ether gave the mixture of XXVI and XXVII (4.2 g): mp 110–120°; uv, λ_{max} 237 (sh), 242.5, 251 (sh) mμ (ε 18,852, 19,820, 13,070); nmr, 3-proton triplet δ 0.92, J = 6.5 cps (18a-H), 3-proton singlet δ 2.08 (acetate CH₃), 1-proton multiplet (broad) δ 3.92 (3ξ-H), 1-proton triplet δ 4.80, J = 8 cps (17α-H), 1-proton doublet, J = 5.5 cps (11-H). An aliquot (166 mg) of the foregoing mixture was shaken at atmospheric pressure with H₂ in methanol (10 ml) containing 5% Pd–C (100 mg) until 12 ml of gas had been absorbed (30 min). Recrystallization of the product from ether–pentane gave a mixture containing III and IV, mp 109–112°, having a closely similar infrared absorption spectrum to a mixture of III and IV obtained from the NaBH₄ reduction of II, and shown by tlc to contain ca. 80% of III and 20% of IV. The mother liquors of this material were shown by tlc to contain the same mixture. The mixture of XXVI and XXVII (2 g) was treated with Zn–Cu couple (10 g) and CH₂I₂ (20 g) in ether (150 ml) for 1 hr as previously described, and the mixture was heated in an autoclave for 3 hr at 90°. Trituration of the crude product with ether gave crystals formulated as XXIX (0.12 g): mp 170–180° (after preliminary softening at 150°); nmr, 2-proton singlet δ 0.70 (19-H), 3-proton triplet δ 0.93, J = 6.5 cps (18a-H), 3-proton singlet δ 2.04 (acetate CH₃), 1-proton multiplet δ 3.63 (broad), half-height width 30 cps (3-H), 1-proton triplet δ 4.82, J = 8 cps (17α-H), 1-proton doublet δ 5.43, J = 5.5 cps (11-H). The residue in the mother liquors was chromatographed on neutral alumina (60 g), benzene–hexane (1:1) eluting unidentified material (0.72 g), possibly 3-alkoxy steroids,[11] and benzene–ethyl acetate (9:1) eluting a gum (0.51 g) formulated as XXVIII: nmr, 2-proton singlet δ 0.55 (19-H),

3-proton triplet δ 0.97, J = 6.5 cps (18a-H), 3-proton singlet δ 2.10 (acetate CH₃), 1-proton multiplet δ 3.63 (broad), half-height width 30 cps (3-H), 1-proton triplet δ 4.91, J = 8 cps (17α-H), 1-proton doublet δ 5.72, J = 5.5 cps (11-H). Benzene–ethyl acetate (8:2) eluted further XXIX (0.04 g). XXVIII (0.04 g) was oxidized with 8 N H₂CrO₄ (0.04 ml) in acetone (10 ml) and the product was worked up as usual to give an oily ketone (0.032 g) uniform by tlc; nmr, 2-proton AB system pair of doublets δ 0.55 and 0.80, J = 5.5 cps (19-H), 3-proton triplet δ 0.97, J = 6.5 cps (18a-H), 3-proton singlet δ 2.08 (acetate CH₃), 2-proton singlet δ 2.52 (4-H), 1-proton triplet δ 4.80, J = 8 cps (17α-H), 1-proton doublet δ 5.70, J = 6 cps (11-H). The ketone (20 mg) was kept for 1.5 hr at room temperature in CHCl₃–HCl. The product was recrystallized successively from ether and acetone to give XXX (16 mg): mp 161–164°; λ_{max} 242 mμ (ε 13,100); nmr, 3-proton triplet δ 0.98, J = 6.5 cps (18a-H), 3-proton singlet δ 2.04 (acetate CH₃), 2-proton AB system, pair of doublets δ 3.42 and 3.68, J = 11 cps (9a-H), 1-proton broad singlet δ 5.95, half-height width 5 cps (4-H).

Anal. Calcd for C₂₂H₃₁ClO₃: Cl, 9.35; M, 378.0. Found: Cl, 9.9; M − 36 (by mass spectroscopy), 342.

The Synthesis of Certain 17α-Alkyl Corticoids

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The preparation of several 17-alkyl-17-deoxy steroids of the corticoid series is described. The 17-alkyl group was introduced via Li–liquid ammonia treatment of 3β-acetoxy-5α-pregna-9(11),16-dien-20-one (I) followed by appropriate alkylation. Methyl groups at the 16α and 17α positions were introduced by a procedure involving 1,4 addition of methylmagnesium iodide to the Δ¹⁶-20-keto system of I, or its corresponding 3-tetrahydropyranyl derivative, followed by methylation of the 16α-methyl-17-enolate anion thus generated. Further elaboration of the resulting 17-alkyl derivatives was carried out by standard procedures. Of particular interest is the synthesis of the 17-methyl and 17-ethyl derivatives of 17-deoxy-9α-fluoroprednisolone 21-acetate and of 17-deoxy-17-methyldexamethasone 21-acetate.

In this paper we report the synthesis of a variety of 17α-methyl and ethyl derivatives of the corticoid type. Previous reports[1a] from this laboratory have described a useful procedure for the preparation of 17-alkyl-pregnan-20-ones, which involves the alkylation of an intermediate 17-enolate anion developed by treatment of a 16-pregnen-20-one with a solution of Li, Ca, or Ba in liquid ammonia. The application of this method to the synthesis of a series of orally effective 17-alkyl-progesterone derivatives has also been described.[1,2] For the present study we have utilized this method and also have developed a convenient process for the simultaneous introduction of methyl groups at the 16α and 17α positions involving Grignard 1,4 addition to a Δ¹⁶-20-ketone followed by methylation of the intermediate enolate anion.

Some years prior to this investigation Engel described the synthesis of 17-methylcorticosterone[3] and its 11-dehydro derivative.[4] From the results reported at that time it appeared that replacement of the hydroxy group at C₁₇ with a methyl group results in a decrease in glucocorticoid and antiinflammatory activity as measured by liver glycogen and local granuloma assays, respectively. On the other hand, the possible effect of this modification on mineralocorticoid activity aroused our interest since it appeared that, with regard to this important parameter of biological activity, there was a qualitative difference between 17-methyl-11-dehydrocorticosterone acetate and cortisone acetate.[4] We have been unable to find any further reports concerning this preliminary observation nor, to our knowledge, has there been an application of the possibilities thus raised to a 9α-fluoro-substituted corticoid.

With the hope that 17-alkylation in the corticoid series might in fact result in a favorable separation of certain of the parameters of corticoid activity and encouraged by our own observations[2] in the progesterone series that at least in some instances 17-ethyl and

(1) (a) M. J. Weiss, R. E. Schaub, G. R. Allen, Jr., J. F. Poletto, C. Pidacks, R. B. Conrow, and C. J. Coscia, *Tetrahedron*, **20**, 357 (1964); (b) see also R. Deghenghi, C. Revesz, and R. Gaudry, *J. Med. Chem.*, **6**, 301 (1963).

(2) M. J. Weiss, R. E. Schaub, J. F. Poletto, G. R. Allen, Jr., and C. Pidacks, *Steroids*, **1**, 608 (1963).

(3) C. R. Engel, *Can. J. Chem.*, **35**, 131 (1957).

(4) C. R. Engel, *J. Am. Chem. Soc.*, **78**, 4727 (1956).

Scheme I

17-propyl derivatives were more effective than the corresponding 17-methyl derivatives, we undertook the synthesis of certain 17-alkyl corticoids, in particular those containing the activity-enhancing 9α-fluoro principle.

As a starting point for our syntheses, we chose 3β-acetoxy-5α-pregna-9(11),16-dien-20-one (I),[5,6] a compound having the requisite 16-dehydro-20-keto system for 17-alkylation, the 9(11) double bond for subsequent ring C elaboration and the 3-oxy function as an entry for ring A development. The preparation of this substance from hecogenin has been described.[6] 17-Methylation of I by the lithium–liquid ammonia procedure[1] was achieved in fair yield (see Scheme I). For the preparation of analogs in the 21-deoxy series, the resulting 17-methyl-5α-pregn-9(11)-en-3β-ol-20-one (IIa) was oxidized (Jones' reagent) to the 3-ketone Va, which on dehydrogenation with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ)[7] afforded the intermediate

triene IVa. Direct treatment of the 17-methyl-3-ol IIa with DDQ[7b] also gave triene IVa, but in poorer yield than the two-step process. Submission of IVa to the usual three-step procedures[8] then furnished the ring C fluorohydrin VIIIa and the chlorohydrin IXa (via HCl treatment of the intermediate 9β,11β-oxide), and reaction with chlorine[9] gave the 9α,11β-dichloro derivative Xa.

For the preparation of the 21-oxy derivatives, 17-methyl-5α-pregn-9(11)-en-3β-ol-20-one (IIa)[10] was subjected to 21-ethoxalylation to give IIIa. This reaction apparently is hindered by the presence of the 17-alkyl group and requires in such instances conditions more vigorous than usual.[11] Treatment of the 21-ethoxalyl derivative IIIa with 1 molar equiv of bromine followed by deethoxalylation gave the 21-bromide

(5) C. Djerassi, H. Martinez, and G. Rosenkranz, J. Org. Chem., 16, 1278 (1951).

(6) R. K. Callow and V. H. T. James, J. Chem. Soc., 4739 (1956).

(7) (a) D. Burn, D. N. Kirk, and V. Petrow, Proc. Chem. Soc., 14 (1960); (b) G. Muller, J. Martel, and C. Huynh, Bull. Soc. Chim. France, 2000 (1961).

(8) J. Fried and E. F. Sabo, J. Am. Chem. Soc., 79, 1130 (1957); R. F. Hirschmann, R. Miller, J. Wood, and R. E. Jones, ibid., 78, 4956 (1956).

(9) M. Heller, R. H. Lenhard, and S. Bernstein, Steroids, 1, 331 (1963); C. H. Robinson, L. E. Finckenor, R. Tiberi, and E. P. Oliveto, J. Org. Chem., 26, 2863 (1961).

(10) See J. Elks, G. H. Phillipps, and W. F. Wall, J. Chem. Soc., 4001 (1958), for the conversion of the corresponding 17-hydroxy compound to 9α-fluorohydrocortisone 21-acetate and 9α-fluoroprednisolone 21-acetate.

(11) R. Deghenghi, Y. Lefebvre, P. Mitchell, P. F. Morand, and R. Gaudry, Tetrahedron, 19, 289 (1963).

VIa, which on displacement with sodium acetate in di-methylformamide[12] (DMF) furnished the 21-acetoxy derivative VIIa. Oxidation to the 3-ketone XIa[13] and DDQ dehydrogenation[7] then afforded the 21-acetoxy-17-methyltriene XIVa. In the usual manner, XIVa was converted to the ring C fluorohydrin XIIIa (17-deoxy-17-methyl-9α-fluoroprednisolone 21-acetate) and the 9α,11β-dichloride XIIa.

17-Ethylpregn-9(11)-en-3β-ol-20-one (IIb) was also prepared by the Li–liquid ammonia procedure and application of the above-described sequences to it afforded the following 17-ethyl corticoid derivatives: VIIIb (21-deoxyfluorohydrin), IXb (21-deoxychlorohydrin), Xb (21-deoxy dichloride), and XIIIb (17-deoxy-17-ethyl-9α-fluoroprednisolone 21-acetate).

The introduction of methyl groups at the 16α and 17α positions (see C) was conveniently achieved by a procedure involving 1,4 addition of CH₃MgI to a Δ¹⁶-20-keto system (A) followed by methylation of the 16α-methyl-17-enolate anion (B) thus generated.[14]
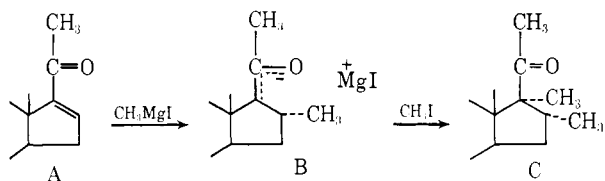
Application of this method to the Δ¹⁶-20-ketone 3-tetrahydropyranyl ether XV gave, after acid hydrolysis, a 40% yield of the 16α,17α-dimethyl derivative IIc. With the 3-acetoxy derivative I, the yield of IIc was only 20%. The assignment of the α configuration to a 16-methyl group introduced by this process is of course well established.[15] The position and α configuration for the 17-methyl group is defined by nmr data (two three-proton singlets for the 17- and 21-methyl groups) and a positive Cotton effect in the ORD curve.[16] Although the enolate anion developed by Li–liquid ammonia treatment of a Δ¹⁶-20-ketone undergoes reaction with a considerable variety of alkylating agents,[1a] we were unable to effect a satisfactory ethylation of the 16α-methyl enolate anion derived from Grignard addition to XV. It is conceivable that in this instance the steric effect of the 16α-methyl group combined with the additional steric requirements of ethyl, in comparison to methyl, was sufficient to inhibit reaction.

Conversion of the 16α,17α-dimethyl derivative IIc to a variety of corticoid analogs was accomplished by the various procedures described above for the 17-
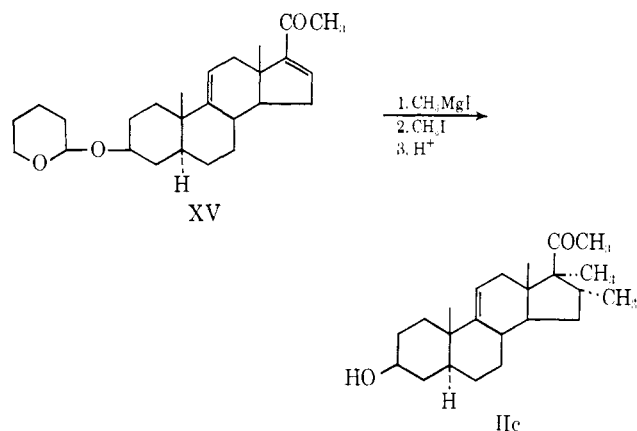
methyl series with the following exception. The 21-bromide VIc was more satisfactorily prepared by direct bromination (presence of HCl)[17] of IIc than via the ethoxalyl intermediate IIIc. Thus this procedure (after acetate displacement) afforded the 21-acetoxy derivative VIIc in 55% yield over-all from IIc, whereas the over-all yield was only 21% when the bromide VIc was prepared by the ethoxalyl route. Superior results were also obtained when this procedure was applied to the 17-ethyl series (see Experimental Section).

The 16α,17α-dimethyl corticoid analogs prepared from IIc were the following: in the 21-deoxy series, VIIIc (ring C fluorohydrin), IXc (chlorohydrin), and Xc (dichloride); in the 21-acetoxy series, XIIc (dichloride) and XIIIc (17-deoxy-17-methyldexamethasone 21-acetate).

Biological Evaluation.—The various compounds of this study were evaluated for corticoid activity in a 48-hr rat thymolytic assay[18] (subcutaneous route of administration). Only four compounds (VIIIc and XIIIa–c) were of any interest, the others being either inactive or approximately no more than one-third as active as hydrocortisone. The potencies determined for these four compounds are given in Table I, which

TABLE I
THYMOLYTIC POTENCIES

Compound	Thymus involution[a]
Hydrocortisone	1
VIIc	1
XIIIa	1
XIIIb	1
XIIIc	14.5 (7.5–29.8)
Prednisolone	2.2 (1.8–2.7)
Triamcinolone	3.8 (3.4–4.1)
Methylprednisolone	7.4 (6.1–8.9)
Dexamethasone	45.0 (37.0–55.0)

[a] All assays were carried out by Dr. G. Tonelli and staff of the Experimental Therapeutics Section of these laboratories by the method described in ref 18; values in parentheses are 95% confidence limits.

also includes comparable values obtained in our laboratories for several clinically useful corticoids. The most active compound of the 17-alkyl series was 17-deoxy-17-methyldexamethasone 21-acetate (XIIIc) with a potency of 14.5 relative to hydrocortisone. Thus, XIIIc

(12) N. N. Suvorov, L. V. Sokolova, Z. A. Yaroslavtseva, Zh. D. Ovchinnikova, V. S. Murasheva, and F. Ya. Leibel'man, Zh. Obshch. Khim., 31, 3715 (1961); Chem. Abstr., 57, 9917d (1962).

(13) A serious effort to introduce the ring C fluorohydrin at this stage was unsuccessful (note the reference cited in footnote 10).

(14) Enolate anions formed by Grignard 1,4 addition have been used to introduce the 17α-hydroxy group via the Δ¹⁷(²⁰)-enol acetate obtained by acetylation of the anion [K. Heusler, J. Kebrle, C. Meystre, H. Überwasser, P. Wieland, G. Anner, and A. Wettstein, Helv. Chim. Acta, 42, 2043 (1959)].

(15) G. E. Arth, D. B. R. Johnston, J. Fried, W. W. Spooncer, D. R. Hoff, and L. H. Sarett, J. Am. Chem. Soc., 80, 3160 (1958).

(16) Various 17-alkylprogesterone 3-ethylene ketals as well as progesterone 3-ethylene ketal give a positive Cotton effect.[1a] On the other hand, several 17α-pregn-20-ones have been reported to show a negative Cotton effect [C. Djerassi, "Optical Rotatory Dispersion," McGraw-Hill Book Co., Inc., New York, N. Y., 1960, p 51; W. A. Struck and R. L. Houtman, J. Org. Chem., 26, 3883 (1961)]. Struck and Houtman also have shown that this diagnostic procedure is valid in the presence of a variety of 16-substituents.

(17) French Patent 1,349,191 (Jan 17, 1964); Chem. Abstr., 61, 4439g (1964).

(18) I. Ringler and R. Brownfield, Endocrinology, 66, 900 (1960).

appears to be more active than several of the clinically established agents, although it is only about one-third as active as dexamethasone 21-acetate. In a mineralocorticoid assay,[19] XIIIc was found to cause an increase in sodium and urine excretion. In this assay, VIIIc, XIIIa, and XIIIb also did not cause Na+ or urine retention. Thus, it is interesting to note that introduction of a methyl or ethyl group into the 17 position of 1-dehydro-9α-fluorocorticosterone results in a reversal of the strong sodium-retaining character of the parent molecule[20] and of the 17-hydroxy derivative[21] as well. However, at least in comparison to the 17-hydroxy derivatives, the 17-alkyl derivatives are substantially less active.[22]

Experimental Section

General.—Melting points were determined in open capillary tubes on a Mel-Temp apparatus and are corrected. Unless otherwise noted, optical rotations were measured at 25° in CHCl₃ (c 0.5-1.0). Ultraviolet spectra were determined in MeOH with a Cary recording spectrophotometer and infrared spectra were obtained in KBr disks with a Perkin-Elmer spectrophotometer (Model 21). Nmr spectra were determined with a Varian A-60 spectrometer in (CDCl₃, Me₄Si). The optical rotatory dispersion curves were obtained with a Perkin-Elmer ORD attachment to a Cary Model 14 spectrophotometer at 25° in dioxane solution (c ~2). The petroleum ether used was that fraction boiling at 60-70°. Solutions were dried (MgSO₄) and all evaporations were carried out at reduced pressure. Physical and analytical results for some of the compounds can be found in Table II.

3β-Hydroxy-17-methyl-5α-pregn-9(11)-en-20-one (IIa).—According to the alkylation procedure described directly below, a solution of 46 g of 3β-acetoxy-5α-pregn-9(11),16-dien-20-one (I) in 350 ml of tetrahydrofuran (THF) was added dropwise to a solution of 3.06 g of Li in about 3 l. of liquid NH₃. The crude product was isolated with CH₂Cl₂ and chromatographed on silica gel. The desired product was eluted with 20% ether in benzene. The combined eluates were taken to dryness and the residue was recrystallized from acetone to give 7.3 g (16%) of product, mp 180-184°.

From a pilot experiment, material melting at 184-189° was obtained after several recrystallizations from acetone; negligible ultraviolet absorption at 20 μg/ml; λmax^CCl₄ 3.42, 5.87 μ; [α]D +10°; nmr, intact CH₃ signals at 36 (18-H), 58 (19-H), 68 (17-CH₃), and 128 (21-H) cps; ORD,[16] positive Cotton effect, [M]₂₆₈,₃₀₇,₃(7.4₅₀,₅₈₉ −3500°, +3130°, +3130°, +76°, +6.6°.

Anal. Calcd for C₂₂H₃₄O₂: C, 79.95; H, 10.37. Found: C, 80.17; H, 10.29.

17-Ethyl-3β-hydroxy-5α-pregn-9(11)-en-20-one (IIb).—A solution of 15.8 g of I[5,6] in 100 ml of purified THF was added to a stirred solution of 0.918 g of Li in approximately 1 l. of liquid NH₃ (dried by the prior addition of the minimum amount of Li necessary to produce a permanent blue color). Toward the end of the addition the blue color faded and finally was completely discharged. To the resulting milky solution was added, dropwise, 25 ml of ethyl iodide and stirring was continued for 18 hr. NH₄Cl (10 g) was added followed by 200 ml of water and 500 ml of ether. The ether layer was separated and the aqueous layer was extracted further with ether. The combined extracts were washed with water, dried, and evaporated to dryness. The resulting amorphous material (18 g) was dissolved in 50 ml of benzene and chromatographed on silica gel. The desired product was eluted

(19) This assay is based on the response of adrenalectomized immature male rats to a 16-μg subcutaneous dose as determined by 5-hr urine collections.

(20) D. Taub, R. D. Hoffsommer, and N. L. Wendler, J. Am. Chem. Soc., 79, 452 (1957).

(21) J. Fried and A. Borman, Vitamins Hormones, 16, 335 (1958).

(22) Neither 9α-fluoroprednisolone nor 1-dehydro-9α-fluorocorticosterone were assayed by the method of ref 18. However, thymus involution potencies ranging from 8 to 17 have been reported for 9α-fluoroprednisolone from four laboratories (see I. Ringler, Methods Hormone Res., 3, 267 (1964)], and a potency range of 3-10 in a mouse oral liver glycogen assay has been reported[20] for 1-dehydro-9α-fluorocorticosterone.

with 15% ether in benzene. The combined eluates were evaporated to dryness and the residue was recrystallized from acetone-petroleum ether to give 2.32 g (16%) of product, mp 199-201°. Further recrystallization from the same solvent pair afforded white crystals: mp 200-202°; [α]D −9.4°; no significant absorption in the ultraviolet; λmax 2.86, 5.94, 6.10 μ; nmr, 35 (18-H), 44 (triplet, J = 7 cps; CH₃ of 17-ethyl), 57 (19-H), 121 (21-H), 212 (5-H), 322 (11-H) cps; ORD,[16] positive Cotton effect, [M]₂₆₈,₃₀₇,₃(7.4₅₀,₅₈₉ −4130°, +4050°, +3270°, +86°, 0°.

Anal. Calcd for C₂₃H₃₆O₂: C, 80.18; H, 10.53. Found: C, 80.29; H, 10.73.

Procedure A. Oxidation of 3β-ol to 3-Ketone by Jones' Reagent. Preparation of 17-Methyl-5α-pregn-9(11)-ene-3,20-dione (Va).—To a solution of 3 g of IIa in 300 ml of reagent acetone, stirred in an ice bath, was added dropwise 2.7 ml of Jones' reagent.[23] After 5 min the mixture was poured into 1500 ml of iced water and the resulting solid was collected and recrystallized from CH₂Cl₂-Et₂O to give 2.42 g (81%) of product, mp 188-190°. In a pilot experiment the product had mp 189-191°; [α]D +30°; no significant ultraviolet absorption; λmax 5.86, 5.90, 6.10 μ.

Anal. Calcd for C₂₂H₃₂O₂·0.375H₂O: C, 78.82; H, 9.84; H₂O, 2.01. Found: C, 79.43; H, 9.84; H₂O, 2.14 (K-F).

Formation of Ring A Dienone by Procedure B. Dehydrogenation of Ring A Ketone with DDQ. Preparation of 17-Methyl-pregna-1,4,9(11)-triene-3,20-dione (IVa) from 17-Methyl-5α-pregn-9(11)-ene-3,20-dione (Va).—A solution of 780 mg of Va and 1.62 g (3 molar equiv) of DDQ[7] in 65 ml of purified dioxane was heated at the reflux temperature for 18 hr. The filtered solution was washed successively (8% NaOH, NaCl, H₂O), dried, and evaporated to dryness. Crystallization of the amorphous residue from acetone-petroleum ether furnished 323 mg (42%) of product, mp 142-145°. Recrystallization from the same solvent pair gave white crystals: mp 146-147°; [α]D −21°; λmax 238 mμ (ε 13,800); λmax 5.89, 6.00, 6.15, 6.23 μ.

Anal. Calcd for C₂₂H₂₈O₂: C, 81.44; H, 8.70. Found: C, 81.41; H, 8.97.

17-Methylpregna-1,4,9(11)-triene-3,20-dione (IVa) from IIa.—A solution of 2 g of IIa and 5 g (3 molar equiv) of recrystallized DDQ[7] in 100 ml of purified dioxane was heated at the reflux temperature for 17 hr. The cooled solution was filtered and evaporated to dryness. The crude product (2.7 g) was partition chromatographed[24] on Celite[25] (diatomaceous earth) using the heptane-2-methoxyethanol partition system. The stationary phase was thoroughly mixed (0.65 ml/g) with Celite (600 g) and the mix was packed into a glass column (4.4 cm i.d. × 120 cm). The reaction product was dissolved in 13 ml of the lower phase, mixed with 20 g of Celite, and packed on top of the column. The hold-back volume (hbv) was 950 ml and the V_m/V_r ratio was 2.36. The product IVa was isolated from the fraction with peak at hbv 6.3 and was recrystallized from acetone-petroleum ether to give 278 mg (14%) as white crystals, mp 138-139°; polarographic assay[26] showed the product to contain 98% Δ¹,⁴-3-one. This material was identical, by the usual criteria, with that obtained by DDQ treatment of the 3-ketone Va.

Procedure C. Ring C Bromohydrin Formation. Preparation of 9α-Bromo-11β-hydroxy-17-methylpregna-1,4-diene-3,20-dione.—To a solution of 948 mg of IVa in 65 ml of purified dioxane containing 10.6 ml of water, stirred in a tap-water bath, was added 880 mg of recrystallized N-bromoacetamide followed by 5.05 ml of 10% aqueous HClO₄. After stirring for 25 min the solution was brought to pH 7 by the addition of aqueous sodium sulfite solution and then poured into about 350 ml of water. The solid was collected to give 1.15 g (90%) of product, mp 167° dec. Recrystallization of material from a similar experiment from CH₂Cl₂-Et₂O furnished white crystals: mp 169° dec; [α]D +92°; λmax 241 mμ (ε 13,700); λmax 2.90, 5.89, 6.01, 6.14, 6.20 μ.

Anal. Calcd for C₂₂H₂₉BrO₃: C, 62.70; H, 6.94; Br, 18.96. Found: C, 62.34; H, 7.07; Br, 19.04.

(23) (a) K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, J. Chem. Soc., 39 (1946); (b) C. Djerassi, R. R. Engle, and A. Bowers, J. Org. Chem., 21, 1547 (1956).

(24) Carried out according to the procedure developed by C. Pidacks and described in detail in ref 1a.

(25) The Celite used in the column had been washed with 6 N HCl and then distilled water until the washings were neutral and finally with methanol. It then was dried to a fluffy powder.

(26) P. Kabasakalian and J. McGlotten, J. Am. Chem. Soc., 78, 5032 (1956).

Table II

Product	Proce-dure	Yield, %	Mp,[a] °C	[α]D, deg[b]	Formula	Carbon, % Calcd	Carbon, % Found	Hydrogen, % Calcd	Hydrogen, % Found	Halogen, % Calcd	Halogen, % Found
17-Ethyl-5α-pregn-9(11)-ene-3,20-dione (Vb)	A	88	190–192 (D–C)	+11	$C_{23}H_{34}O_2 \cdot 0.25H_2O$	79.61	79.85	10.02	9.93		
21-Acetoxy-17-methyl-5α-pregn-9(11)-ene-3,20-dione (XIa)	A	70	175–177 (gas) (A)	+13	$C_{27}H_{30}O_4 \cdot$ acetone	72.94	73.13	9.07	9.16		
21-Acetoxy-17-ethyl-5α-pregn-9(11)-ene-3,20-dione (XIb)	A	71	198–200 (D–C)	+6	$C_{25}H_{36}O_4$	74.94	74.83	9.06	9.34		
16α,17-Dimethyl-5α-pregn-9(11)-ene-3,20-dione (Vc)	A	62	198–200 (D–C)	+8	$C_{23}H_{34}O_2 \cdot 0.25H_2O^c$	79.61	79.63	10.02	10.20		
21-Acetoxy 16α,17-dimethyl-5α-pregn-9(11)-ene-3,20-dione (XIc)	A	87	133–135 (C–B)	+13	$C_{25}H_{36}O_4 \cdot 0.5H_2O^d$	73.32	73.68	9.11	9.07		
17-Ethylpregna-1,4,9(11)-triene-3,20-dione (IVb)	B	39	191–192 (D–B)	−85	$C_{23}H_{30}O_2 \cdot 0.4H_2O^e$	81.04	80.99	9.00	9.18		
21-Acetoxy-17-methylpregna-1,4,9(11)-triene-3,20-dione (XIVa)	B	44	159–160[f] (A–B)	−16	$C_{24}H_{30}O_4$	75.36	74.94	7.91	7.90		
21-Acetoxy-17-ethylpregna-1,4,9(11)-triene-3,20-dione (XIVb)	B	57	171–173 (D–B)	−22	$C_{25}H_{32}O_4$	75.72	75.92	8.13	8.37		
16α,17-Dimethylpregna-1,4,9(11)-triene-3,20-dione (IVc)	B	42	165–166 (C–B)	−48	$C_{23}H_{30}O_2$	81.61	81.41	8.93	9.15		
21-Acetoxy-16α,17-dimethylpregna-1,4,9(11)-triene-3,20-dione (XIVc)	B	37	126–128[g] (C–B)	−64	$C_{25}H_{32}O_4$	75.72	75.52	8.13	7.81		
9α-Bromo-17-ethyl-11β-hydroxypregna-1,4-diene-3,20-dione	C	93	147–148 dec (D–C)	+88	$C_{23}H_{31}BrO_3$	63.44	63.00	7.18	7.25	18.35	18.76
21-Acetoxy-9α-bromo-11β-hydroxy-17-methylpregna-1,4-diene-3,20-dione	C	60	164 dec (D–C)	+91	$C_{24}H_{31}BrO_5$	60.13	60.15	6.52	6.72	16.67	16.57
21-Acetoxy-9α-bromo-17-ethyl-11β-hydroxypregna-1,4-diene-3,20-dione	C	51	142–143 (D–C)	+49	$C_{25}H_{33}BrO_5$	60.85	60.71	6.74	6.99	16.19	16.02
9α-Bromo-11β-hydroxy-16α,17-dimethylpregna-1,4-diene-3,20-dione	C	89	180 dec (D–C)	+59	$C_{23}H_{31}BrO_3$	63.44	63.00	7.18	7.25	18.35	17.88
21-Acetoxy-9α-bromo-11β-hydroxy-16α,17-dimethylpregna-1,4-diene-3,20-dione	C	85	161 dec (D–C)	+74	$C_{25}H_{33}BrO_5$	60.85	60.86	6.74	6.64	16.19	16.22
9β,11β-Epoxy-17-ethylpregna-1,4-diene-3,20-dione	D	89	185–187 (A–B)	0	$C_{23}H_{30}O_3$	77.93	77.52	8.53	8.68		
21-Acetoxy-9β,11β-epoxy-17-methylpregna-1,4-diene-3,20-dione	D	74	146–148 (A–B)	+3	$C_{24}H_{30}O_5$	72.33	72.09	7.59	7.65		
21-Acetoxy-9β,11β-epoxy-17-ethylpregna-1,4-diene-3,20-dione	D	51	163–166 (C)	+12	$C_{25}H_{32}O_5 \cdot 0.5H_2O$	71.2	71.6	7.9	8.4		
9β,11β-Epoxy-16α,17-dimethylpregna-1,4-diene-3,20-dione	D	66	175–177 (A–B)	−16	$C_{23}H_{30}O_3$	77.93	77.66	8.53	8.93		
21-Acetoxy-9β,11β-epoxy-16α,17-dimethylpregna-1,4-diene-3,20-dione	D	62	148–150[h] (D–B)	−6	$C_{25}H_{32}O_5$	72.79	72.48	7.82	7.92		
17-Ethyl-9α-fluoro-11β hydroxypregna-1,4-diene-3,20-dione (VIIIb)	E	60	259–260 (A–B)	+52	$C_{23}H_{31}FO_3$	73.76	73.72	8.34	8.41	5.07	4.96
21-Acetoxy-9α-fluoro-11β-hydroxy-17-methylpregna-1,4-diene-3,20-dione (XIIIa)	E	41	181–182[i] (C–B)	+58	$C_{24}H_{31}FO_5$	68.87	68.65	7.47	7.69	4.54	4.48
21-Acetoxy-17-ethyl-9α-fluoro-11β-hydroxypregna-1,4-diene-3,20-dione (XIIIb)	E	27	197–199[j] dec (C–B)	+61	$C_{25}H_{33}FO_5$	69.42	69.77	7.69	7.60	4.39	4.18
9α-Fluoro-11β-hydroxy-16α,17-dimethylpregna-1,4-diene-3,20-dione (VIIIc)	E	52	288 dec (A–B)	+37	$C_{23}H_{31}FO_3$	73.76	73.09	8.34	8.17	5.07	4.95
21-Acetoxy-9α-fluoro-11β-hydroxy-16α,17-dimethylpregna-1,4-diene-3,20-dione (17-deoxy-16α,17-dimethyl-9α-fluoroprednisolone 21-acetate, XIIIc)	E	40	228–230[k] (D–C)	+50	$C_{25}H_{33}FO_5$	69.42	70.06	7.69	8.03	4.39	4.41
9α,11β-Dichloro-17-ethylpregna-1,4-diene-3,20-dione (Xb)	F	40	201 dec (A–B)	+121	$C_{23}H_{30}Cl_2O_2$	67.47	66.95	7.39	7.37	17.32	18.01
21-Acetoxy-9α,11β-dichloro-17-methylpregna-1,4-diene-3,20-dione (XIIa)	F	48	225 dec (D–C)	+96	$C_{24}H_{30}Cl_2O_4$	63.57	63.34	6.67	7.06	15.64	16.08
9α,11β-Dichloro-16α,17-dimethylpregna-1,4-diene-3,20-dione (Xc)	F	98	221–223 dec (D–C)	+91	$C_{23}H_{30}Cl_2O_2$	67.47	67.22	7.39	7.66	17.32	17.61
21-Acetoxy-9α,11β-dichloro-16α,17-dimethylpregna-1,4-diene-3,20-dione (XIIc)	F	33	201 dec (D–C)	+77	$C_{25}H_{32}Cl_2O_4$	64.24	63.89	6.90	7.10	15.17	16.01

[a] Analytical melting point. Recrystallization solvents: A, acetone; B, petroleum ether (bp 60–70°); C, ether; D, methylene chloride. [b] Rotations were measured in $CHCl_3$ at a concentration of 0.4–1.0%. Compounds Vb, XIa, XIb, Vc, and XIc had no significant ultraviolet absorption; the other compounds had λ_{max} 234–248 mμ (ϵ 8000–19,800); λ_{max} 2.86–3.00, 5.70–5.73, 5.80–5.89, 5.99–6.02, 6.14–6.18, 6.20–6.25, 8.09–8.16 μ. [c] Broadened band at 2.90 μ. [d] Anal. Calcd: $0.5H_2O$, 2.18. Found: $0.5H_2O$, 2.58 (Karl Fischer). [e] Anal. Calcd: $0.4H_2O$, 2.08. Found: $0.4H_2O$, 2.70 (Karl Fischer). [f] Purified by partition chromatography[24] on Celite[25] (diatomaceous earth), using the heptane–methanol system; hbv 6.5 (V_m/V_s = 3.2); polarographic assay[26] showed the product to contain 93% $\Delta^{1,4}$-3-one. [g] Purified by partition chromatography using the heptane–methanol system; hbv 4.5 (V_m/V_s = 3.1). [h] Purified by elution from silica gel with 15–20% ether in benzene. [i] Product isolated by elution with 35% ether in benzene from silica gel. [j] Product isolated by partition chromatography using the heptane–ethyl acetate–methanol–water (80:20:15:6) system; hbv 4 (V_m/V_s = 2.7). [k] Product isolated by partition chromatography with system used in j; hbv 10 (V_m/V_s = 3.0).

Procedure D. Ring C Epoxide Formation. Preparation of 9β,11β-Epoxy-17-methylpregna-1,4-diene-3,20-dione.—A solution of 1 g of 9α-bromo-11β-hydroxy-17-methylpregna-1,4-diene-3,20-dione and 500 mg of KOAc in 125 ml of absolute alcohol was heated at the reflux temperature for 18 hr. After concentration to a small volume, the solution was diluted with water and filtered to give 597 mg (74%), mp 156–158°. In a pilot run, the product had mp 155–157°. Recrystallization from acetone-petroleum ether afforded white crystals: mp 160–162°; [α]D +22°; λ_{max} 248 mμ (ϵ 15,100); λ_{max} 5.88, 5.99, 6.14, 6.23 μ.

Anal. Calcd for $C_{22}H_{28}O_3$: C, 77.61; H, 8.29. Found: C, 77.72; H, 8.18.

Procedure E. Ring C Fluorohydrin Formation. Preparation of 9α-Fluoro-11β-hydroxy-17-methylpregna-1,4-diene-3,20-dione (VIIIa).—To 5 ml of CH_2Cl_2 previously chilled to −50° was added 3 ml of anhydrous HF. This solution was added to a solution of 200 mg of 9β,11β-epoxy-17-methylpregna-1,4-diene-3,20-dione in 5 ml of CH_2Cl_2 and 5 ml of purified THF which previously had been chilled to −50°. The mixture was stirred at −50° for 10 min and then at 0° for 4 hr. The reaction mixture was poured into excess $NaHCO_3$ solution and diluted with CH_2Cl_2. The organic layer was washed with water, dried, and evaporated to dryness. The residue was recrystallized from acetone-petroleum ether to give 122 mg (58%) of VIIIa: mp 253–254°;

[α]D +59° (0.6%); λmax 238 mμ (ε 15,900); λmax 2.98, 5.90, 6.01, 6.18, 6.23 (sh) μ.

Anal. Calcd for C₂₂H₂₉FO₃: C, 73.29; H, 8.11; F, 5.27. Found: C, 73.64; H, 8.36; F, 5.12.

9α-Chloro-11β-hydroxy-17-methylpregna-1,4-diene-3,20-dione (IXa).—To a solution of 200 mg of 9β,11β-epoxy-17-methylpregna-1,4-diene-3,20-dione in 4 ml of CHCl₃, cooled to ice-bath temperature, was added 20 ml of CHCl₃ saturated with HCl. The solution was kept at 0-5° for 5 hr, then evaporated to dryness. Recrystallization of the residual solid from acetone gave 159 mg (72%) of IXa in two crops, mp 226-235° dec. Recrystallization from acetone–petroleum ether afforded white crystals: mp 237° dec; [α]D +87° (0.6%); λmax 238 mμ (ε 14,900); λmax 2.95, 5.89, 6.01, 6.18, 6.23 (sh) μ.

Anal. Calcd for C₂₂H₂₉ClO₃: C, 70.10; H, 7.75; Cl, 9.41. Found: C, 70.26; H, 7.95; Cl, 9.85.

9α-Chloro-17-ethyl-11β-hydroxypregna-1,4-diene-3,20-dione (IXb).—9β,11β-Epoxy-17-ethylpregna-1,4-diene-3,20-dione (200 mg) was treated with HCl in the manner described immediately above for the preparation of IXa to give 166 mg (76%) of product IXb: mp 235° dec; [α]D +88° (0.5%); λmax 238 mμ (ε 15,500); λmax 2.93, 5.88, 6.00, 6.17, 6.20 (sh) μ.

Anal. Calcd for C₂₃H₃₁ClO₃: C, 70.67; H, 7.99; Cl, 9.07. Found: C, 70.01; H, 7.84; Cl, 9.17.

Procedure F. Formation of 9α,11β-Dichloro Derivatives. Preparation of 9α,11β-Dichloro-17-methylpregna-1,4-diene-3,20-dione (Xa).—Chlorine was bubbled through a solution of 150 mg of IVa in 10 ml of CHCl₃ containing 1 ml of reagent pyridine for 45 sec.[9] The solution was stirred for 30 min when CH₂Cl₂ was added. The resulting solution was washed successively (Na₂S₂O₃, dilute H₂SO₄, K₂CO₃, H₂O). The dried extract was evaporated to dryness and the solid residue was recrystallized from CH₂Cl₂–Et₂O to give 107 mg (59%) of product as white crystals: mp 222-225° dec; [α]D +114°; λmax 238 mμ (ε 13,800); λmax 5.88, 6.01, 6.14, 6.21 μ.

Anal. Calcd for C₂₂H₂₈Cl₂O₂: C, 66.82; H, 7.14; Cl, 17.93. Found: C, 66.70; H, 7.35; Cl, 18.55.

Sodium Salt of 21-Ethoxalyl-3β-hydroxy-17-methyl-5α-pregn-9(11)-en-20-one (IIIa).—To a solution of 665 mg of Na in 75 ml of dry ethanol was added 7 g of IIa followed by a solution of 9.95 g of freshly distilled ethyl oxalate in 35 ml of ethanol. The resulting solution was heated at the reflux temperature, under N₂, for 10 hr followed by concentration to about one-half the original volume.[10] Dilution with ether and filtration furnished 8.33 g (86%) of amorphous product: λmax 2.90, 5.83, 6.02 (sh), 6.16, 6.70, 8.15 μ.

21-Ethoxalyl-3β-hydroxy-17-methyl-5α-pregn-9(11)-en-20-one (IIIa).—A solution of 8.33 g of the sodium salt of IIIa in 100 ml of methanol was clarified by filtration and then acidified with 2 N HCl. The resulting solution was diluted with 500 ml of water and extracted three times with CH₂Cl₂. The combined extracts were washed with water, dried, and taken to dryness to give 6.2 g (68%) of fluffy powder. Material from a pilot experiment gave: λmax 0.1 N HCl 283 mμ; λmax 0.1 N NaOH 302 mμ; λmax 2.85, 5.75, 6.12, 6.30, 8.00 μ. The compound gave a deep red color with 1% alcoholic FeCl₃.

Sodium Salt of 21-Ethoxalyl-17-ethyl-3β-hydroxy-5α-pregn-9(11)-en-20-one (IIIb).—Application of the procedure described above for the preparation of the sodium salt of IIIa to 10 g of IIb with a heating time of 96 hr gave 9.77 g (76%) of product as an amorphous solid: λmax 2.90, 5.80, 6.00-6.62 (broad), 8.15 μ.

21-Ethoxalyl-17-ethyl-3β-hydroxy-5α-pregn-9(11)-en-20-one (IIIb).—Treatment of 7.9 g of the sodium salt IIIb as described above for the preparation of IIIa furnished 3.2 g of a fluffy powder: λmax 2.85, 5.75, 6.12, 6.30, 8.00 μ. The compound gave a deep red color with 1% alcoholic FeCl₃.

21-Bromo-3β-hydroxy-17-methyl-5α-pregn-9(11)-en-20-one (VIa). A.—To a stirred solution of 2.21 g of IIIa and 2 g of anhydrous KOAc in 90 ml of methanol (cooled to 0°) was added dropwise 12.4 ml of a solution of 50 ml of reagent CHCl₃ containing 3.509 g of Br₂. After 1 hr at 0° there was added 5 ml and then 15 ml of 1 N methanolic NaOCH₃ solution. After stirring at room temperature for 1 hr and then refluxing for 5 min, the solution was concentrated to half-volume and diluted with 275 ml of water. The resulting mixture was extracted three times with CH₂Cl₂. The combined extracts were washed with water, dried, and evaporated to dryness to furnish 2.35 g of a semisolid. Trituration with methanol gave 1.45 g (69%) of product in two crops, mp 110-115° (gas). Recrystallization from acetone–petroleum

ether furnished white crystals: mp 135° dec; [α]D −2°; no significant absorption in the ultraviolet; λmax 2.94, 5.83, 6.10 μ.

Anal. Calcd for C₂₂H₃₃BrO₂: C, 64.54; H, 8.12; Br, 19.52. Found: C, 64.31; H, 8.37; Br, 18.80.

B. From the Sodium Salt of the Ethoxalyl Derivative IIIa. Treatment of 5.18 g of the sodium salt of IIIa and 5 g of KOAc in 210 ml of methanol with 31.8 ml of a solution of 3.019 g of Br₂ in 50.0 ml of reagent CHCl₃ in the manner described directly above in A gave 3.6 g (77%) of product VIa; the infrared of this substance was identical with that of the product described in A.

21-Bromo-17-ethyl-3β-hydroxy-5α-pregn-9(11)-en-20-one (VIb).—IIIb (1.31 g) was brominated in the manner described above for the preparation of VIa to give 1.27 g (100%) of a fluffy powder: λmax 2.89, 5.84, 6.14 μ. This material was used without further purification.

21-Acetoxy-3β-hydroxy-17-methyl-5α-pregn-9(11)-en-20-one (VIIa).—To a solution of 6.54 g of VIa in 300 ml of DMF was added 20 g of anhydrous NaOAc.[12] The resulting mixture was stirred at 60-65°, under N₂, for 18 hr. After dilution with water the solid was collected and extracted into CH₂Cl₂. The extract was washed with water, dried, and evaporated to dryness to furnish 5.49 g (89%) of product VIIa, mp 143° (gas).

In a pilot experiment the product had mp 144-147° (gas). Recrystallization from acetone–petroleum ether gave white needles: mp 156-157° (gas); [α]D −7°; no significant absorption in the ultraviolet: λmax 2.90, 5.70, 5.82, 8.12 μ.

Anal. Calcd for C₂₄H₃₆O₄·0.25H₂O: C, 73.54; H, 9.24; H₂O, 1.1. Found: C, 72.95; H, 9.54; H₂O, 0.71 (Karl Fischer).

21-Acetoxy-17-ethyl-3β-hydroxy-5α-pregn-9(11)-en-20-one (VIIb).—Treatment of 1.37 g of VIb according to the procedure described above for the preparation of VIIa gave 1 g of an amorphous solid. Chromatography on silica gel gave product VIIb, which after two recrystallizations from acetone–petroleum ether amounted to 288 mg (7% from IIb): mp 139-141°; [α]D −5°; no significant absorption in the ultraviolet; λmax 2.90, 5.70, 5.84, 8.15 μ. A more satisfactory procedure for the preparation of this compound, *via* direct bromination of IIb, is described below.

Anal. Calcd for C₂₅H₃₈O₄·0.75H₂O: C, 72.14; H, 9.57. Found: C, 72.30; H, 9.57.

3β-Tetrahydropyranyl-5α-pregna-9(11),16-dien-20-one (XV). —A solution of 17.8 g of 3β-hydroxy-5α-pregna-9(11),16-dien-20-one in 600 ml of dry benzene containing 800 mg of p-toluenesulfonic acid and 40 ml of freshly distilled dihydropyran was allowed to stand at room temperature for 5 days. After washing (saturated NaHCO₃, H₂O), the solution was dried and taken to dryness. The residual syrup was chromatographed on 600 g of alumina. The column was washed with 500 ml of hexane and 500 ml of 5% benzene–hexane, and evaporation of the latter eluate furnished crystalline material, recrystallization of which from petroleum ether (bp 30-60°) furnished 11.8 g (52%) of product, mp 114-117°. A sample of this compound obtained from a similar experiment was recrystallized twice from petroleum ether to give white crystals: mp 118-120°; [α]D +106°; λmax 238 mμ (ε 8600); λmax 6.00, 6.16, 6.30, 9.75 μ.

Anal. Calcd for C₂₆H₃₈O₃: C, 78.35; H, 9.61. Found: C, 77.82; H, 9.62.

3β-Hydroxy-16α-17-dimethyl-5α-pregn-9(11)-en-20-one (IIc). A. From 3β-Tetrahydropyranyl-5α-pregna-9(11),16-dien-20-one (XV).—To a Grignard solution prepared from 3.6 g of Mg and 13 ml of CH₃I in 50 ml of ether under N₂ was added 350 ml of purified THF dropwise, whereupon the Grignard reagent separated as a finely divided solid. After the distillation of 250 ml of solvent the mixture was cooled to 20° and CuBr (720 mg) was added, followed by the dropwise addition of 10.5 g of 3β-tetrahydropyranyl-5α-pregna-9(11),16-dien-20-one (XV) in 100 ml of THF. After 1.5 hr 30 ml of CH₃I was added dropwise, and the resulting mixture was stirred for 18 hr. Saturated NH₄Cl (200 ml) was added followed by 50 ml of water and 500 ml of ether. The ethereal solution was washed successively (aqueous Na₂S₂O₃, NH₄Cl, H₂O), dried, and taken to dryness to give 11.6 g of fluffy powder. Hydrolysis of the tetrahydropyranyl group was effected by treatment of this substance in 300 ml of methanol with 3 ml of concentrated HCl at room temperature for 1 hr to give 9.5 g of semisolid. This material was treated with 9.5 g of Girard's "T" reagent[15] in 140 ml of absolute alcohol, containing 14 ml of AcOH, at the reflux temperature for 2 hr. The solution was cooled and added to aqueous NaOH (9 g in 610 ml). The resulting mixture was extracted four times with ether and the

combined extracts were washed (dilute $NaHCO_3$, H_2O). After drying, the solvent was removed under reduced pressure to give 5.18 g (55%) of crude product. Recrystallization from ether–petroleum ether furnished 3.6 g (40%) of white crystals, mp 192–195°.

In a pilot experiment, the product was recrystallized from ether–petroleum ether to give white crystals: mp 195–197°; $[\alpha]_D$ −11°; no significant absorption in the ultraviolet; λ_{max} 2.94, 5.91, 6.10 μ; nmr, 38.5 (18-H), 53 (doublet, $J = 7$ cps; 16-CH₃), 56.5 (19-H), 62 (17-CH₃), 114 (OH), 125 (21-H), 215 (3-H), 322 (11-H) cps; ORD,[16] positive Cotton effect, $[M]_{368,315}$ +3120°, +2740°.

Anal. Calcd for $C_{23}H_{36}O_2$: C, 80.18; H, 10.73. Found: C, 79.99; H, 10.76.

B. From 3β-Acetoxy-5α-pregna-9(11),16-dien-20-one (I).— By the methylation procedure described in method A, 9.62 g of I gave 8.84 g of fluffy powder. Hydrolysis of the acetoxy group was ensured by treatment of the material in 400 ml of methanol with 12 ml of 10% K_2CO_3 solution at the reflux temperature for 30 min. The resulting cooled solution was neutralized with AcOH (5 ml), concentrated to a small volume, diluted with water, and extracted several times with CH_2Cl_2. The combined extracts were washed with water, dried, and taken to dryness to give 8.8 g of syrup. Treatment of this material with Girard's "T" reagent as described in method A gave 1.88 g (20%) of product, mp 184–186°. This material was identical, by the usual criteria, with that obtained in A.

Sodium salt of 21-ethoxalyl-3β-hydroxy-16α,17-dimethyl-5α-pregn-9(11)-en-20-one (IIIc) was prepared from IIc (2.5 g) by the procedure described above for the preparation of the sodium salt of IIIa; there was obtained 3.4 g (100%) of amorphous product which gave a deep red color with 1% alcoholic $FeCl_3$; λ_{max} 2.85, 5.83, 6.02, 6.16, 6.70, 8.15 μ.

21-Bromo-16α,17-dimethyl-3β-hydroxy-5α-pregn-9(11)-en-20-one (VIc). A. From the Ethoxalyl Derivative IIIc.—When prepared by the A procedure for the preparation of VIa (above), 3.5 g of the sodium salt furnished 2.4 g (76%) of amorphous material, which did not give any color with 1% alcoholic $FeCl_3$; λ_{max} 2.88, 5.84, 6.13 μ. This material was used without further purification.

B. By Direct Bromination of 3β-Hydroxy-16α,17-dimethyl-5α-pregn-9(11)-en-20-one (IIc).—To a stirred solution of 5 g of IIc in 100 ml of absolute alcohol (cooled to 0°) was added 10 ml of a solution of 50 ml of absolute alcohol containing 18 g of HCl[17] followed by dropwise addition (1 hr) of 65 ml of a solu-

tion of 100 ml of absolute alcohol containing Br_2 (5.81 g). After an additional 5 min the solution was poured into 800 ml of water and filtered to give 5.88 g (96%) of amorphous material, which was used without further purification.

21-Acetoxy-3β-hydroxy-16α,17-dimethyl-5α-pregn-9(11)-en-20-one (VIIc).—A solution of 5.9 g of VIc (prepared by method B above) and 3.4 g of anhydrous NaOAc in 55 ml of DMF containing 0.2 ml of AcOH was stirred under N_2 at 55–60° for 72 hr. The cooled solution was poured into 300 ml of water and the resulting solution was extracted three times with CH_2Cl_2. The combined extracts were washed with water, dried, and evaporated to dryness to furnish an amorphous solid, which was chromatographed on silica gel. Elution with 3 l. of 10% ether in benzene, followed by evaporation of the eluate, furnished 3.2 g (55% from IIc) of product, mp 122–126°. Two recrystallizations from acetone–petroleum ether gave white crystals: mp 131–132°; $[\alpha]_D$ −5°; no significant absorption in the ultraviolet; λ_{max} 2.90, 5.72, 5.83, 6.10, 8.13 μ.

Anal. Calcd for $C_{25}H_{38}O_4 \cdot 0.5H_2O$: C, 72.96; H, 9.55; H_2O, 2.18. Found: C, 73.41; H, 9.43; H_2O, 1.72 (Karl Fischer).

In another experiment treatment of 2.4 g of crude 21-bromide VIc, prepared by method A above, in 130 ml of DMF with 7 g of anhydrous NaOAc, furnished 616 mg (21% from IIc), mp 128–130°.

21-Acetoxy-17-ethyl-3β-hydroxy-5α-pregn-9(11)-en-20-one (VIIb) *via* Direct Bromination of IIb.—Direct bromination of 1 g of IIb in the manner described above in method B for the preparation of VIc furnished 1.2 g of VIb, 1 g of which was treated with NaOAc according to the procedure described above for the preparation of VIIc to give 1 g of amorphous material. The product was chromatographed on 40 g of silica gel. Elution with 1 l. of 15% ether in benzene followed by evaporation of the eluate furnished 504 mg (50% from IIb) of VIIb, mp 139–143°.

Some 17α-Cyclopropyl Steroids

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Cyclopropyllithium was employed to prepare 17α-cyclopropylestradiol 3-methyl ether, the parent member of a series of 17α-cyclopropylestrenes, and for the preparation of 17α-cyclopropyltestosterone. Various chemical transformation products of the former compound are described, and the biological activities that were found are reported.

The description by Seyferth and Cohen[1] of a convenient preparation of cyclopropyllithium led us to the application of this reagent to the synthesis of a number of 17α-cyclopropyl-substituted steroids, which were at that time unknown. More recently, Lehmann, *et al.*,[2] have reported the synthesis of several of these compounds by the use of the Simmons–Smith reagent upon appropriate olefinic precursors; in this way compounds **2**, **5**, and **15** were prepared.

The reaction of cyclopropyllithium with estrone 3-methyl ether afforded a single 17-cyclopropyl-substi-

tuted product, which was presumed, on the basis of prior experience[3] with various organometallic reagents, to be the 17α-alkylated isomer **2** (Chart I).

A substantial amount of the ketone always remained unconverted and had to be removed either by chromatography or by condensation with a Girard reagent (see Experimental Section). Reduction of **2** with Li and alcohol in liquid ammonia[4] afforded the 1,4-dihydroenol ether **3** in high yield; oxalic acid hydrolysis[4] of **3** then provided the useful intermediate 17α-cyclopropyl-17-hydroxyestr-5(10)-en-3-one (**4**).

(1) D. Seyferth and H. M. Cohen, *J. Organometal. Chem.* (Amsterdam), **1**, 15 (1963).

(2) H. G. Lehmann, H. Muller, and R. Weichert, *Ber.*, **98**, 1470 (1965).

(3) L. F. Fieser and M. Fieser, "Steroids," Reinhold Publishing Corp., New York, N. Y., 1959, p 467.

(4) A. L. Wilds and N. A. Nelson, *J. Am. Chem. Soc.*, **75**, 5366 (1953).