and

$$1/[H^+] = [OH^-]/K_w \qquad (22)$$

so that in substitution of (21) and (22) into (20)

$$d[\text{Ester}]/dt = \frac{kK_s}{K_w}[OH^-]\ [RO\overset{O}{\overset{\|}{C}}(CH_2)_2\overset{O}{\overset{\|}{C}}—OH] \qquad (23)$$

Thus, intramolecular catalysis (equation 20) need not necessarily be favored over its kinetic equivalent (equation 23).

Acknowledgments are made to Dr. A. R. Hanze for the synthesis of most of the hemiesters and Mrs. L. G. Snyder and Mr. Max Royer for excellent technical assistance.

Certain Steroid Ketals and Their Biological Activity

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By straightforward procedures the 20-ketals of 6α-methylhydrocortisone, 6α-methylprednisolone, 6α-methylprednisone, 9α-fluoro-6α-methylprednisone, 21-deoxy-9α-fluoro-6α-methylprednisone, prednisone, 9α-fluorocortisone, 9α-fluoroprednisone, 9α-fluoro-16α-hydroxycortisone, triamcinolone, 2α-methylhydrocortisone, 2α,6α-dimethylhydrocortisone, and 2,6α-dimethylprednisolone have been prepared. These ketal derivatives, although less active than the parent 20-ones, showed substantial glucocorticoid activity.

The observation made in the course of routine screening of steroid intermediates, that 6α-methylhydrocortisone 20-ethylene ketal (II), prepared as a substrate for ethoxalylation studies at C-2 of the steroid nucleus, possesses substantial glucocorticoid activity, prompted the study which is the subject of this paper. To our knowledge biolog-

(1) To whom inquiries concerning this paper should be addressed.

ical activity for 20-ketal derivatives of steroid hormones had not been observed[2] previously and we therefore undertook the preparation of the 20-ketals of various 11-oxygenated corticoid derivatives.

The lead compound, 6α-methylhydrocortisone 20-ketal (II), had been prepared[3] in excellent yield by preferential hydrolysis[4] of the 3-ketal group in bisketal I, followed by base-catalyzed elimination of the 5α-hydroxy group and concomitant epimerization of the 6β-methyl group.[5] The starting compound I for this sequence is available from 3,20-bisethylenedioxy-5α,6α-epoxy-11β,17β,21-trihydroxypregnane by reaction with methylmagnesium bromide followed by 21-acetylation.[6] Conversion of II to the 1-dehydro derivative (V) was accomplished in poor yield by a selenium dioxide dehydrogenation. Subsequently, a more satisfactory dehydrogenation was effected from the 21-acetate III by treatment with 2,3-dichloro-5,6-dicyanobenzoquinone (DCBQ).[7] In addition, the 1-dehydro-11-keto analog VI was prepared by ketalization of 6α-methylprednisone (IV).[8]

Similarly, ketalization of 9α-fluoro-6α-methylprednisone (VII)[9] followed by acetylation gave the 20-ketal IX. A preliminary attempt to prepare a 20-ketal in the 9α-fluoro-6α-methyl series *via* the ketalization of 17α,21-dihydroxy-6α-methyl-1,4,9(11)-pregna-

(2) S. Bernstein of these Laboratories and R. Dorfman of the Worcester Foundation and their associates have noted corticoid activity for the 20-ethylene ketal and the 3,20-bisethylene ketal of hydrocortisone, private communication.

(3) Experiments carried out by J. F. Poletto of these Laboratories.

(4) R. Antonucci, S. Bernstein, M. Heller, R. Lenhard, R. Littell and J. H. Williams, *J. Org. Chem.*, **18**, 70 (1953).

(5) Based on the procedure recently reported for the synthesis of the corresponding 11-keto derivatives.[6]

(6) S. Bernstein and R. Littell, *J. Am. Chem. Soc.*, **82**, 1235 (1960).

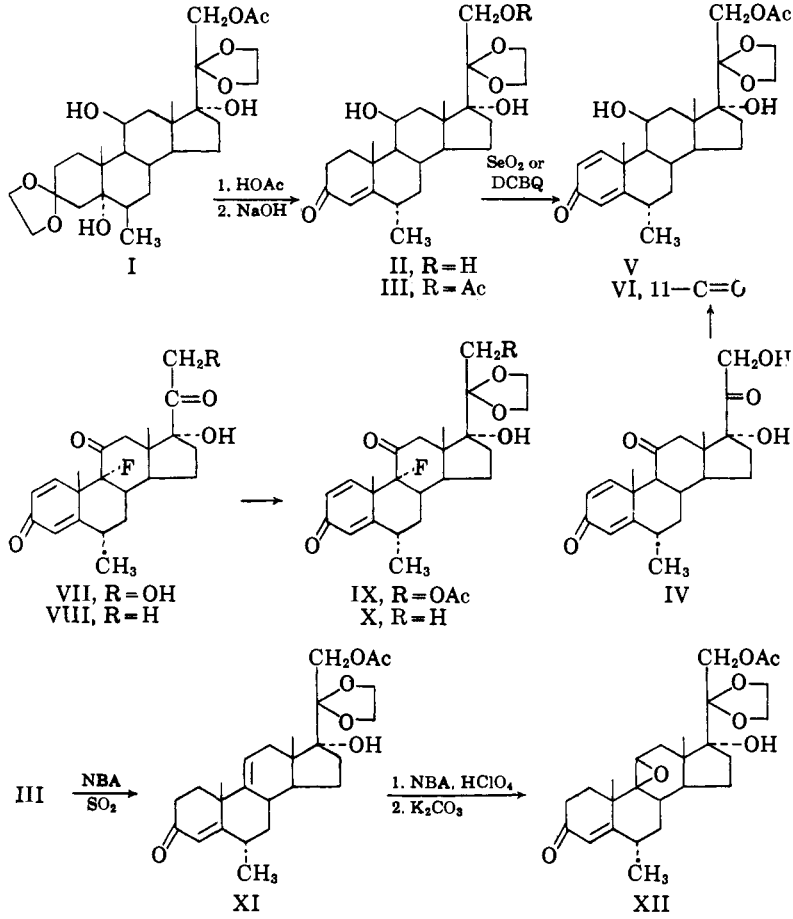
(7) D. Burn, D. N. Kirk and V. Petrow, *Proc. Chem. Soc.*, 14 (1960).

(8) G. B. Spero, J. L. Thompson, B. J. Magerlein, A. R. Hanze, H. C. Murray, O. K. Sebek and J. A. Hogg, *J. Am. Chem. Soc.*, **78**, 6213 (1956). Details for the preparation of IV from 6α-methylprednisolone *via* 21-acetylation (97%), oxidation with chromic oxide (65%) and de-*O*-acetylation (88%) are given in the experimental section.

(9) 9α-Fluoro-6α-methylprednisone (VII) was obtained from 9α-fluoro-6α-methylprednisolone acetate, the preparation of which from 6α-methylprednisolone acetate has been reported previously without details.[10] Procedures for this transformation are given in the experimental section. One point worthy of comment is the apparent relative inactivity of the intermediate 9β,11β-oxide to hydrogen fluoride. Thus, using the same conditions [R. F. Hirschmann, *et al.*, *J. Am. Chem. Soc.*, **78**, 4956 (1956)] whereby 21-acetoxy-17α-hydroxy-9β,11β-oxido-1,4-pregnadiene-3,20-dione afforded 73% of fluorohydrin,[11] the corresponding 6α-methyl derivative gave mixtures containing substantial amounts of unreacted oxide.

(10) G. B. Spero, J. L. Thompson, F. H. Lincoln, W. P. Schneider and J. A. Hogg, *J. Am. Chem. Soc.*, **79**, 1515 (1957).

(11) Experiment by Mrs. Bernice Kliebard of the Chemical Process Improvement Department of these Laboratories.



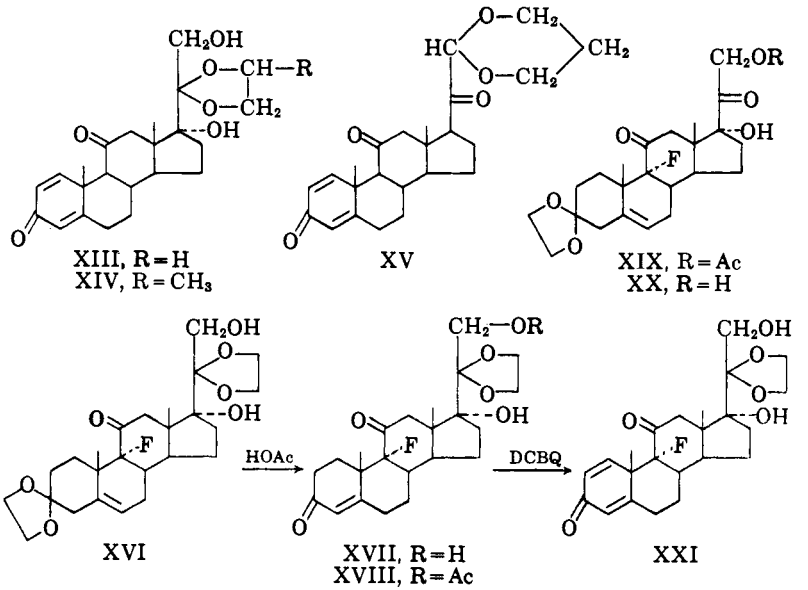
triene-3,20-dione was unsuccessful, possibly as a result of interaction between the ring A dienone and ethylene glycol. Also unsuccessful was an approach involving treatment with hydrogen fluoride of the 20-ketal-9β,11β-oxide XII, prepared as indicated from 6α-methylhydrocortisone 20-ketal 21-acetate (III). Here the attempted transformation of XII to the corresponding ring C fluorohydrin gave complex mixtures containing much blue tetrazolium-positive material. Apparently the 20-ethylenedioxy grouping was not stable to the experimental conditions from which it is difficult to exclude moisture.

The 6α-methyl series was completed with the preparation of the 21-deoxy-20-ketal X by ketalization of 9α-fluoro-17α-hydroxy-6α-methyl-1,4-pregnadiene-3,11,20-trione (VIII), available by oxidation with the chromic oxide–pyridine complex of the corresponding 11β-ol.[12]

In order to evaluate the effect on biological activity of structural variations in the 20-alkylenedioxy moiety, the preparation of a series of prednisone 20-ketal derivatives was undertaken. Thus, treatment of prednisone in the usual manner with the appropriate glycol gave the ethylene ketal XIII and the 1,2-propylene ketal XIV. Satisfactory analyses could not be obtained for these two ketals, presumably because of solvation difficulties. However, conversion to the 21-acetates gave products which afforded satisfactory analytical values. Methanolic-sulfuric acid hydrolysis of the ethylene ketal XIII regenerated prednisone, indicating that XIII is not the ketal of a rearrangement product. With 1,3-propanediol, the desired ketal was not obtained but instead there was isolated in 45% yield a substance which is apparently a Mattox-rearrangement[13] product (XV). The assignment of structure XV to this product is based on combustion analyses and the infrared spectrum which showed no appreciable hydroxy absorption, the apparent presence of a 20-carbonyl band and its shift[14] to a lower wave length, and heavy C—O—C absorption. The isolation of analogous products has been observed previously from the ethylene glycol ketalization of cortisone[14] and of compound S.[15] Although Tsuda *et al.*[15] reported that the 21-ethylene acetal from compound S could undergo acid hydrolysis, an attempt to hydrolyze XV by heating with 8% methanolic-sulfuric acid failed and starting material was recovered. However, resistance to hydrolysis by an 11-keto-21-ethylenedioxy steroid has been noted.[14] Attempts to effect the condensation of prednisone with 2-mercaptoethanol and with 1,2-ethanedithiol were essentially unsuccessful. These experiments gave complex mixtures which could not be resolved even after extensive chromatography.

Continuing our exploration of this field, the 20-ethylene ketal (XVII) of 9α-fluorocortisone was prepared by 3,20-bisketalization

(12) German Patent 1,056,605 (May 6, 1959).
(13) V. R. Mattox, *J. Am. Chem. Soc.*, **74**, 4340 (1952).
(14) S. Bernstein, M. Heller and W. S. Allen, *J. Org. Chem.*, **26**, 1333 (1961).
(15) K. Tsuda, N. Ikekawa and S. Nozoe, *Chem. and Pharm. Bulletin* (Tokyo), **1**, 519 (1959).



of 9α-fluorocortisone[16] followed by preferential[4] 3-ketal hydrolysis. This sequence also afforded an example of a 3,20-bisketal, the intermediate XVI.[17] For the preparation of a 3-monoketal, 9α-fluorocortisone 21-acetate was submitted to an exchange reaction with 2-ethyl-2-methyl-1,3-dioxolane[18] and the desired XIX was obtained in 87% yield[19]; de-*O*-acetylation then gave the 21-ol XX. Acetylation of 20-ketal XVII and treatment of the resulting XVIII with the 1,2-dehydrogenating agent DCBQ[7] with subsequent de-*O*-acetylation, afforded 9α-fluoroprednisone 20-ethylene ketal (XXI).

For the synthesis of 20-ketal derivatives in the 9α-fluoro-16α-hydroxy series,[17] 9α-fluorocortisone bisethylene ketal 21-acetate (XVI 21-acetate) was treated with phosphorus oxychloride to give the 16-dehydro derivative XXII which was converted to the 16α,17α-diol XXIII by reaction with osmium tetroxide. Preferential 3-ketal hydrolysis of XXIII afforded 16α-hydroxy-9α-fluorocortisone 20-ethylene ketal 21-acetate (XXV). Reduction of the 11-carbonyl

(16) J. Fried and E. F. Sabo, *J. Am. Chem. Soc.*, **79**, 1130 (1957).

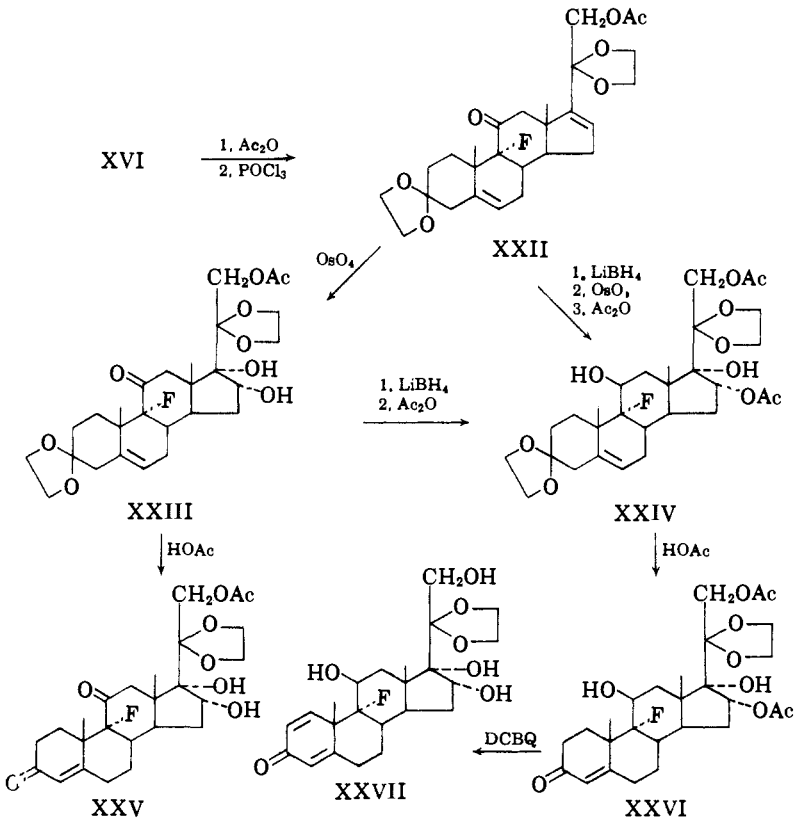
(17) J. Fried and G. H. Thomas (U. S. Patent 2,963,496, Dec. 6, 1960) after the conclusion of our work, described the preparation by similar procedures of compounds XVI and XXII and in U. S. Patent 2,929,496 (March 22, 1960) the preparation of XXIII and the 16-acetate of XXV.

(18) H. J. Dauben, Jr., B. Löken and H. J. Ringold, *J. Am. Chem. Soc.*, **76**, 1359 (1954).

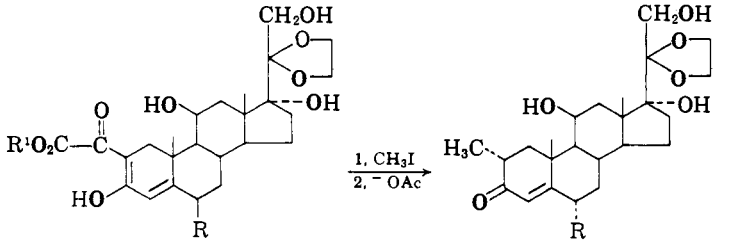
(19) Experiment carried out by Mrs. Arlene Small Hoffman of these Laboratories.

in bisketal XXIII with lithium borohydride gave the 11β-ol (as a probable 16,17-cycloborate ester)[19] which, after 16,21-di-*O*-acetylation to XXIV and 3-ketal hydrolysis, furnished 16α-hydroxy-9α-fluorohydrocortisone 20-ethylene ketal 16,21-diacetate (XXVI). An alternate synthesis of XXIV by lithium borohydride reduction of the 16-dehydro derivative XXII, osmylation and acetylation gave results somewhat superior to the procedure *via* XXIII. Finally, 1,2-dehydrogenation of XXVI with 2,3-dichloro-5,6-dicyanobenzoquinone,[7] followed by de-*O*-acetylation, afforded triamcinolone 20-ethylene ketal (XXVII).

Several 2-methyl derivatives also were prepared. Methoxalyl-



ation of hydrocortisone 20-ketal[20,21] gave the 2-methoxalyl derivative XXVIII,[22] alkylation of which with methyl iodide and then base-catalyzed demethoxalylation furnished 2α-methylhydrocortisone 20-ketal (XXX).[19,23] By a similar procedure the 20-ethylene ketal (XXXI) of 2α,6α-dimethylhydrocortisone was prepared from 6α-methylhydrocortisone 20-ketal (II) *via* the 2-ethoxalyl derivative XXIX. Dehydrogenation with DCBQ[7] then afforded the 20-ethylene ketal (XXXII) of 2,6α-dimethylprednisolone.



XXVIII, R = H, R^1 = CH_3
XXIX, R = CH_3, R^1 = C_2H_5

XXX, R = H
XXXI, R = CH_3
XXXII, Δ^1 of XXXI

Biological Evaluation

The glucocorticoid, thymolytic and mineralocorticoid assay results obtained with the various 20-ketal derivatives are summarized in Table I. Included in this Table are the activities of most of the parent 20-ketones. In general, the thymolytic and glucocorticoid activities of the 20-ketals approximate about one-third to one-half that of the parent 20-ones. Nevertheless, certain of the 20-ketal derivatives show substantial activity in these assays. Of particular interest are several 6α-methyl derivatives, namely, 6α-methylhydrocortisone 20-ethylene ketal (II) having an activity of about 2–3 times hydrocortisone, 6α-methylprednisolone 20-ethylene ketal 21-acetate (V) showing an activity about equal to that of triamcinolone (4–6 times hydrocortisone) and 9α-fluoro-6α-methylprednisone 20-ethylene ketol 21-acetate (IX) with an activity of 15 (9–24) or about 4

(20) Australian Patent Application 23,672, May 12, 1956 (Merck and Co., Inc.).

(21) H. M. Kissman, A. M. Small and M. J. Weiss, *J. Am. Chem. Soc.*, **82**, 2312 (1960).

(22) The enolic structures XXVIII and XXIX for the alkoxalyl derivatives are indicated by spectroscopic evidence (W. Fulmor and G. Morton, unpublished work). See also N. A. Nelson and R. N. Schut, *ibid.*, **80**, 6630 (1958).

(23) Compound XXX already has been reported in ref. 20.

TABLE I

ADRENOCORTICOID ACTIVITY OF VARIOUS KETAL DERIVATIVES AND CERTAIN RELATED COMPOUNDS

Name	Relative potency (× hydrocortisone)[e] — Thymus involution[a]	Liver glycogen deposition[a]	Mineralocorticoid[b]
6α-Methylhydrocortisone 20-ethylene ketal (II)	2.4(2.0–2.8)	3.0(2.5–3.7)	Excretor[c]
6α-Methylhydrocortisone 20-ethylene ketal 21-acetate (III)	~2[d]		Excretor
6α-Methylprednisolone 20-ethylene ketal 21-acetate (V)	4.0(4.3–4.7)	5.3(4.3–6.5)	Excretor[c]
6α-Methylprednisone 20-ethylene ketal 21-acetate (VI)	1.2(0.9–1.7)	1.3(0.7–2.4)	Excretor[c]
9α-Fluoro-6α-methylprednisone 20-ethylene ketal 21-acetate (IX)	15(10–22)[d]		Retainer
21-Deoxy-9α-fluoro-6α-methylprednisone 20-ethylene ketal (X)	3.3(1.7–6.4)		No effect
Prednisone 20-ethylene ketal (XIII)	~0.1	0.9(0.5–1.7)	Excretor[c]
Prednisone 20-propylene ketal (XIV)	1.0(0.6–1.8)[d]		No effect
9α-Fluorocortisone 20-ethylene ketal (XVII)	2.1(1.8–2.4)	3.4(2.5–4.6)	Retainer
9α-Fluorocortisone 3,20-bisethylene ketal (XVI)	1.8(1.5–2.2)	2.3(1.8–2.9)	Retainer[c]
9α-Fluorocortisone 3-ethylene ketal (XX)	3.7(2.5–5.7)	5.3(3.7–7.7)	Retainer
9α-Fluoroprednisone 20-ethylene ketal (XXI)	6.7(3.5–12.7)[d]		Retainer
16α-Hydroxy-9α-fluorocortisone 20-ethylene ketal 21-acetate (XXV)	~0.2		
Triamcinolone 20-ethylene ketal (XXVII)	~1[d]		Excretor
2α-Methylhydrocortisone 20-ethylene ketal (XXX)	2.8(2.0–4.0)[d]		Retainer
2α,6α-Dimethylhydrocortisone 20-ethylene ketal (XXXI)	4.5(3.1–6.5)		No effect
2,6α-Dimethylprednisolone 20-ethylene ketal (XXXII)	1[d]		Excretor
6α-Methylhydrocortisone 21-acetate	6	5.8(3.9–8.6)	Excretor[c]
6α-Methylprednisolone	10(8–13)	8.4(5.3–10.4)	Excretor[c]
9α-Fluoro-6α-methylprednisone (VII)	32(22–47)[d]		Retainer
21-Deoxy-9α-fluoro-6α-methylprednisone (VIII)	10(4–24)[d]		No effect
Prednisone	2.9(1.7–4.9)[d]		No effect
9α-Fluorocortisone	8.6(5.4–13.7)	14.2(8.1–24.7)	Retainer
Triamcinolone	3.7(3.3–4.2)[d]		Excretor
	3.9(3.6–4.3)	6.1(5.5–6.7)	Excretor[c]

NOTES TO TABLE I

[a] Unless otherwise noted these assays (subcutaneous) were carried out according to the procedure reported by S. Bernstein, R. Littell, J. J. Brown and I. Ringler, *J. Am. Chem. Soc.*, 81, 4573 (1959). [b] This assay is based on the response of adrenalectomized male rats to a single subcutaneous 16 mcg. dose of compound as measured after a 5-hr. urine collection. [c] This assay is based on the response of adrenalectomized immature male rats to graded subcutaneous doses as determined by 5 hr. urine collections. [d] Assay (subcutaneous) carried out by the procedure of I. Ringler and R. Brownfield, *Endocrinology*, 66, 900 (1960). [e] Figures in parentheses represent 95% confidence limits.

times triamcinolone. This last compound (IX) is the most active of the 20-ketals prepared in this study.

With regard to the mineralocorticoid results, 20-ketalization did not reverse the sodium-retaining property of strong sodium retainers such as 2α-methylhydrocortisone[24a] and 9α-fluorocortisone,[24b] or of what is presumably a weak retainer—9α-fluoro-6α-methylprednisone.[24a]

It should be noted too that the 3-ketal (XX) as well as the 3,20-bisketal (XVI) derivatives of 9α-fluorocortisone also demonstrate significant corticoid activity. Both XX and XVI are sodium retainers.

It is of course interesting to speculate as to whether the 20-ketals have biological activity *per se* or whether they must first undergo ketal hydrolysis to the active dehydroxyketone derivatives. In view of the relative stability of 20-ketals in general to weak acid, it is unlikely that these derivatives undergo chemical hydrolysis in the course of a subcutaneous assay. Concerning the possibility of enzymatic hydrolysis we can offer little evidence to bear. However, *in vitro* incubation studies of certain 20-ketals with liver brei indicate that under these conditions at least enzymatic hydrolysis does not occur.[25]

In connection with this study, deoxycorticosterone acetate 20-ethylene ketal,[26] progesterone 20-ethylene ketal,[27] testosterone 3-ethylene ketal,[18] and estrone methyl ether 17-ethylene ketal[28,29]

(24)(a) J. Hogg, Sixth National Medicinal Chemistry Symposium of the American Chemical Society, U. of Wisconsin, Madison, Wisconsin, June 23–25, 1958. (b) J. Fried and A. Borman, *Vitamins and Hormones*, XVI, 303 (1958).

(25) I. Ringler and J. Perrine, *Endocrinology*, in press.

(26) F. Sondheimer and Y. Klibansky, *Tetrahedron*, 5, 15 (1959).

(27) M. Gut, *J. Org. Chem.*, 21, 1327 (1956).

(28) P. de Ruggieri, *Gass. Chim. Ital.*, 87, 795 (1957).

(29) We wish to thank Dr. E. W. Cantrall for a sample of this compound.

were tested for activity in their respective endocrinological areas. The 20-ketal of deoxycorticosterone acetate was a sodium retainer, but less effective than deoxycorticosterone acetate.[30] Progesterone 20-ketal at a 1 mg. total dose in the Clauberg assay in rabbits gave a negative response.[31] In this assay progesterone at a 0.5 mg. total dose gives a 2+ response. Testosterone 3-ketal in the levator ani assay[32] showed weak androgenic activity (less than one-half that of testosterone) and little or no anabolic action. Estrone methyl ether 17-ketal had an activity somewhat less than one-half that of the parent estrone methyl ether.[33]

Acknowledgments.—We wish to thank Mr. J. Poletto, Mrs. A. S. Hoffman and Mrs. B. Kliebard for certain of the experiments reported here, Dr. H. G. Arlt, Jr., for his kind cooperation, Miss E. Heyder, Miss R. Partridge and associates for assistance with the biological assays, Mr. C. Pidacks and staff for the partition chromatographic work, Mr. W. Fulmor and staff for the spectroscopic and polarimetric data, and Mr. L. Brancone and staff for the microanalytical data.

Experimental

General.—Melting points, unless otherwise indicated, were taken in an open capillary tube and are uncorrected values. The **ultraviolet spectra** were determined in methanol on a Cary recording spectrophotometer and the **infrared spectra** (pressed potassium bromide discs) were carried out with a Perkin-Elmer spectrophotometer (Model 21). **Polarimetric** data were obtained in chloroform solution (*c* 0.5–1.3) unless stated otherwise. All **evaporations** were carried out under reduced pressure. Except where otherwise noted, the **petroleum ether** fraction used boiled at 60–70°. Unless otherwise stated R_f **values** were determined with the system benzene–acetic acid–heptane–water (65:80:35:20). The material used in the partition chromatography columns was **Celite 545**[34] diatomaceous earth which had been washed with 6 *N* hydrochloric acid and then distilled water until the washings were neutral, and finally with methanol. The substance then was dried to give a fluffy powder. **Hold back volume (h.b.v.)** is the volume of solvent required to fill the chromatographic column.

21-Acetoxy-20-ethylenedioxy-5α,11β,17α-trihydroxy-6β-methylpregnan-3-one.[3] —To 2.3 g. (0.0044 mole) of 21-acetoxy-3,20-bisethylenedioxy-6β-methylpreg-

(30) See footnote *c* in Table I for a description of this assay.

(31) Testing by the Endocrine Laboratories, Madison, Wisconsin.

(32) This assay is a modification of that reported by L. G. Hershberger, E. G. Shipley and R. K. Meyer, *Proc. Soc. Exp. Biol. and Med.*, **79**, 1123 (1957).

(33) Estrogen activity was determined by the measurement of uterine weight in immature female rats after oral dosing.

(34) Johns-Manville and Co.

nane-5α,11β,17α-triol[6] (I) in 30 ml. of glacial acetic acid heated on a steam bath was added 10 ml. of water. Heating was continued for 40 min. after which time 70 ml. of water was added. The product crystallized out. The reaction mixture was cooled to 0° and the product was filtered. The yield of crude product was 1.4 g. (66%), m.p. 245–247°. A sample was recrystallized twice from acetone–petroleum ether to give pure product, m.p. 255–256°; $[\alpha]^{25}D \pm 0$; $\nu_{max.}$ 3544, 1750, 1718, 1228, and 1050 cm.$^{-1}$.

Anal. Calcd. for $C_{26}H_{40}O_6$: C, 64.97; H, 8.38. Found: C, 64.68; H, 8.50.

In a 42 g. experiment, 31.7 g. (82%) of product, m.p. 250–255°, was obtained.

6α-Methylhydrocortisone 20-Ethylene Ketal (20-Ethylenedioxy-11β,17α,21-trihydroxy-6α-methyl-4-pregnen-3-one, II).[3]—To 1 g. (0.002 mole) of 21-acetoxy-20-ethylenedioxy-5α,11β,17α-trihydroxy-6β-methylpregnan-3-one in 86 ml. of methanol under a stream of nitrogen was added 86 ml. of 0.1 *N* NaOH. The solution was allowed to stand for 17 hr. at room temperature under nitrogen and 1.05 ml. of acetic acid was added. The solution was concentrated (the bath temperature 60° or below) until crystals formed. The mixture was chilled and the product filtered; 0.4 g. (46%); m.p. 223–225°. A sample was recrystallized twice from acetone–petroleum ether to give material melting at 232–233°; $[\alpha]^{25}D$ +76.3; $\lambda_{max.}$ 241 mμ (ε 14,400); $\nu_{max.}$ 3490, 1680, 1668 (sh.), 1614, 1050 cm.$^{-1}$.

Anal. Calcd. for $C_{24}H_{36}O_6$: C, 68.54; H, 8.62. Found: C, 68.30; H, 8.67.

A 30 g. experiment afforded 22.5 g. (85.5%) of II, m.p. 227–229°.

6α-Methylhydrocortisone 20-Ethylene Ketal 21-Acetate (21-Acetoxy-20-ethylenedioxy-11β,17α-dihydroxy-6α-methyl-4-pregnan-3-one, III).—A solution of 6α-methylhydrocortisone 20-ethylene ketal (II) (1 g.) in pyridine (10 ml.) was treated with acetic anhydride (3 ml.) for 16 hr. at room temperature. Ice water was added and the mixture was extracted with chloroform. The extract was washed with water, dried and evaporated. This gave a glass which, when crystallized from acetone–petroleum ether, yielded 1.0 g. (95%) of III, m.p. 180–181°. Three recrystallizations from the same solvent pair gave plates, m.p. 182–183°, or needles, m.p. 195–196°; $[\alpha]^{25}D$ +68°; $\lambda_{max.}$ 242 mμ (ε 14,900); $\nu_{max.}$ 3392, 1740, 1650, 1602, 1234, 1052 cm.$^{-1}$.

Anal. Calcd. for $C_{26}H_{38}O_7$: C, 67.51; H, 8.28. Found: C, 67.23; H, 8.47.

6α-Methylprednisolone 20-Ethylene Ketal 21-Acetate (21-Acetoxy-20-ethylenedioxy-11β,17α-dihydroxy-6α-methyl-1,4-pregnadien-3-one, V): A. Selenium Dioxide Procedure.—A solution of 11β,17α,21-trihydroxy-6α-methyl-4-pregnen-3-one 20-ethylene ketal (II) (3 g.) in a mixture of *tert*-butyl alcohol (300 ml.) and water (21 ml.) containing selenium dioxide (3 g.) was refluxed for a period of 50 hr. The metallic residue was removed by filtration and the filtrate neutralized with saturated sodium bicarbonate solution. The mixture was evaporated and the residue triturated with chloroform. The chloroform solution was dried over anhydrous magnesium sulfate and evaporated to give a glass, which upon treatment with methanol yielded an insoluble material which was removed by filtration. The methanol solution was treated with deactivated Raney nickel for a period of 2 hr. at room temperature. The nickel was removed by filtration and the filtrate evaporated. The residue was dissolved in benzene and chromatographed on silica gel. Elution with chloroform gave a mixture of products, and the eluates were combined and evaporated. The residue, which contained 6α-methyl-

prednisolone 20-ethylene ketal, was acetylated under the usual mild conditions. After work-up, partition chromatography on Celite with the system heptane 5, ethyl acetate 2, methanol 5, water 2, gave two minor non-polar components absorbing at 240 mμ. These fractions were set aside and the column was washed with methanol. The methanol wash was evaporated to dryness and the residue was crystallized from acetone–petroleum ether to give 281 mg. (9%) of XV, m.p. 206–209°. Recrystallization from the same solvent pair raised the melting point to 213–215°; $[\alpha]^{25}D$ +35°; $\lambda_{max.}$ 243 mμ (ε 14,500); $\nu_{max.}$ 3440, 1750, 1662, 1610, 1252, 1052, 890 cm.$^{-1}$.

Anal. Calcd. for $C_{26}H_{36}O_7$: C, 67.80; H, 7.88. Found: C, 67.49; H, 8.07.

B. Dichlorodicyanobenzoquinone Procedure.—A solution of 21-acetoxy-20-ethylenedioxy-11β,17α-dihydroxy-6α-methyl-4-pregnen-3-one (III) (956 mg., 2.06 mmoles) and of 2,3-dichloro-5,6-dicyanobenzoquinone[35] (635 mg.) in 75 ml. of dioxane was allowed to reflux for 3 days and then evaporated. The residue was mixed with 120 ml. of benzene and was filtered. The filtrate was washed several times with 1% aqueous potassium hydroxide solution and then with water to neutrality. The dried solution was evaporated and the residue was crystallized from ether to afford 685 mg. of yellow solid. In order to remove colored impurities, the solid was dissolved in 100 ml. of 20% acetone-in-ether and the solution was passed through a column (2 cm. high) of neutral alumina. The column was washed with 30% acetone-in-ether until the ultraviolet absorption of the effluent became very weak. The total effluent (colorless) was evaporated and the residue was crystallized from ether to afford 603 mg. (64%) of V, m.p. 205–209°.[36] Polarography[37] showed this material to contain less than 2% Δ^4-3-ketone.

The infrared spectrum was identical with that obtained for the product of procedure A.

For achieving the purification of this compound, 2.44 g. of material prepared as above and recrystallized from methylene chloride–hexane was dissolved in 40 ml. of the upper and 40 ml. of the lower phase of the solvent system heptane–ethyl acetate–methanol–water (70:30:15:6), and 80 g. of Celite was added. The mixture was packed on top of a column which had been prepared from 500 g. of Celite and 1000 ml. of the lower phase. The column (5.5 × 90 cm; 900 ml. h.b.v.) was eluted with the upper phase and the effluent stream was monitored at 240 mμ. A broad peak was eluted in the 4th–9th h.b.v. and the material contained therein was isolated by evaporation and crystallization from methylene chloride–ether. There was obtained 2.34 g. of V, m.p. 204–209°[36]; $[\alpha]D$ +39°; $\lambda_{max.}$ 240 mμ (ε 15,400) with a small bulge at 305 mμ (ε 2,070); $\nu_{max.}$ 1748(s), 1658(s), 1607(s), cm.$^{-1}$; R_f 0.74.

Anal. Calcd. for $C_{26}H_{36}O_7$: C, 67.80; H, 7.88. Found: C, 67.80; H, 7.39.

6α-Methylprednisone 20-Ethylene Ketal 21-Acetate (21-Acetoxy-20-ethylenedioxy-17α-hydroxy-6α-methyl-1,4-pregnadiene-3,11-dione, VI).—A benzene solution (55 ml.) containing 6α-methylprednisone (IV)[8] (1.0 g.), ethylene glycol (7 ml.), and *p*-toluenesulfonic acid (35 mg.) was refluxed 4.5 hr. (water trap). Excess solid sodium bicarbonate was added, the mixture was cooled, water was added

(35) E. A. Braude, A. G. Brook and R. P. Linstead, *J. Chem. Soc.*, 3569 (1954).
(36) Melting point was taken on Kofler micro hot-stage and is corrected.
(37) P. Kabasakalian and J. McGlotten, *J. Am. Chem. Soc.*, **78**, 5032 (1956).

and the combined phases were extracted with ethyl acetate (400 ml.). The extract was washed to neutrality with saturated saline solution, dried over anhydrous magnesium sulfate and evaporated to dryness. The resulting hard glass gave a slightly positive α-ketol test and could not be crystallized. It was dissolved in benzene and chromatographed on silica gel (30 g.). An initial fraction (0.15 g.) obtained by elution with chloroform was discarded. Elution with acetone afforded a second fraction (0.75 g.) which gave a negative α-ketol test. This material (6α-methylprednisone 20-ethylene ketal) could not be crystallized; it was acetylated with acetic anhydride in pyridine solution in the usual manner to give a glass which crystallized when triturated with ether, affording 215 mg. of product (VI), m.p. 170–172°. Several recrystallizations from acetone–petroleum ether raised the melting point to 173–174°; $[\alpha]^{25}D$ +109°; $\lambda_{max.}$ 235 mμ (ϵ 16,800); $\nu_{max.}$ 3596, 1746, 1707, 1665, 1624, 1603, 1238, 1044 cm.$^{-1}$.

Anal. Calcd. for $C_{26}H_{34}O_7$: C, 68.10; H, 7.47. Found: C, 68.14; H, 7.43.

21-Acetoxy-17α-hydroxy-6α-methyl-1,4,9(11)-pregnatriene-3,20-dione.—To a solution of 7.92 g. (19.04 mmoles) of 21-acetoxy-11β,17α-dihydroxy-6α-methyl-1,4-pregnadiene-3,20-dione[8] in 75 ml. of pyridine was added 3.9 g. of freshly recrystallized N-bromoacetamide. The solution was stirred in the dark for 30 min. and then was cooled to 0°. Sulfur dioxide was bubbled through the mixture until a negative starch–iodide test was obtained (3–4 min.) and the solution was added slowly to 300 ml. of ice water. The mixture was extracted with several portions of chloroform and the extracts were washed with water, dried and evaporated. The residual glass was dissolved in a minimum amount of methylene chloride, and ether was added at the boiling point till crystallization started. The product was collected in three fractions which melted[36] at 164–170°, 166–173°, 180–188° (lit.[8] m.p. 192–194°). All fractions had identical infrared absorption spectra and a single spot with R_f 0.77 on paper chromatograms. The total yield of product was 6.11 g. (82%). The preparation of this compound by the thionyl chloride–pyridine dehydration procedure has been reported previously.[10]

17α,21-Dihydroxy-6α-methyl-1,4,9(11)-pregnatriene-3,20-dione.—This compound was obtained by de-*O*-acetylation of the corresponding 21-acetate (200 mg.) according to the procedure given above for IV. The product was crystallized from acetone–hexane to give 103 mg. (57%) of material with m.p. 186–194°.[36] Recrystallization from ethyl acetate gave a sample with m.p. 193–196°.

Anal. Calcd. for $C_{22}H_{28}O_4 \cdot {}^1/_4H_2O$: C, 73.19; H, 7.95; for $C_{22}H_{28}O_4$: C, 74.13; H, 7.92. Found: C, 73.51; H, 7.99.

21-Acetoxy-9α-fluoro-11β,17α-dihydroxy-6α-methyl-1,4-pregnadiene-3,20-dione.—To a cooled (−35°) mixture of 1.33 g. (3.26 mmoles) of 21-acetoxy-17α-hydroxy-6α-methyl-9β,11β-oxido-1,4-pregnadiene-3,20-dione[10], 20 ml. of methylene chloride and 3.25 ml. of dry tetrahydrofuran, was added 2 ml. of anhydrous hydrogen fluoride. The purple solution was kept at 5° for 6.5 hr. (shorter reaction periods caused incomplete conversion of the oxide and gave mixtures of starting material and product which were difficult to separate) and then was added to a stirred mixture of methylene chloride, sodium bicarbonate and ice water. The layers were separated and the organic phase was washed with a little water, dried and evaporated. As shown by paper chromatography the residue (1.6 g.) was partially deacetylated and it was, therefore, reacetylated in the usual manner

with pyridine and acetic anhydride. Crystallization from ether gave 983 mg. (69%) of fluorohydrin, m.p. 220–228°[36] (lit. m.p.[10] 237–239°), R_f 0.41 (single spot). Additional fractions which were obtained from the filtrate were contaminated with starting material (R_f 0.74) and were not used.

21-Acetoxy-9α-fluoro-17α-hydroxy-6α-methyl-1,4-pregnadiene-3,11,20-trione.—To a cooled solution of 1.14 g. (2.62 mmoles) of the fluorohydrin described directly above, in 25 ml. of pyridine, was added the complex obtained from 1.12 g. of chromic oxide and 30 ml. of pyridine. The mixture was stirred in an ice bath for 30 min. and at room temperature overnight. Ethyl acetate was added and the mixture was filtered. The filtrate was added to 200 ml. of ice water and the organic phase was separated. The water phase was extracted with several portions of ethyl acetate and the combined organic extracts were washed with water, dried and evaporated. The residue was crystallized from methylene chloride–ether with decolorizing charcoal to give 700 mg. (62%) of triketone, m.p. 190–197°.[36] A sample obtained from a similar experiment and recrystallized from ethyl acetate had m.p. 210–214°; $[\alpha]^{25}D$ +152°; $\lambda_{max.}$ 236 mμ (ε 17,300); ν_{max} 1748 (s), 1724 (s), 1661 (s), 1618 (s) cm.$^{-1}$.

Anal. Calcd. for $C_{24}H_{29}FO_6 \cdot 0.25\ H_2O$: C, 65.96; H, 6.80; F, 4.35; for $C_{24}H_{29}FO_6$: C, 66.64; H, 6.76; F, 4.40. Found: C, 66.07; H, 6.81; F, 4.42.

9α-Fluoro-17α,21-dihydroxy-6α-methyl-1,4-pregnadiene-3,11,20-trione (VII).—A solution of 1.1 g. (2.53 mmoles) of 21-acetoxy-9α-fluoro-17α-hydroxy-6α-methyl-1,4-pregnadiene-3,11,20-trione in 30 ml. of methanol was stirred with 1.5 ml. of a 10% aqueous potassium carbonate solution under nitrogen for 1 hr. The usual work-up (crystallization from ether) afforded 840 mg. (85%) of VII, m.p. 200–205°,[36] R_f 0.27. Two recrystallizations from methylene chloride–ether gave material, after drying *in vacuo* over phosphorus pentoxide at 110° for 5 hr., with m.p. 218–222°; $[\alpha]^{24}D$ +114° (*C*, 1.13); $\lambda_{max.}$ 237 mμ (ε 15,580); $\nu_{max.}$ 1670, 1666 cm.$^{-1}$.

Anal. Calcd. for $C_{22}H_{27}FO_2 \cdot 0.25\ H_2O$: C, 66.89; H, 7.02; F, 4.81; H_2O, 1.14. Found: C, 67.22; H, 7.37; F, 4.12; H_2O, 1.12.

9α-Fluoro-6α-methylprednisone 20-Ethylene Ketal 21-Acetate (21-Acetoxy-20-ethylenedioxy-9α-fluoro-17α-hydroxy-6α-methyl-1,4-pregnadiene-3,11-dione, IX).—This compound was prepared by ketalization of ketone VII (400 mg., 0.92 mmole) with ethylene glycol according to the procedure already given for VI, and isolated by dilution with benzene. Evaporation of solvent afforded 331 mg. of colorless glass. This was purified further by chromatography on 35 g. of magnesium silicate from a benzene solution. Washing with benzene, increasing amounts of ether-in-benzene and finally with ether eluted small portions of gums which were discarded. Further washing with methylene chloride–ether (10% and 20%) eluted a total of 176 mg. of gum (negative blue-tetrazolium test) which could not be crystallized. The material was acetylated with pyridine and acetic anhydride in the usual way to give 180 mg. of gum which crystallized from ether, one recrystallization giving 39 mg. (8.8%) of IX, m.p. 214–216°[36]; $[\alpha]^{25}D$ +85°; $\lambda_{max.}$ 236 mμ (ε15,700); $\nu_{max.}$ 1754 (s), 1724 (s), 1666 (s), 1628 (m), cm.$^{-1}$.

Anal. Calcd. for $C_{26}H_{33}FO_7$: C, 65.54; H, 6.96; F, 3.97. Found: C, 65.86; H, 6.97; F, 4.00.

In subsequent preparations magnesium silicate chromatography was omitted and the crude, acetylated material was partitioned on a Celite column from the system heptane–ethyl acetate–methanol–water (70:30:17:4). Compound IX was eluted in the 4th h.b.v.

21-Acetoxy-20-ethylenedioxy-17α-hydroxy-6α-methyl-1,4,9(11)-pregnatrien-3-one (XI).—This compound was prepared from the 11β-ol III (300 mg., 0.65 mmole) by the procedure described above for the preparation of 21-acetoxy-17α-hydroxy-6α-methyl-1,4,9(11)-pregnatriene-3,20-dione. Evaporation of the chloroform extracts gave 270 mg. (94%) of material which was crystallized from ether, m.p. 180–185°; R_f 0.85; the starting material had R_f 0.51 [the system benzene–heptane–methanol–water (5:5:7:3) was used].

21-Acetoxy-20-ethylenedioxy-17α-hydroxy-6α-methyl-9β,11β-oxido-1,4-pregnadien-3-one (XII).—A mixture of 270 mg. (0.61 mmole) of the $\Delta^{9(11)}$-derivative XI, 11.2 ml. of methylene chloride, 28 ml. of *tert*-butyl alcohol, 0.56 ml. of 70% perchloric acid in 5.6 ml. of water and 101 mg. of pure N-bromoacetamide was stirred at room temperature in the dark for 15 min. A solution of 134 mg. of sodium sulfite in 7 ml. of water was added and the mixture was partially evaporated below room temperature. Water (40 ml.) was added and the mixture was extracted several times with chloroform. The combined extracts were washed with aqueous sodium bicarbonate solution and with water, and then dried and evaporated. Trituration with ether afforded 324 mg. of crude 21-acetoxy-9α-bromo-20-ethylenedioxy-11β,17α-dihydroxy-6α-methyl-1,4-pregnadiene-3-one. This product was redissolved in 12 ml. of tetrahydrofuran and heated under reflux with 100 mg. of potassium carbonate in 7 ml. of water for 45 min. The reaction mixture was neutralized with acetic acid and evaporated. The gum was dissolved in chloroform and water and the organic phase was washed with water, dried and evaporated. The residual gum (326 mg.) was acetylated in the usual manner with pyridine and acetic anhydride to afford 194 mg. (69%) of 21-acetate with m.p. 205–210°[36]; $\lambda_{max.}$ 249 mμ (ε 13,740); negative blue-tetrazolium test; R_f 0.74 [the system used was benzene–heptane–methanol–water (5:5:7:3)]. The starting material (XI) chromatographed on the same strip had R_f 0.80.

Reaction of 21-Acetoxy-20-ethylenedioxy-17α-hydroxy-6α-methyl-9β,11β-oxido-1,4-pregnadien-3-one (XII) with Hydrogen Fluoride.—A solution of 190 mg. (0.415 mmole) of the 9,11-oxide XII in 11 ml. of methylene chloride and 0.92 ml. of tetrahydrofuran was cooled to −60°. Approximately 0.9 ml. of liquid hydrogen fluoride was added and the mixture was allowed to warm to −2° at which temperature it was kept for 3 hr. The dark solution then was slurried with a mixture of sodium bicarbonate, water and methylene chloride and the organic phase was separated, washed with a little water, dried and evaporated. The residue (140 mg.) crystallized only with difficulty from ether and was shown to be a mixture by paper chromatography and Celite partition chromatography. All the components of this mixture gave positive blue-tetrazolium tests and further work on this experiment was discontinued.

9α-Fluoro-17α-hydroxy-6α-methyl-1,4-pregnadiene-3,11,20-trione (VIII).—This compound was prepared by oxidation of 9α-fluoro-11β,17α-dihydroxy-6α-methyl-1,4-pregnadiene-3,20-dione[12] by the procedure given above for the preparation of 21-acetoxy-9α-fluoro-17α-hydroxy-6α-methyl-1,4-pregnadiene-3,11,-

20-trione. Chloroform was used as the extracting solvent, evaporation of which afforded a solid residue which was crystallized from acetone–petroleum ether to give 0.81 g. (62%) of VIII, m.p. 230–233°. Three recrystallizations of a portion raised the melting point to 247–248°; $[\alpha]^{25}D$ +92° (dioxane); $\lambda_{max.}$ 233 mμ (ε 15,800); $\nu_{max.}$ 3460, 1724, 1708, 1626, 1612 cm.$^{-1}$.

Anal. Calcd. for $C_{23}H_{27}FO_4$: C, 70.57; H, 7.27; F, 5.07. Found: C, 70.46; H, 7.44; F, 4.93.

20-Ethylenedioxy-9α-fluoro-17α-hydroxy-6α-methyl-1,4-pregnadiene-3,11-dione (X).—This compound was prepared by ketalization of VIII (0.6 g.) by the procedure given above for the preparation of VI. Evaporation of solvent afforded a solid residue which was recrystallized from acetone–petroleum ether to give 479 mg. (71%) of X, m.p. 237–239°. Recrystallization from the same solvent pair raised the melting point to 243–245°; $[\alpha]^{25}D$ +79° (dioxane); $\lambda_{max.}$ 237 mμ (ε 14,900); $\nu_{max.}$ 3494, 1722, 1670, 1638, 1614, 1052 cm.$^{-1}$.

Anal. Calcd. for $C_{24}H_{31}FO_5$: C, 68.88; H, 7.47; F, 4.54. Found: C, 69.16; H, 7.79; F, 4.46.

Prednisone 20-Ethylene Ketal (17α,21-Hydroxy-20-ethylenedioxy-1,4-pregnadiene-3,11-dione, XIII).—This compound was prepared by ketalization of prednisone with ethylene glycol by the procedure already given for VI. After the reflux period, the mixture was cooled, neutralized with sodium bicarbonate and the benzene layer separated. This layer was washed to neutrality, dried and evaporated to give a glass which resisted crystallization. The ethylene glycol layer then was extracted with ethyl acetate after addition of water. The ethyl acetate extract was washed to neutrality, dried and evaporated. The residue was slurried with acetone to give 1.8 g. of XIII, m.p. 230–232°; negative α-ketol test. A mixture melting point with starting material was 201–208°. Crystallization from chloroform–acetone raised the melting point to 231–233°. A satisfactory combustion analysis could not be obtained and infrared analysis indicated solvation with chloroform. A portion of the material was crystallized from ethyl acetate–petroleum ether (90–100°) giving material melting at 232–234°; $[\alpha]^{25}D$ +115°; $\lambda_{max.}$ 237 mμ ($E^{1\%}_{1\,cm.}$ 341); infrared analysis indicated solvation with ethyl acetate, $\nu_{max.}$ 3670, 1746, 1710, 1666, 1622, 1604, 1210, 1046, 896 and 675 cm.$^{-1}$. Hydrolysis of this product by heating in 8% methanolic sulfuric acid gave material (m.p. 221–223°) identical by mixture melting point, infrared and ultraviolet comparisons with authentic prednisone.[38]

Prednisone 20-Ethylene Ketal 21-Acetate (21-Acetoxy-20-ethylenedioxy-17α-hydroxy-1,4-pregnadiene-3,11-dione).—17α,21-Dihydroxy-1, 4-pregnadiene-3, 11-dione 20-ethylene ketal (XIII) (300 mg.) was acetylated in the usual manner with acetic anhydride in pyridine solution. Crystallization and recrystallization of the product from acetone–petroleum ether gave 0.23 g. (70%) of ketal acetate, m.p. 207–209°; $[\alpha]^{25}D$ +132°; $\lambda_{max.}$ 237 mμ (ε 15,500); $\nu_{max.}$ 3364, 1754, 1706, 1666, 1624, 1608, 1226, 1046 cm.$^{-1}$.

Anal. Calcd. for $C_{25}H_{32}O_7$: C, 67.24; H, 7.68. Found: C, 67.12, 67.38; H, 7.39, 7.48.

(38) H. L. Herzog, C. C. Payne, M. A. Jevnik, D. Gould, E. L. Shapiro, E. P. Oliveto and E. B. Hershberg, *J. Am. Chem. Soc.*, **77**, 4781 (1955).

Prednisone 20-Propylene Ketal (17α,21-Dihydroxy-20-propylenedioxy-1,4-pregnadiene-3,11-dione, XIV).—A mixture of 17α,21-dihydroxy-1,4-pregnadiene-3,11,20-trione (4.0 g.), benzene (250 ml.), 1,2-propanediol (30 ml.), and *p*-toluenesulfonic acid monohydrate (150 mg.) was stirred and refluxed for 4.5 hr. with constant water take-off. After the usual workup a glass was obtained which crystallized on the addition of benzene. The solid was collected by filtration giving 1.22 g. (26%) of XIV, m.p. 148–152°; negative α-ketol test with blue tetrazolium. Recrystallization from acetone–benzene raised the melting point to 156–159°; $[\alpha]^{25}D$ +109°; λ_{max}. 238 mμ (ϵ 14,900); ν_{max}. 3424, 1708, 1670, 1630, 1610, 1043, 14.50 (benzene) cm.$^{-1}$.

Anal. Calcd. for $C_{24}H_{32}O_6 \cdot 0.5C_6H_6$: C, 71.18; H, 8.11. Found: C, 71.18, 71.04; H, 7.93, 7.92.

Prednisone 20-Propylene Ketal 21-Acetate (21-Acetoxy-17α-hydroxy-20-propylenedioxy-1,4-pregnadiene-3,11-dione.—Prednisone 20-propylene ketal (XIV) (300 mg.) was acetylated in the usual manner with acetic anhydride in pyridine solution. Water was added to the reaction solution and the mixture was extracted with ethyl acetate. The extract was washed with water, dried over anhydrous magnesium sulfate and evaporated to dryness. The residual semi-solid was crystallized from acetone–petroleum ether to yield 209 mg. (63%) of ketal acetate, m.p. 197.5–198.5°; $[\alpha]^{25}D$ +119°; λ_{max}. 238 mμ (ϵ 15,300); ν_{max}. 3260, 1752, 1714, 1670, 1636, 1612, 1244, 1048 cm.$^{-1}$.

Anal. Calcd. for $C_{26}H_{34}O_7$: C, 68.10; H, 7.47. Found: C, 68.43; H, 7.70.

Treatment of Prednisone with 1,3-Propanediol. Formation of 21-(1,3-Propylenedioxy)-1,4-pregnadiene-3,11,20-trione (XV).—A mixture of prednisone (4.0 g.), benzene (250 ml.), 1,3-propanediol (30 ml.) and *p*-toluenesulfonic acid monohydrate (150 mg.) was stirred and refluxed for 4.5 hr. with constant water take-off. After the usual workup, a glass was obtained which could not be crystallized. It was dissolved in benzene and chromatographed on silica gel (150 g.). Chloroform eluted a crystalline product which was dissolved in acetone and crystallized by addition of petroleum ether to give 1.96 g. (45%) of a material, m.p. 156–160°; negative α-ketol test with blue tetrazolium. Recrystallization from the same solvent pair raised the melting point to 159–162°; $[\alpha]^{25}D$ +230°; λ_{max}. 238 mμ (ϵ 15,700); ν_{max}. 1740, 1712, 1670, 1638, 1610, 1095 cm.$^{-1}$.

Anal. Calcd. for $C_{24}H_{30}O_5$: C, 72.33, H, 7.59. Found: C, 72.14; H, 7.75.

9α-Fluorocortisone 20-Ethylene Ketal (20-Ethylenedioxy-9α-fluoro-17α,21-dihydroxy-4-pregnene-3,11-dione, XVII).—A solution of 3,20-bis-ethylenedioxy-9α-fluoro-17α,21-dihydroxy-5-pregnen-11-one (XVI)[17] (550 mg.) in 50% aqueous acetic acid (50 ml.) was heated for 30 min. on a steam bath. The clear solution was chilled and water was added producing a gummy precipitate. The mixture was extracted with chloroform, washed with saturated sodium bicarbonate solution and then to neutrality with saturated saline solution. The solution was dried over anhydrous magnesium sulfate and evaporated to give solid XVII (0.28 g., m.p. 205–207°). The analytical sample was crystallized from acetone–petroleum ether, m.p. 226–228°; $[\alpha]^{25}D$ +102°; λ_{max}. 234 mμ (ϵ 16,500); ν_{max}. 3412, 1720, 1667, 1630, 1048 cm.$^{-1}$.

Anal. Calcd. for $C_{23}H_{31}FO_6$: C, 65.38; H, 7.40; F, 4.50. Found: C, 65.38; H, 7.79; F, 4.58.

9α-Fluorocortisone 20-Ethylene Ketal 21-Acetate (21-Acetoxy-20-ethylenedioxy-9α-fluoro-17α-hydroxy-4-pregnene-3,11-dione XVIII).—A mixture of 9α-fluorocortisone 20-ethylene ketal (XVII) (1.0 g.) in pyridine (10 ml.) was treated with acetic anhydride (2 ml.) and allowed to stand overnight at room temperature. Water was added to effect crystallization and the product (1.09 g., 100%), collected by filtration, m.p. 227–229°. Recrystallization from acetone–petroleum ether raised the melting point to 229–230°; $[\alpha]^{25}D$ +111°; $\lambda_{max.}$ 234 mμ (ε 17,600) $\nu_{max.}$ 3560, 1754, 1730, 1648, 1234, 1050 cm.$^{-1}$.

Anal. Calcd. for $C_{25}H_{33}FO_7$: C, 64.64; H, 7.16; F, 4.09. Found: C, 64.83, 64.35, 64.66; H, 7.31, 7.23, 7.35; F, 4.20.

9α-Fluorocortisone 3-Ethylene Ketal 21-Acetate (21-Acetoxy-3-ethylenedioxy-9α-fluoro-17α-hydroxy-5-pregnene-11,20-dione XIX).[19]—A mixture of 840 mg. (2 mmoles) of 21-acetoxy-9α-fluoro-17α-hydroxy-4-pregnene-3,11,20-trione (9α-fluorocortisone 21-acetate),[16] 30 mg. of *p*-toluenesulfonic acid, 15 ml. of dry dioxane and 15 ml. of 2-ethyl-2-methyl-1,3-dioxolane[18] was distilled with partial reflux through a glass helix packed column (head temperature 90–117°). The steroid went into solution after 2 hr. (5 ml. of distillate) and after another 2 hr. a solid began to precipitate. Dioxane (5 ml.) was added and heating was continued for an additional 3 hr. when a total of 15 ml. of distillate had been collected. The mixture was cooled and the precipitate was collected, washed with ether and dried to give 822 mg. (87%) of XIX, m.p. 265–275°. The analytical sample, obtained from another experiment, was recrystallized from pyridine–ethyl acetate; m.p. 282–283°; $[\alpha]^{25}D$ 0° (pyridine).

Anal. Calcd. for $C_{25}H_{33}FO_7$: C, 64.64; H, 7.16; F, 4.09. Found: C, 64.46; H, 7.23; F, 3.99.

9α-Fluorocortisone 3-Ethylene Ketal (3-Ethylenedioxy-9α-fluoro-17α,21-dihydroxy-5-pregnene-11,20-dione, XX).[19]—A suspension of 21-acetoxy-3-ethylenedioxy-9α-fluoro-17α-hydroxy-5-pregnene-11,20-dione (XIX) (820 mg., 1.76 mmoles) in 50 ml. of dioxane and 50 ml. of methanol was stirred under nitrogen with 2 ml. of 10% aqueous potassium carbonate solution for 3 hr. The resulting solution was neutralized with a few drops of acetic acid and the mixture was filtered to remove traces of solid. The filtrate was evaporated and the residue dissolved in water and methylene chloride. The organic phase was washed with a little water, dried and evaporated to afford a crystalline residue which was collected with ether; 257 mg. (29%); m.p. 229–240°. (The low yield was the result of accidental spillage of part of the methylene chloride solution.) The analytical sample obtained from another experiment was recrystallized from chloroform–acetone; m.p. 242–244°; $[\alpha]^{25}D$ 0° (dioxane).

Anal. Calcd. for $C_{23}H_{31}FO_6$: C, 65.38; H, 7.40; F, 4.50. Found: C, 64.97; H, 7.27; F, 4.10.

9α-Fluoroprednisone 20-Ethylene Ketal (20-Ethylenedioxy-9α-fluoro-17α,21-dihydroxy-1,4-pregnadiene-3,11-dione, XXI).—This compound was prepared from XVIII (464 mg., 1 mmole) by the dichlorodicyanobenzoquinone[35] procedure described above for V; the reflux period was 5 days. Evaporation of the benzene–dioxane solvent gave a gummy residue which was redissolved in 25 ml. of methanol and stirred with 1 ml. of 10% aqueous potassium carbonate solution at room temperature for 1 hr. under nitrogen. The solution was evaporated to a small

volume, diluted with water and extracted with several portions of chloroform. The extracts were dried, filtered, evaporated and triturated with ether to afford 288 mg. of solid, m.p. 187–189°. Polarography[37] and the ultraviolet spectrum showed this to be a mixture of $\Delta^{1,4}$- and $\Delta^{4,6}$-3-keto steroids. The solid (250 mg.) was dissolved in 5 ml. of the lower and 5 ml. of the upper phase of the solvent system cyclohexane–dioxane–water (60:40:8) and the solution was thoroughly mixed with 10 g. of Celite. This was added to a column which had been prepared from 150 g. of Celite and 75 ml. of the lower phase. The column (72 cm. × 30 cm.), which had a hold-back-volume of 310 ml., was eluted with the upper phase of the solvent system and the effluent stream was monitored by a recording ultraviolet spectrophotometer. A peak with adsorption at 240 mμ was eluted in the 3–4.5 h.b.v. Evaporation of relevant fractions and trituration with ether afforded 138 mg. (32%) of XXI, m.p. 236–240°. Recrystallization from methylene chloride–ether gave a sample with m.p. 239–240°; $[\alpha]^{25}D$ +42.6°; $\lambda_{max.}$ 237 mμ (ϵ 14,700). The substance was shown to be essentially pure $\Delta^{1,4}$-3-keto steroid by polarography.

Anal. Calcd. for $C_{23}H_{29}FO_6$: C, 65.69; H, 6.95; F, 4.52. Found: C, 65.35; H, 7.02; F, 4.35.

9α-Fluorocortisone 3,20-Bis-ethylene Ketal 21-Acetate (21-Acetoxy-3,20-bis-ethylenedioxy-9α-fluoro-17α-hydroxy-5-pregnen-11-one, XVI 21-Acetate).—A solution of 3,20-bis-ethylenedioxy-9α-fluoro-17α,21-dihydroxy-5-pregnen-11-one (XVI) (2.17 g.) in pyridine (35 ml.) was treated with acetic anhydride (10 ml.) in the usual manner to give 2.23 g. (95%) of XVI acetate; m.p. 210–215° dec. Recrystallization from acetone raised the melting point to 227° dec.; $[\alpha]^{25}D$ −26°; $\nu_{max.}$ 3522, 1748, 1726, 1234, 1050 cm.$^{-1}$.

Anal. Calcd for $C_{27}H_{37}FO_8$: C, 63.77; H, 7.34; F, 3.74. Found: C, 64.10; H, 7.40; F, 3.73.

21-Acetoxy-3,20-bis-ethylenedioxy-9α-fluoro-5,16-pregnadien-11-one (XXII).[17]—A solution of 21-acetoxy-3,20-bis-ethylenedioxy-9α-fluoro-17α-hydroxy-5-pregnen-11-one (XVI acetate) (2.03 g.) in pyridine (85 ml.) was chilled to −5° and thionyl chloride (8 ml.) was added. The mixture was allowed to stand overnight at −5°, and then poured into ice water. The oily mixture was extracted with ethyl acetate, the extract was washed with saturated saline, dried and evaporated. The residue was titurated with methanol to give crystalline XXII (0.68 g.), m.p. 110–113°. An additional 0.1 g., m.p. 110°, was obtained by concentration of the mother liquor (combined yield, 37%). Recrystallization of the combined fractions from methanol raised the melting point to 126–129°; $[\alpha]^{25}D$ −32°; $\nu_{max.}$ 1733, 1616, 1240, 1042 cm.$^{-1}$; [lit.[17] m.p. 115 and 130–132°; $[\alpha]D$ −42.3° (*c*, 0.86)].

Anal. Calcd. for $C_{27}H_{35}FO_7$: C, 66.10; H, 7.19; F, 3.87. Found: C, 66.02; H, 7.50; F, 3.99.

21-Acetoxy-3,20-bis-ethylenedioxy-16α,17α-dihydroxy-9α-fluoro-5-pregnen-11-one (XXIII).[17]—A solution of 21-acetoxy-3,20-bis-ethylenedioxy-9α-fluoro-5,16-pregnadien-11-one (XXII) (0.48 g.) in benzene (15 ml.) containing pyridine (0.3 ml.) was treated with osmium tetroxide (0.25 g.) and the mixture was allowed to stand overnight at room temperature. The osmium complex formed then was discharged by stirring for 4 hr. with a mixture of benzene (50 ml.), methanol

(7 ml.), potassium bicarbonate (1.7 g.) and sodium sulfite (1.7 g.). The red precipitate was removed by filtration and the filtrate diluted with chloroform. The extract was washed to neutrality with water, dried and evaporated. This gave a solid residue which was crystallized from chloroform–acetone to give 126 mg. of XXIII, m.p. 262–264°. Recrystallization from the same solvent pair gave material melting at 259–261°; $\nu_{max.}$ 3414, 1738, 1703, 1246, 1103, 1336 cm.$^{-1}$.

Anal. Calcd. for $C_{27}H_{37}FO_9$: C, 61.82; H, 7.11; F, 3.62. Found: C, 62.21; H, 7.38; F, 3.74.

9α-Fluoro-16α-hydroxycortisone 20-Ethylene Ketal 21-Acetate (21-Acetoxy-20-ethylenedioxy-9α-fluoro-16α,17α-dihydroxy-4-pregnene-3,11-dione, XXV).—A solution of 21-acetoxy-3,20-bis-ethylenedioxy-9α-fluoro-16α,17α-dihydroxy-5-pregnen-11-one (XXIII) (0.21 g.) in 50% acetic acid (30 ml.) was heated on a steam bath for 1 hr. Water was added and the product collected by filtration, which gave 90 mg. (47%) of XXV, m.p. 268–269° dec.; $[\alpha]^{25}D$ +107°; $\lambda_{max.}$ 233 mμ (ε 17,400); $\nu_{max.}$ 3510, 1740, 1690, 1640, 1248, 1048 cm.$^{-1}$.

Anal. Calcd. for $C_{25}H_{33}FO_8$: C, 62.49; H, 6.92; F, 3.95. Found: C, 62.25; H, 7.10; F, 3.89.

3,20-Bis-ethylenedioxy-9α-fluoro-11β,16α,17α,21-tetrahydroxy-5-pregnene [Presumed] 16,17-Cycloborate Ester.—A solution of 21-acetoxy-3,20-bis-ethylenedioxy-9α-fluoro-16α,17α-dihydroxy-5-pregnen-11-one (XXIII) (1.7 g.) in tetrahydrofuran (125 ml.) was chilled to 0°, treated with lithium borohydride (1.5 g.) and stirred for 5 hr. at room temperature. The mixture was neutralized carefully with acetic acid, water was added and the mixture was extracted with chloroform. The extract was washed with saturated saline solution, dried over anhydrous magnesium sulfate and evaporated. This gave 0.46 g. of product, m.p. 290° dec. The water layer was re-extracted with chloroform to give an additional 0.38 g., m.p. >290° dec. (combined yield 51%). Recrystallization of a portion changed the melting point to 268° dec. Analysis for this product indicated the probable formation of a cycloborate ester.[17] The product was used as such for acetylation to the 16,21-di-*O*-acetate.

Anal. Calcd. for $C_{25}H_{36}BFO_9$: C, 58.83; H, 7.11; F, 3.72. Found: C, 58.49; H, 7.44; F, 3.79; ash 4.1.

3,20-Bis-ethylenedioxy-9α-fluoro-11β,21-dihydroxy-5,16-pregnadiene.—Lithium borohydride reduction of XXII (4.9 g.) in tetrahydrofuran–benzene (5:1) was carried out by the procedure described directly above for the preparation of the corresponding 16α,17α-diol-presumed cycloborate ester. Solvent evaporation afforded a semi-solid substance which was crystallized from acetone–petroleum ether to give 1.58 g. of product, m.p. 202° dec. The mother liquor yielded an additional 1.00 g., m.p. 199° dec. (combined yield 57%). A portion was recrystallized from the same solvent pair, raising the melting point to 215–217°; $[\alpha]^{25}D$ − 31°; $\lambda_{max.}$ none; $\nu_{max.}$ 3440, 1622, 1034 cm.$^{-1}$.

Anal. Calcd. for $C_{25}H_{35}FO_6$: C, 66.65; H, 7.83; F, 4.22. Found: C, 66.87; H, 7.96; F, 4.53.

3,20-Bis-ethylenedioxy-9α-fluoro-11β,16α,17α,21-tetrahydroxy-5-pregnene.—Osmylation of 3,20-bis-ethylenedioxy-9α-fluoro-11β,21-dihydroxy-5,16-pregnadiene (1.26 g.) was effected by the procedure described above for the preparation of XXIII. Evaporation of the chloroform extracts gave 0.75 g. of product, m.p.

235–236°. The water layer then was re-extracted with chloroform, the extract washed with water, dried and evaporated to give an additional 0.63 g. of product, m.p. 230–231° (combined yield 100%). Crystallization from acetone–petroleum ether raised the melting point to 245–247°; $[\alpha]^{25}D$ −28° (methanol); $\nu_{max.}$ 3500, 1056 cm.$^{-1}$.

Anal. Calcd. for $C_{25}H_{37}FO_6$: C, 61.97; H, 7.70; F, 3.92. Found: C, 62.12; H, 7.97; F, 3.62.

3,20-Bis-ethylenedioxy-16α,21-diacetoxy-9α-fluoro-11β,17α-dihydroxy-5-pregnene (XXIV). A.—A solution of 3,20-bis-ethylenedioxy-9α-fluoro-11β,16α,17α,21-tetrahydroxy-5-pregnene (1.05 g.) was acetylated in the usual manner with acetic anhydride in pyridine solution to give 1.11 g. (90%) of product, m.p. 170–215° (dec. at 215°). The infrared spectrum was identical with that of the material prepared by procedure B (below).

B.—A solution of 3,20-bis-ethylenedioxy-9α-fluoro-11β,16α,17α,21-tetrahydroxy-5-pregnene presumed 16,17-cycloborate ester (0.5 g.) in pyridine was treated with acetic anhydride in the usual manner to give 0.42 g. (72%) of XXIV, m.p. 164–234° (dec. at 234°). Crystallization from acetone–petroleum ether gave a gelatin-like precipitate, m.p. 147–183°. This material was dissolved in acetone, treated with decolorizing charcoal, filtered and evaporated; m.p. 147–235° (dec. at 235°); $[\alpha]^{25}D$ −46°; $\lambda_{max.}$ none; $\nu_{max.}$ 3460, 1748, 1244, 1050 cm.$^{-1}$.

Anal. Calcd. for $C_{29}H_{41}FO_{10}$: C, 61.25; H, 7.29; F, 3.34. Found: C, 61.48; H, 7.67; F, 3.54.

9α-Fluoro-16α-hydroxyhydrocortisone 20-Ethylene Ketal 16,21-Diacetate (16α,21-Diacetoxy-20-ethylenedioxy-9α-fluoro-11β,17α-dihydroxy-4-pregnen-3-one, XXVI).—A solution of 16α,21-diacetoxy-3,20-bis-ethylenedioxy-9α-fluoro-11β,17α-dihydroxy-5-pregnene (XXIV) (1.0 g.) in aqueous acetic acid (75%, 40 ml.) was heated on the steam bath for 1 hr., water was added and the mixture extracted with chloroform. The extract was washed with saturated sodium bicarbonate solution and then to neutrality with water, dried and evaporated to give 0.77 g. of XXVI, m.p. 158–250° (dec. at 250°); $[\alpha]^{25}D$ +23°.

Anal. Calcd. for $C_{27}H_{37}FO_9$: C, 61.82; H, 7.11; F, 3.62. Found: C, 61.46; H, 7.45; F, 3.52.

Triamcinolone 20-Ethylene Ketal 16,21-Diacetate (16α,21-Diacetoxy-9α-fluoro-20-ethylenedioxy-11β,17α-dihydroxy-1,4-pregnadien-3-one).—A solution of 16α,21-diacetoxy-20-ethylenedioxy-9α-fluoro-11β,17α-dihydroxy-4-pregnen-3-one (XXVI) (0.51 g.) in dioxane (200 ml.) was refluxed with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone[35] (350 mg.) for 50 hr. The mixture was evaporated to dryness and the residue taken up in benzene. The benzene solution was washed to neutrality with water, 1% potassium hydroxide (cold) and again with water. The extract was then evaporated to dryness to give 0.46 g. of dienone; m.p. 232° dec.; $\lambda_{max.}$ 238 mμ (ε 3,100); $\nu_{max.}$ 3510, 1754, 1668, 1614, 1244, 1062 cm.$^{-1}$.

Anal. Calcd. for $C_{27}H_{35}FO_9$: F, 3.64. Found: F, 3.19.

Triamcinolone-20-ethylene Ketal (20-Ethylenedioxy-9α-fluoro-11β,16α,17α,21-tetrahydroxy-1,4-pregnadien-3-one, XXVII).—This compound was prepared by deacetylation of the corresponding 16,21-diacetate (0.45 g.) according to the procedure described above for the preparation of IV. After neutralization with

glacial acetic acid, the solution was evaporated to near dryness. Water was added to effect crystallization and the product collected by filtration to give 53 mg. (14%) of XXVII; m.p. 224–230° (dec. at 258°); negative α-ketol blue-tetrazolium test. Recrystallization of the crystalline fraction from acetone–petroleum ether raised the melting point to 235–236°; $[\alpha]^{25}D$ +38° (methanol); $\nu_{max.}$ 3448 (s), 1675 (s), 1631 (m), 1612 (sh.) cm.$^{-1}$; λ_{max} 239 mμ (ε 15,048).

Anal. Calcd. for $C_{23}H_{31}FO_7 \cdot H_2O$: C, 60.52; H 7.29; F, 4.16. Found: C, 60.90; H, 7.28; F, 4.01.

2α-Methylhydrocortisone 20-Ethylene Ketal (20-Ethylenedioxy-11β,17α,21-trihydroxy-2α-methyl-4-pregnen-3-one, XXX).[19,23]—To a stirred mixture of 872 mg. (1.77 mmoles) of 20-ethylenedioxy-3,11β,17α,21-tetrahydroxy-2-methoxalyl-2,4-pregnadiene (XXVIII),[20–22] 1.76 g. of freshly powdered anhydrous potassium carbonate and 21 ml. of acetone was added 2.1 ml., and after 24 hr. another 2 ml., of methyl iodide. After 48 hr., the mixture was filtered and the filtrate evaporated. Precipitate and residue were dissolved in chloroform-water, and the layers were separated. The organic layer was washed with a little water, dried and evaporated. The residue (898 mg.) was dissolved in 14 ml. of methanol and stirred under reflux with 7.1 ml. of 10% aqueous sodium carbonate solution for 1 hr. Water (30 ml.) was added and most of the methanol was evaporated. The mixture was extracted with chloroform and the water phase, which contained most of the yellow color and gave a positive enol test, was discarded. The dried chloroform solution was evaporated and the residue was crystallized from ether to afford 226 mg. (30% crude yield) of solid with m.p. 226–240°. Several recrystallizations from methylene chloride gave material with m.p. 244–248°; $[\alpha]^{25}D$ +107°; $\lambda_{max.}$ 242 mμ (ε 14,100); $\nu_{max.}$ 1669–1658 (s) cm.$^{-1}$.

Anal. Calcd. for $C_{24}H_{36}O_6 \cdot 0.5\ H_2O$: C, 67.11; H, 8.68; H_2O, 2.09. Found: C, 66.96; H, 8.35; H_2O, 2.41.

2-Ethoxalyl-20-ethylenedioxy-3,11β,17α,21-tetrahydroxy-6α-methyl-2,4-pregnadiene (XXIX).—To an azeotropically dried solution of 2 g. (4.76 mmoles) of 20-ethylenedioxy-11β,17α,21-trihydroxy-6α-methyl-4-pregnen-3-one (II) in 75 ml. of benzene was added 3.9 ml. of diethyl oxalate and then, under a blanket of nitrogen, 1 g. of sodium hydride (50% oil dispersion). The reaction was started by the addition of a few drops of ethanol, the mixture was stirred under nitrogen for 24 hr. and then diluted with 50 ml. of benzene and extracted with four 40 ml. portions of water. The dark extracts were added to 30% aqueous sodium dihydrogen phosphate solution and this mixture was in turn extracted several times with chloroform. The combined extracts were washed with water, dried and evaporated. The residue (1.23 g.) was a yellow glass (strong enol test) which could not be crystallized.

2α,6α-Dimethylhydrocortisone 20-Ethylene Ketal (20-Ethylenedioxy-11β,17α,-21-trihydroxy-2α,6α-dimethyl-4-pregnen-3-one, XXXI).—The crude ethoxalyl derivative XXIX (1.23 g.), was methylated by the procedure described above for the preparation of XXX. The residue (1.09 g.) from evaporation of the acetone filtrate was dissolved in 30 ml. of methanol and heated under reflux with 1.6 g. of potassium acetate for 2 hr. The mixture was evaporated and the residue chromatographed on Celite. The material (740 mg.) was dissolved in 15 ml. of the upper and 25 ml. of the lower phase of the system ethyl acetate–heptane–

methanol–water (20:80:12:8). Celite (50 g.) was added and the mixture was packed on top of a column which had been prepared from 400 g. of Celite thoroughly mixed with 200 ml. of the lower phase. The column (5.5 × 60 cm., 900 ml. h.b.v.) was developed with the upper phase and the effluent stream was monitored at 240 mμ. The desired product was eluted in the 5.5–7.5 h.b.v. and was isolated by evaporation of pooled fractions and crystallization from ether–methylene chloride. There was obtained 130 mg. (6.3% over all from II) of XXXI, m.p. 220–223°. A sample recrystallized from the same mixture showed m.p. 221–223°; $[\alpha]^{25}D$ + 54°; λ_{max}. 243 mμ (ε 13,400); ν_{max}. 1666 cm.$^{-1}$.

Anal. Calcd. for $C_{25}H_{38}O_6$: C, 69.09; H, 8.81. Found: C, 68.53; H, 8.98.

2,6α-Dimethylprednisolone 20-Ethylene Ketal (21-Acetoxy-20-ethylenedioxy-11β,17α-dihydroxy-2,6α-dimethyl-1,4-pregnadien-3-one, XXXII).—Acetylation of XXXI in the usual manner with acetic anhydride in pyridine gave a crude acetate, which was treated with dichlorodicyanobenzoquinone[7] by the procedure described above for V. Evaporation of the washed and dried benzene solution gave a solid which was dissolved in a small amount of acetone and filtered through activated charcoal. Hexane was added at the boiling point until a solid precipitated as a gel. The dried material weighed 13 mg.; m.p. 163–168°; 92.5% $\Delta^{1,4}$-3-one by polarography[37]; λ_{max}. 250 mμ (ε value inaccurate for lack of sample); ν_{max}. 1748, 1663, 1626 cm.$^{-1}$.

Anal. Calcd. for $C_{27}H_{38}O_7$: C, 68.33; H, 8.07. Found: C, 67.48; H, 7.71.

Synthesis of Sulfonylhydrazine Derivatives with Monoamine Oxidase Inhibitory Activity[1]

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A number of aralkylsulfonylhydrazine derivatives were prepared as possible inhibitors of monoamine oxidase. *In vitro* results, as well as *in vivo* effects on mouse brain serotonin levels, are reported. Several 1-sulfonyl-1-aralkylhydrazines were strongly active in both tests. Methods of preparation of 1-substituted-sulfonyl-1-aralkylhydrazines are described.

The discovery of the clinically useful antidepressant activity of