the adrenal incubation of both I and IV introduced a C-11 hydroxyl group. The 11β-stereochemistry of the hydroxyl group follows from its method of introduction[25] and its inertness to acetylation with acetic anhydride and pyridine[26] (see Experimental section).



In view of the known effect of a 9α-fluorine atom on biological activity[3,4] it was of considerable interest to prepare 6α,9α-difluorohydrocortisone acetate (XVI) and its Δ^1-analog (XVII). The introduction of the 9α-fluorine atom into 6α-fluorohydrocortisone (II) was carried out using essentially the method of Fried and Sabo.[3] Treatment of II with methane sulfonyl chloride in pyridine-dimethyl formamide at 80° for 2 hr[27] led in good yield to 6α-fluoro-$\Delta^{9(11)}$-Compound "S" (XIV). Conversion of XIV to the 9β,11β-epoxide (XV) followed the usual procedure of treatment with hypobromous acid to afford the 9α-bromo-11β-hydroxybromohydrin which without purification was cylized to the β-epoxide (XV) with potassium acetate in acetone. Finally, rupture of the epoxide with hydrogen fluoride by the Merck modification[28] of Fried and Sabo's original method[3] gave 6α,9α-difluorohydrocortisone acetate (XVI). Selenium dioxide[14] oxidation of XVI afforded 6α,9α-difluoroprednisolone (XVII).

Biological activities

As can be seen from Table 1, the introduction of a 6α-fluorine atom increases anti-inflammatory and thymolytic activities by a factor of from five to ten.[29] VIIa exhibited neither sodium retention nor sodium excretion properties while compounds

[25] Adrenal incubation of all ring C desoxy steroids reported to date has always resulted in 11β-hydroxylation.[9,10]

[26] 11α-Hydroxy Compound "S" (epi-hydrocortisone) is readily acetylated at C-11 under these conditions; cf. [a] J. Romo, A. Zaffaroni, J. Hendrichs, G. Rosenkranz, C. Djerassi and F. Sondheimer, *Chem. & Ind.* 783 (1952); [b] J. Romo, G. Rosenkranz, C. Djerassi and F. Sondheimer, *J. Amer. Chem. Soc.* **75**, 1277 (1953).

[27] J. Fried, K. Florey, E. F. Sabo, J. E. Herz, A. R. Restivo, A. Borman and F. M. Singer, *J. Amer. Chem. Soc.* **77**, 4181 (1955). We are very grateful to Dr. J. Fried for supplying us with the details of this method prior to publication.

[28] R. F. Hirschmann, R. Miller, J. Wood and R. E. Jones, *J. Amer. Chem. Soc.* **78**, 4956 (1956).

II, III and VIIIa were sodium excretors.[29] In contrast to the very high sodium retaining properties of 9α-fluorohydrocortisone acetate[3] and 9α-fluoroprednisolone acetate[30] the corresponding 6α-fluoro analogs XVI and XVII were only mild sodium retainers.[29]

TABLE 1. BIOLOGICAL ACTIVITIES OF 6α-FLUORO AND 6α,9α-DIFLUORO CORTICOIDS

Compound	Anti-inflammatory activity[a]	Thymolytic activity[a]
6α-Fluorocortisone acetate (VIIa)	10	6
6α-Fluorohydrocortisone acetate (II)	10	8
6α-Fluoroprednisone acetate (VIIIa)	20	23
6α-Fluoroprednisolone acetate (III)	20	62
6α,9α-Difluorohydrocortisone acetate (XVI)	50	100
6α,9α-Difluoroprednisolone acetate (XVII)	200	200

[a] Anti-inflammatory (cotton pellet implant) and thymolytic activities in immature adrenalectomized rats, oral route, hydrocortisone acetate = 1.

EXPERIMENTAL

For general directions see the preceding paper.

Boron trifluoride-etherate treatment of compound L

Boron trifluoride-etherate (1·0 cc) was added to a suspension of compound L (allopregnane-3β,17α-diol-20-one) (1·0 g) in dry benzene (100 cc) and ether (100 cc) at room temp. After 3 hr at room temp. (complete solution after 15 min) the solution was washed with water to neutrality, dried, evaporated to 50 cc and then adsorbed onto neutral alumina. Elution with benzene–ether (95 : 5; 400 cc) afforded a product (160 mg) m.p. 193–196°, raised by several crystallizations from acetone to 196–197°, $[\alpha]_D$ +120°. It exhibited no selective absorption in the ultraviolet. λ_{max}^{KBr} 3390, 1700 and 1685 cm.$^{-1}$. (Found: C, 78·70; H, 10·40%).

Further elution with benzene–ether (80 : 20; 900 cc) afforded 3β,17α-dihydroxy-17β-methyl-D-homoandrostane-17a-one (510 mg) m.p. 172–176°, raised by several crystallizations to 181–182°, $[\alpha]_D$ +28°. Lit[14b] reports m.p. 182–182·5°. $[\alpha]_D$ +32·9°.

6α-Fluorohydrocortisone acetate (II)

The following solutions were used for the incubation medium:

(a) *Saline solution.* A mixture of: 200 cc of 4·5% sodium chloride, 8 cc of 5·75% potassium chloride and 2 cc of 19·1% magnesium sulfate was diluted to 1 l.

[29] The biological assays were carried out by Dr. R. I. Dorfman, at the Worcester Foundation for Experimental Biology and Endocrine Laboratories, Madison, Wisconsin. The salt assays were carried out in adrenalectomized rats without sodium load, subcutaneous route.

[30a] R. F. Hirschmann, R. Miller, R. E. Beyler, L. H. Sarett and M. Tishler, *J. Amer. Chem. Soc.* 77, 3166 (1955); [b] J. Fried, K. Florey, E. F. Sabo, J. E. Herz, A. R. Restivo, A. Borman and F. M. Singer, *Ibid.* 77, 4181 (1955).

(b) *Buffer solution.* (Phosphate buffer solution, 0·1 M, pH 7·4). Consists of a mixture of 850 cc of 0·1 M K_2HPO_4 (17·42 g/l.) and 150 cc of 0·1 M NaH_2PO_4 (13·8 g/l.).

(c) *Sodium fumarate solution.* Fumaric acid (17·4 g) and sodium hydroxide (12·0 g) were dissolved in water (approx 500 cc) and the pH of the mixture was adjusted to 7·0 with a potentiometer by the addition of small amounts of fumaric acid or sodium hydroxide. The solution was then diluted to 1000 cc with distilled water.

The incubation medium was made by mixing 1000 cc of solution (a), 110 cc of solution (b) and 270 cc of solution (c). For the incubation there were used 2 parts of medium for 1 part of glands.

Procedure. The bovine adrenal glands were obtained from the slaughter house just before use and kept in ice during the time of transportation to the laboratory, covered with 1% sodium chloride solution. The superficial fat was removed prior to use.

Five kilograms of the clean glands were ground in a meat grinder and suspended in 10 l. of the aforementioned incubation medium. 6α-Fluoro-Compound "S" (I) (5 g) in propylene glycol (40 cc) was then added and the mixture was stirred for 3 hr at 22°. Acetone (30 l.) was then added and the suspension stirred for 2 hr and filtered. The residue was extracted with a further 5 l. of hot acetone and the combined filtrates were concentrated *in vacuo* at 30–35° until the distillate was almost free of acetone. The residual solution was then extracted with hexane (5 l.) to remove fat and then with methylene dichloride (40 l.) (10 × 4 l.). The methylene dichloride was removed at 30° *in vacuo* and the residue was dissolved in pyridine (50 cc) containing acetic anhydride (5·0 cc) and kept at room temp for 18 hr (alternatively it was heated at 95° for 45 min). Addition of ice water afforded a product which was extracted with ethyl acetate. The ethyl acetate solution was washed with water, 2 N HCl, 5% sodium bicarbonate solution and finally water. After drying (Na_2SO_4) and removal of the solvent *in vacuo* the residue was crystallized from acetone–hexane to afford *6α-fluorohydrocortisone acetate* (II) (3·3 g), m.p. 209–211°, raised by several crystallizations from acetone–hexane to 215–217°, $[\alpha]_D$ +153° (dioxane), λ_{max}^{EtOH} 236–238 mμ, ε 16,600, λ_{max}^{KBr} 3500, 1750, 1725, 1660, 1600 (sh.) cm.$^{-1}$. R.D. (*c*, 0·0565): $[\alpha]_{700}$ +111°, $[\alpha]_{589}$ +149°, $[\alpha]_{390}$ +384°, $[\alpha]_{370}$ +318°, $[\alpha]_{357\cdot5}$ +444°, $[\alpha]_{355}$ +418°, $[\alpha]_{317\cdot5}$ +2860°, $[\alpha]_{300}$ −1280°. (Found: C, 65·30; H, 7·61; F, 4·79. $C_{23}H_{31}O_6F$ requires: C, 65·04; H, 7·47; F, 4·54%).

6α-Fluoroprednisolone acetate (*6α-fluoro-Δ^{1,4}-pregnadiene-11β,17α,21-triol-3,20-dione 21-acetate*) (III)

(a) *By the selenium dioxide oxidation of* II. Selenium dioxide (150 mg) was added to a solution of 6α-fluorohydrocortisone acetate (II) (300 mg) in t-butyl alcohol (30 cc) containing pyridine (0·04 cc) and heated under reflux with stirring in a nitrogen atmosphere for 24 hr. Ethyl acetate (30 cc) was added and the solution filtered through celite. After removal of the solvent the residue was triturated with water (50 cc), filtered, dried and adsorbed from benzene (100 cc) onto alumina (25 g). Elution with benzene–ether (50 : 50; 375 cc) afforded *6α-fluoroprednisolone acetate* (III) (157 mg), m.p. 235–240°, raised by several crystallizations from ethyl acetate–hexane to 237–239°, $[\alpha]_D$ +114° (dioxane), λ_{max}^{EtOH} 242 mμ, ε 17,750, λ_{max}^{KBr} 3450, 1755, 1730, 1677, 1620 and 1608 cm.$^{-1}$. R.D. (*c*, 0·0642): $[\alpha]_{700}$ +84·1°, $[\alpha]_{589}$ +106°, $[\alpha]_{317\cdot5}$ +3170°, $[\alpha]_{300}$ +1380°, $[\alpha]_{285}$ −836°. (Found: C, 65·34; H, 7·04; F, 4·50. $C_{23}H_{29}O_6F$ requires: C, 65·36; H, 7·02; F, 4·56%).

(b) *By the adrenal incubation of* Δ^1-*6α-fluoro-Compound "S"* (IV). Using the same technique as described above for the preparation of 6α-fluorohydrocortisone acetate (I → II) adrenal incubation of Δ^1-6α-fluoro-Compound "S" (3·0 g) afforded after acetylation and crystallization from ethyl acetate–hexane *6α-fluoroprednisolone acetate* (III) (1·23 g), m.p. 229–234°, raised by crystallizations from ethyl acetate–hexane to 236–238°, undepressed on admixture with a sample prepared by method (a). The infrared spectra were identical.

6α-Fluorocortisone acetate (Va)

6α-Fluorohydrocortisone acetate (II) (150 mg) in acetone (7·0 cc) at 0° was treated with a slight excess of 8 N chromic acid[13] (permanent orange color) and then kept at 0–5° for 2 min. Addition of water and filtration afforded *6α-fluorocortisone acetate* (Va) (140 mg), m.p. 215–220°, raised by crystallizations from acetone–hexane to 222–223°, $[\alpha]_D$ +190°, λ_{max} 233 mμ, ε 16,220. (Found: C, 65·05; H, 7·20; F, 4·97. $C_{23}H_{31}O_6F$ requires: C, 65·36; H, 7·02; F, 4·56%).

6α-Fluoroprednisone acetate (VIa)

6α-Fluoroprednisolone acetate (III) (61 mg) in acetone (6 cc) at 0° was treated with a slight excess of 8 N chromic acid[13] (permanent orange color) and then kept at 0–5° for 2 min. Addition of water

and filtration afforded 6α-*fluoroprednisone acetate* (VIa) (52 mg), m.p. 223–225° raised by crystallizations from acetone–hexane to 224–226°, $[\alpha]_D$ +142° (dioxane), λ_{max} 238 mμ, ε 15,500. (Found: C, 65·39; H, 6·61; F, 4·40. $C_{23}H_{27}O_6F$ requires: C, 65·67; H, 6·57; F, 4·59%).

Cortisone diacetate (Δ⁴-*pregnene*-17α,21-diol-3,11,20-*trione* 17,21-*diacetate*) (IX)

(a) Cortisone acetate (VII) (5·0 g) dissolved in acetic acid (225 cc) and acetic anhydride (33·7 cc) containing *p*-toluenesulfonic acid monohydrate (4·5 g) was kept at 20° during 16 hr. Addition of ice water and filtration afforded a product which was adsorbed from benzene onto alumina (300 g). Elution with benzene–ether (90 : 10; 400 cc) and one crystallization from methanol gave cortisone diacetate (IX) (1·97 g), m.p. 223–225°, $[\alpha]_D$ +140°, λ_{max}^{EtOH} 238 mμ, ε 16,600. Lit[18] reports m.p. 221–222°, $[\alpha]_D$ +133°.

(b) Cortisone acetate (10 g) in acetic anhydride (200 cc) was heated under reflux in an atmosphere of nitrogen for 24 hr. The solution was then concentrated to 50 cc *in vacuo* and the product precipitated by addition of ice water (500 cc). Crystallization from methanol afforded cortisone diacetate (IX) (4.3 g) m.p. 221–223° undepressed on admixture with a sample prepared as in (a).

Cortisone diacetate-3-*cycloethylene-ketal* (Δ⁵-*pregnene*-17α,21-*diol*-11,20-*dione* 3-*cycloethylene ketal diacetate*) (X)

(a) *By ketalization of cortisone diacetate.* A solution of cortisone diacetate (IX) (10 g) in methyl ethyl dioxolane (180 cc) containing *p*-toluenesulfonic acid hydrate (200 mg) was distilled at such a rate that 135 cc of distillate was collected after 1 hr. Water (250 cc) containing sodium carbonate (1·0 g) was then added and the product extracted with benzene. Removal of the solvent afforded a product having λ_{max}^{EtOH} 234–236 mμ, ε 1,950. A solution in benzene (200 cc) was adsorbed onto alumina (500 g). Elution with benzene–ether (80 : 20; 2·5 l.) followed by one crystallization from benzene–ether afforded *cortisone diacetate* 3-*cycloethylene ketal* (X) (5·91 g), m.p. 173–176°, raised by several crystallizations from benzene–ether to 180–182°, $[\alpha]_D$ −20°; X exhibited no selective absorption in the ultraviolet. (Found: C, 66·81; H, 7·21; O, 25·66. $C_{27}H_{36}O_8$ requires: C, 66·37; H, 7·43; O, 26·20%).

(b) *By acetylation of cortisone acetate* 3-*cycloethylene ketal.* Cortisone acetate-3-cycloethylene ketal[20] (VIII) (21·0 g) was added to a suspension of finely divided calcium carbonate (4·0 g) in acetic anhydride (550 cc) and heated under reflux in an atmosphere of nitrogen for 24 hr. After concentrating the solution to approximately 100 cc *in vacuo* the suspension was added to ice water (2· 5l. containing sodium carbonate (125 g). Extraction with ethyl acetate gave a solution which was washed with water, dried (Na_2SO_4), concentrated to 75 cc and the hot solution was then diluted with ether and hexane to afford a crystalline precipitate of the ketal-diacetate (X) (11·9 g) m.p. 167–176°, raised by one crystallization from benzene–ether to 179–182°, undepressed on admixture with a sample prepared as in method (a).

5α,6α-*Oxidopregnane*-17α,21-*diol*-11,20-*dione* 3-*cycloethylene ketal* 17,21-*diacetate* (XI)

A solution of permonophthalic acid (7·0 g) in ether (80 cc) was added at 0° to a solution of the ketal (X) (8·9 g) in chloroform (90 cc). After keeping at 0–5° for 18 hr the solution was washed with water, cold 2% sodium hydroxide solution and finally water. After drying (Na_2SO_4) the solution was evaporated and the product crystallized from acetone–hexane to afford the 5α,6α-*epoxide* (8·0 g) m.p. 225–232°, raised by several crystallizations from benzene–hexane to 232–234°, $[\alpha]_D$ −18°. (Found: C, 64·62; H, 7·19; O, 28·19. $C_{27}H_{36}O_9$ requires: C, 64·27; H, 7·19; O, 28·54%).

6β-*Fluoro*-Δ⁵-*pregnene*-5α,17α,21-*triol*-11,20-*dione* 3-*cycloethylene ketal* 17,21-*diacetate* (XII)

Boron trifluoride etherate (freshly distilled) (5·6 cc) was added to a solution of the α-epoxide (XI) (5·6 g) in benzene–ether (1 : 1; 600 cc). After 3 hr at room temp the solution was washed with water until neutral, evaporated to approximately 100 cc and adsorbed onto alumina (280 g). Elution with benzene–ether (90 : 10; 3 l.) afforded 6β-*fluoro*-Δ⁵-*pregnene*-5α,17α,21-*triol*-11,20-*dione* 3-*cycloethylene ketal* 17,21-*diacetate* (XII) (2·6 g) m.p. 224–229°, raised by several crystallizations from benzene–hexane to 232–234°, $[\alpha]_D$ −9°. (Found: C, 61·81; H, 7·09; F, 3·72. $C_{27}H_{37}O_9F$ requires: C, 61·81; H, 7·11; F, 3·62%).

6β-Fluorocortisone diacetate (XIII)

Dry hydrogen chloride was passed through a solution of 6β-fluoro-Δ^5-pregnene-5α,17α,21-triol-11,20-dione 3-cycloethylene ketal 17,21-diacetate (XII) (3·85 g) in acetic acid (125 cc) at 15° for 25 min. Addition of water and filtration afforded *6β-fluorocortisone diacetate* (XIII) (2·72 g) m.p. 210–214° raised by crystallizations from acetone–hexane to 214–216°, $[\alpha]_D$ +62°, λ_{max}^{EtOH} 232–234 mμ, ε 11,480. (Found: C, 64·93; H, 7·00; F, 4·36. $C_{25}H_{31}O_7F$ requires: C, 64·89; H, 6·75; F, 4·10%).

6α-Fluorocortisone diacetate (Vb)

A solution of 6β-fluoro-Δ^5-pregnene-5α,17α,21-triol-11,20-dione 3-cycloethylene ketal 17,21-diacetate (XII) (600 mg) in acetic acid (40 cc) at 15° was saturated with dry hydrogen chloride and then kept at room temp for 24 hr. Addition of water afforded *6α-fluorocortisone diacetate* (Vb) m.p. 235–240°, raised by chromatography over silica–celite (1 : 1; 30 g) to 268–272° (200 mg). The analytical sample from acetone-hexane had m.p. 270–272°, $[\alpha]_D$ +108°, λ_{max}^{EtOH} 232–234 mμ, ε 16,000. (Found: C, 63·27; H, 6·70; F, 3·90. $C_{25}H_{31}O_7F.1/2\ H_2O$ requires: C, 63·68; H, 6·84; F, 4·03%).

Alkaline hydrolysis of 6α-fluorocortisone diacetate (Vb)

A suspension of the diacetate (Vb) (250 mg) in methanol (2·5 cc) containing potassium hydroxide (25 mg) was stirred at 0° under nitrogen for 1¾ hr. After 1¼ hr a complete solution was obtained. After acidification with acetic acid addition of water and isolation with ethyl acetate gave a product which was dissolved in pyridine (5·0 cc) containing acetic anhydride (0·5 cc) and kept at room temp for 16 hr. Addition of water and isolation with ethyl acetate gave a product which was adsorbed from methylene dichloride onto silica–celite (1 : 1; 25 g). Elution with methylene dichloride–acetone (80 : 20; 300 cc) afforded a fraction which after crystallization from acetone–hexane gave 6α-fluorocortisone acetate (Va) (30 mg) m.p. 207–210°, raised by crystallization from acetone–hexane to 217–219°, undepressed on admixture with an authentic sample. The infrared spectra of the two samples were identical.

6α-Fluoroprednisone diacetate (VIb)

Selenium dioxide (2·5 g) was added to a solution of 6α-fluorocortisone diacetate (Vb) (5·0 g) in t-butyl alcohol (250 cc) containing pyridine (0·8 cc) and heated under reflux in an atmosphere of nitrogen for 24 hr. The reaction mixture was then diluted with ethyl acetate (250 cc) and filtered through celite. After removal of the solvent the residue was triturated with water (500 cc), filtered, dried and crystallized from ethyl acetate–hexane to afford *6α-fluoroprednisone diacetate* (VIb) (2·25 g), m.p. 255–258°, raised by crystallizations from ethyl acetate–hexane to 260–262°, $[\alpha]_D$ +68°, λ_{max}^{EtOH} 236–238 mμ, ε 15,100. (Found: C, 64·85; H, 6·55; F, 3·92. $C_{25}H_{29}O_7F$ requires: C, 65·17; H, 6·35; F, 4·12%).

6α-Fluoro-$\Delta^{4,9(11)}$-pregnadiene-17α,21-diol-3,20-dione 21-acetate (XIV)

Methane sulphonyl chloride (1·6 cc) was added to a solution of 6α-fluorohydrocortisone acetate (II) (2·9 g) in dimethyl formamide (24·7 cc) and pyridine (3·4 cc) and then heated at 80° for 1½ hr. Addition of ice water and isolation with ethyl acetate afforded a product which was adsorbed from benzene onto silica–celite (3 : 1; 160 g). Elution with benzene–ether (80 : 20; 1·5 l.) afforded *6α-fluoro-$\Delta^{4,9(11)}$-pregnadiene-17α,21-diol-3,20-dione 21-acetate* (XIV) (2·04 g) m.p. 219–221° raised by crystallizations from acetone to 222–224°, $[\alpha]_D$ +71°, λ_{max} 234–236 mμ, ε 15,850. (Found: C, 68·08; H, 7·17; F, 4·47. $C_{23}H_{29}O_5F$ requires: C, 68·29; H, 7·23; F, 4·69%).

9β,11β-Oxido-Δ^4-pregnene-17α,21-diol-3,20-dione 21-acetate (XV)

N-Bromoacetamide (1·75 g) was added portionwise over 1 hr to a stirred suspension of 6α-fluoro-$\Delta^{4,9(11)}$-pregnadiene-17α,21-diol-3,20-dione 21-acetate (XIV) (3·75 g) in dioxane (37·5 cc) containing 0·46 N perchloric acid (5·6 cc) at 20°. After a further hour at room temp the excess of hypobromous acid was destroyed by the addition of sodium sulphite solution (10%). Ice water was then added and the product was extracted with ether. The combined extracts were washed with water, dried (Na_2SO_4) and the solvent removed at 25° *in vacuo*. Potassium acetate (3·75 g) was then added to a solution of the crude product in acetone (140 cc) and heated under reflux for 18 hr. Removal of the bulk of the solvent on the steam bath, addition of water and filtration gave a product which was

adsorbed from benzene onto silica–celite (3 : 1; 200 g). Elution with benzene–ether (70 : 30; 2·9 l.) afforded the 9β,11β-*epoxide* (XV) (2·65 g) m.p. 198–201° raised by several crystallizations from acetone to 205–206°, $[\alpha]_D$ +60°, λ_{max} 236–238 mμ, ε 12,600. (Found: C, 65·96; H, 7·15; F, 4·86. $C_{23}H_{29}O_6F$ requires: C, 65·69; H, 6·95; F, 4·51%).

6α,9α-*Difluorohydrocortisone acetate* (XVI)

9β,11β-Oxido-Δ^4-pregnene-17α,21-diol-3,20-dione 21-acetate (1·49 g) in methylene dichloride (50 cc) was added with stirring over 10 min to a mixture of anhydrous hydrofluoric acid (2·73 g) and tetrahydrofuran (4·8 g) at −80°. After a further 10 min at −80° the reaction mixture was kept at 0° for 7 hr when it was added to an excess of aqueous sodium bicarbonate solution. Isolation with methylene dichloride gave a product which was dissolved in pyridine (15 cc) and acetic anhydride (2 cc) and heated on the steam bath for 1 hr. Addition of ice water and extraction with ethyl acetate gave a product which was adsorbed from benzene onto silica–celite (3 : 1; 100 g). Elution with benzene–ether (70 : 30; 450 cc) afforded 6α,9α-*difluorohydrocortisone acetate* (XVI) (1·05 g) m.p. 220–222° raised by crystallizations from aqueous methanol to 224–226°, $[\alpha]_D$ +118°, λ_{max} 234 mμ, ε 19,900. (Found: C, 62·98; H, 6·66; F, 8·39. $C_{23}H_{30}O_6F_2$ requires: C, 62·71; H, 6·87; F, 8·63%).

6α,9α-*Difluoroprednisolone acetate* (XVII)

Selenium dioxide (320 mg) was added to a solution of 6α,9α-difluorohydrocortisone acetate (XVI) (640 mg) in t-butyl alcohol (60 cc) containing pyridine (0·08 cc) and heated under reflux with stirring in a nitrogen atmosphere for 40 hr. The precipitate of selenium was removed by filtration through celite and the filtrate evaporated to dryness *in vacuo*. The residue was dissolved in ethyl acetate (50 cc), washed several times with water, dried (Na_2SO_4) and the solvent was again removed *in vacuo* to afford a product which was adsorbed from benzene onto silica–celite (3 : 1; 30 g). Elution with benzene–ether (70 : 30; 400 cc) afforded 6α,9α-*difluoroprednisolone acetate* (XVII), (210 mg) m.p. 218–222°, raised by crystallizations from acetone–hexane to 224–226°, $[\alpha]_D$ +114°; λ_{max} 238 mμ, ε 15,100. (Found: C, 62·73; H, 6·41; F, 8·22. $C_{23}H_{28}O_6F_2$ requires: C, 62·98 H, 6·43; F, 8·65%).