product failed to crystallize from a number of solvents, it was dehydrogenated without further purification.

General Procedure for the Dehydrogenation of 2-Hydroxymethylene-3-keto Steroids.—All reactions were carried out at room temperature. The dioxane was purified by distillation from sodium hydroxide pellets and redistillation from sodium.

A solution of the steroid (0.5 g.) in 12.5–25 ml. of dioxane was treated with 1.1–1.5 molar equiv. of DDQ in an equal volume of the same solvent. After standing for 1–5 min. the reaction mixture was diluted with 150–500 ml. of methylene chloride, and the product was isolated by employing either of the following procedures.

Method A.—The above methylene chloride solution was washed with several portions of 2% aqueous sodium hydroxide solution and then with water until neutral. The sodium sulfate dried extract was treated with decolorizing carbon, filtered through Celite, and concentrated to dryness *in vacuo*.

Method B.—The above methylene chloride solution was filtered through a column of neutral alumina (40 times the weight of starting material). The column was washed with an additional quantity of methylene chloride, then with ethyl acetate, if necessary, and the combined eluates were evaporated.

Usually the crude dehydrogenation products so obtained were nicely crystalline solids and could be purified further by direct crystallization. Compounds which could not be purified in this manner were chromatographed on alumina or silica gel.

2-Formyl-5α-pregn-1-ene-3,20-dione (IIc).—A solution of 1.2 g. of DDQ in 20 ml. of dioxan was added to a solution of 2 g. of 20-cycloethylenedioxy-2-hydroxymethylene-5α-pregnan-3-one (If) in 100 ml. of dioxane. After 1.5 min. methylene chloride (200 ml.) was added, and the resulting solution was filtered through a column of 120 g. of alumina. One liter of solvent was passed through the column and then the combined eluates were evaporated to dryness. An acetone solution (100 ml.) of the oily product containing 15 drops of concentrated hydrochloric acid was left standing at room temperature for 1 hr. and then diluted with ethyl acetate. This solution was washed with water, dried (Na_2SO_4), and evaporated. A benzene solution of the oily residue was adsorbed on a column of 50 g. of silica gel and the 2-formyl-5α-pregn-1-ene-3,20-dione (IIc) was eluted with benzene–ethyl acetate (9:1). Several crystallizations from acetone–hexane gave 0.25 g. of IIc, m.p. 194–196°. Additional constants are reported in Table I.

2-Formyl-11β,17α,21-trihydroxypregna-1,4-diene-3,20-dione 21-Acetate (2-Formylprednisolone 21-Acetate, IIi).—A solution of 60% formic acid (18 ml.) was heated to boiling and then cooled briefly. After the addition of 0.5 g. of 17α,20:20,21-bismethylenedioxy-2-formyl-11β-hydroxypregna-1,4-dien-3-one (IIh), the hot solution was heated quickly to the boiling point, in a nitrogen atmosphere, maintained at this temperature for 3.5 min. and then cooled rapidly in an ice bath. The cold reaction mixture was poured into 200 ml. of saturated brine, and the product was extracted with methylene chloride. The combined methylene chloride extracts were washed with dilute sodium carbonate solution and water, dried (Na_2SO_4), and concentrated.

A second 0.5-g. portion of IIh was processed in the same manner, and the product was added to the residue of the first hydrolysis with 50 ml. of methanol. The resulting solution was cooled to 0° and treated with an equal volume of 1% methanolic sodium hydroxide. After standing for 30 min. at 0° in a nitrogen atmosphere, the reaction mixture was neutralized with acetic acid and poured into 250 ml. of saturated brine. Isolation with methylene chloride afforded 0.7 g. of oil which was acetylated in the usual manner with 20 ml. of acetic anhydride–pyridine mixture (1:2) at room temperature for 5 hr. The semicrystalline acetate (0.5 g.) was dissolved in methylene chloride and chromatographed on 20 g. of silica gel. Elution with methylene chloride–ethyl acetate mixtures (1:4 and 1:1) provided 0.2 g. of 2-formylprednisolone 21-acetate, m.p. 240–245°. A pure sample of this substance, prepared by crystallization from acetone–hexane, exhibited m.p. 253–255°; $[\alpha]_D$ +76°; λ_{max} 220 and 244 mμ (log ε 4.18 and 4.08); λ_{max}^{KBr} 5.75, 5.90, 6.03, 6.17, and 6.25 μ.

Anal. Calcd. for $C_{21}H_{30}O_7$: C, 66.96; H, 7.02; O, 26.02. Found: C, 67.24; H, 7.17; O, 25.62.

17α,21-Dihydroxy-2-formylpregna-1,4-diene-3,11,20-trione (2-Formylprednisone, IIk).—A solution of 0.35 g. of 2-formylprednisone-BMD (IIj) in 20 ml. of 60% formic acid was heated under reflux for 15 min., and the product was isolated as described in the preceding experiment. Treatment of the crude residue (0.33 g.) in methanol (16 ml.) with a solution of 0.12 g. of sodium hydroxide in an equal volume of methanol according to the hydrolysis conditions for the preceding experiment gave 0.3 g. of crude 2-formylprednisone (IIk). Purification on a column of silica gel (12 g.) followed by crystallization (acetone–hexane) of the fractions eluted with methylene chloride–acetone (6:1) furnished 0.1 g. of IIk: m.p. 246–248°; $[\alpha]_D$ +96°; λ_{max} 215 mμ (log ε 4.18); λ_{max}^{KBr} 5.80–5.90, 6.00, 6.15, and 6.25 μ.

Anal. Calcd. for $C_{22}H_{26}O_6$: C, 68.38; H, 6.78; O, 24.84. Found: C, 68.14; H, 6.75; O, 25.05.

Synthesis and Chemistry of 16-Methylene and Δ^{15}-16-Methyl Cortical Steroids

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Received June 15, 1964

The synthesis of 16-methylene cortical steroids by two routes is described. The first route consists of the four-step conversion of 3α,17α-dihydroxy-16-methylenepregnane-11,20-dione (Ia) into 16-methyleneprednisone 21-acetate (IV). The second process, involving formation and acid-catalyzed opening of 16β-methyl 16α,17α-oxides, is illustrated by the conversion of 9α-fluoroprednisolone 21-acetate (XIV) into 16-methylene-9α-fluoroprednisolone 21-acetate (XXVII) and its endocyclic isomer, Δ^{15}-16-methyl-9α-fluoroprednisolone 21-acetate (XXVIII). During the course of this work, the reaction of 16-methylene and Δ^{15}-16-methyl-17-hydroxypregnenes with bromonium ion to yield bromo oxides and the Kägi–Miescher rearrangement of certain 17α-hydroxy-20-ketopregnane-20-semicarbazones were studied.

In this paper we present the details of our studies on the isomeric 16-methylene and Δ^{15}-16-methyl cortical steroids.[1,2]

Our first objective was 16-methyleneprednisone 21-acetate (IV) which we hoped to prepare by suitable modification of 3α,17α-dihydroxy-16-methylenepregnane-11,20-dione (Ia)[3,4] utilizing procedures compatible with the reactivity of the 16-*exo* double bond. Reaction of Ia with 1.2 molar equiv. of bromine led to the 21-bromide IIa in 80% yield.[5] The 21-acetate IIb

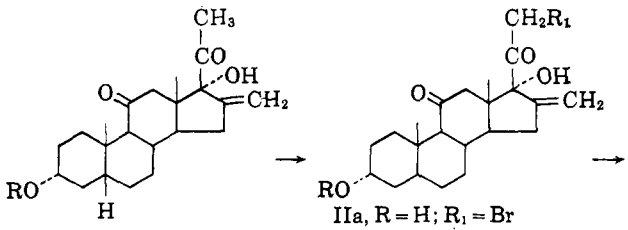
(1) For preliminary accounts of portions of this work, see (a) D. Taub, R. D. Hoffsommer, and N. L. Wendler, *J. Org. Chem.*, **25**, 2258 (1960); (b) R. D. Hoffsommer, D. Taub, and N. L. Wendler, *Chem. Ind.* (London), 251 (1961).

(2) Aspects of this field have been investigated by other groups: *inter alia* (a) H. J. Mannhardt, F. v. Werder, K. H. Bork, H. Metz, and K. Brückner, *Tetrahedron Letters*, **No. 16**, 21 (1960); (b) E. Batres, T. Cardenas, J. A. Edwards, G. Monroy, O. Mancera, C. Djerassi, and H. Ringold, *J. Org. Chem.*, **26**, 871 (1961).

(3) D. Taub, R. D. Hoffsommer, H. L. Slates, C. H. Kuo, and N. L. Wendler, *J. Am. Chem. Soc.*, **80**, 4435 (1958); **82**, 4012 (1960).

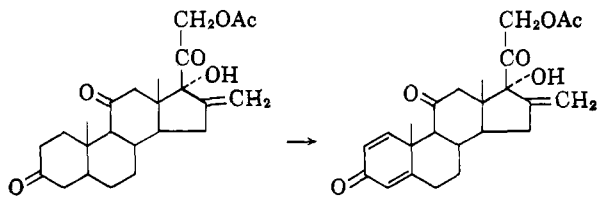
(4) G. Nominé, D. Bertin, and A. Pierdet, *Tetrahedron*, **8**, 217 (1960).

was obtained by reaction of the 21-bromide IIa with potassium iodide and potassium acetate in acetone–acetic acid.[6]



Ia, R = H
b, R = Ac

IIa, R = H; R_1 = Br
b, R = H; R_1 = OAc
c, R = Ac; R_1 = OAc



III IV

Oxidation of the 3-hydroxyl group to the 3-ketone occurred with complications in the present series. Under a variety of conditions including chromium trioxide–pyridine, chromium trioxide–acetic acid, and N-bromosuccinimide–*t*-butyl alcohol (see below), the yield of 3-ketone III ranged from negligible to poor, strongly indicating concomitant involvement of the 16-methylene group. The best direct yield of III (*ca.* 60%) was obtained by utilizing sodium dichromate in acetic acid at 25° for 3 hr. The crude 16-methylene 3-ketone III was contaminated with a mobile impurity (paper chromatography) which could not be removed by crystallization or alumina chromatography. It proved expedient to convert III without purification into 16-methylene prednisone 21-acetate IV by 2,4-dibromination followed by dehydrobromination.[7] The 1,4-dien-3-one IV obtained in this manner was purified by alumina chromatography and characterized by the usual spectral and analytical criteria. Of special diagnostic value for the *exo*-methylene part structure in IV and its precursors was the n.m.r. doublet at τ 4.71 and 4.88.[8] Also characteristic for the 16-methylene group was the levorotatory shift in optical rotation relative to the parent steroid. By contrast, the 16β-methyl and 16α-methyl groups are strongly dextrorotatory. Furthermore, the 16-methylene steroids were uniformly slightly more polar on paper than their 16β-methyl counterparts.

Direct dehydrogenation of III by selenium dioxide in refluxing *t*-butyl alcohol[9] gave as the sole crystalline product (*ca.* 10% yield) an unknown substance, m.p. 206–210°, more mobile than IV on paper, which contained 1,4-dien-3-one, 11,20-dione 21-acetate, and hydroxyl functionality (infrared). This substance, which was not further investigated, may have been produced by selenium dioxide reaction in the vicinity of the *exo* double bond (*e.g.*, allylic oxidation at C-15) as well as in ring A.

Returning to the oxidation study IIb → III, the employment of N-bromosuccinimide to effect this transformation led in good yield to a new substance with no indication of the formation of the 16-methylene-3-ketone III. The product was a more mobile, bromine-containing, hydroxyl-free, crystalline compound, m.p. 190–196° dec. This substance could be formulated reasonably as 16α,17α-oxido-16β-bromomethylpregnan-21-ol-3,11,20-trione 21-acetate (Va) formed by internal displacement on the intermediate 16-methylene bromonium ion by the favorably positioned 17α-hydroxyl function.[1b,10] The systems Ib and IIc with N-bromsuccinimide similarly gave the respective bromo oxides Vb, m.p. 154–156°, and Vc, m.p. 153–155°, in excellent yield. The latter on treatment with zinc in acetic acid regenerated the respective 17α-hydroxy-16-methylenepregnanes Ib and IIc.[1b,11] Similarly, zinc treatment of Va produced the 16-methylene 3-ketone III in pure form for the first time. The N-bromosuccinimide–zinc sequence is superior to the direct oxidative procedures for conversion of the 3-hydroxyl group to the 3-ketone in the 16-methylene series. Further structural evidence for the bromooxide formulation was obtained by catalytic hydrogenolysis of Vb which removed bromine producing the known 16α,17α-oxido-16β-methylpregnane-3α,17α-diol-11,20-dione 3-acetate (VI).[3,4] (See Chart I.)

The Δ^{15}-16-methyl isomer of Ib, namely, 16-methyl-Δ^{15}-pregnene-3α,17α-diol-11,20-dione 3-acetate (VII),[3,4] behaved analogously with N-bromosuccinimide producing a mobile 15-bromo-16β-methyl 16α,17α-oxide, m.p. 130–140° dec., in which the bromine is assigned the 15β-configuration (*cf.* VIII) on the basis of the above mechanistic condiderations.[12] It proved possible to obtain the 15α-bromo epimer of VIII, namely, X, m.p. 182–183°, by reaction of the 15α-bromo-Δ^{16}-pregnene IX with peroxytrifluoroacetic acid. In turn, IX had previously been obtained by treatment of VII with hydrogen bromide in acetic acid.[3] The 15α-bromo configuration in IX had been assigned on the basis of the compound's ultraviolet absorption and the assump-

(5) It may be noted that simultaneous attack of bromine at the C-16 *exo* double bond did not occur, whereas, as described below, the 16-methylene group is capable of forming a bromonium ion on treatment with N-bromosuccinimide.

(6) *Cf.* G. Rosenkranz, J. Pataki, St. Kaufmann, J. Berlin, and C. Djerassi, *J. Am. Chem. Soc.*, **72**, 4081 (1950).

(7) *Cf.* J. Day, R. Erickson, and R. Pettebone, U. S. Patent 2,873,284 (1959).

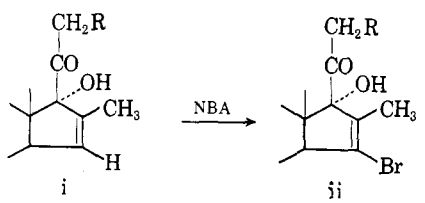
(8) The characteristic *exo*-methylene infrared band in the 11.2-μ region (C–H out-of-plane bending) is masked in IV by absorption derived from the 1,4-dien-3-one system.

(9) C. Ch. Meystre, H. Frey, N. Voser, and A. Wettstein, *Helv. Chim. Acta*, **39**, 734 (1956).

(10) See also F. v. Werder, K. Brückner, K. H. Bork, H. Metz, B. Hampel, and H. J. Mannhardt, *Chem. Ber.*, **95**, 2110 (1962). An analogous example is the formation of 14β-bromo 8α,17α-oxides on reaction of $\Delta^{8(14)}$17α-hydroxyl systems with N-bromosuccinimide [F. W. Bollinger and N. L. Wendler, *Chem. Ind.* (London), 441 (1960)].

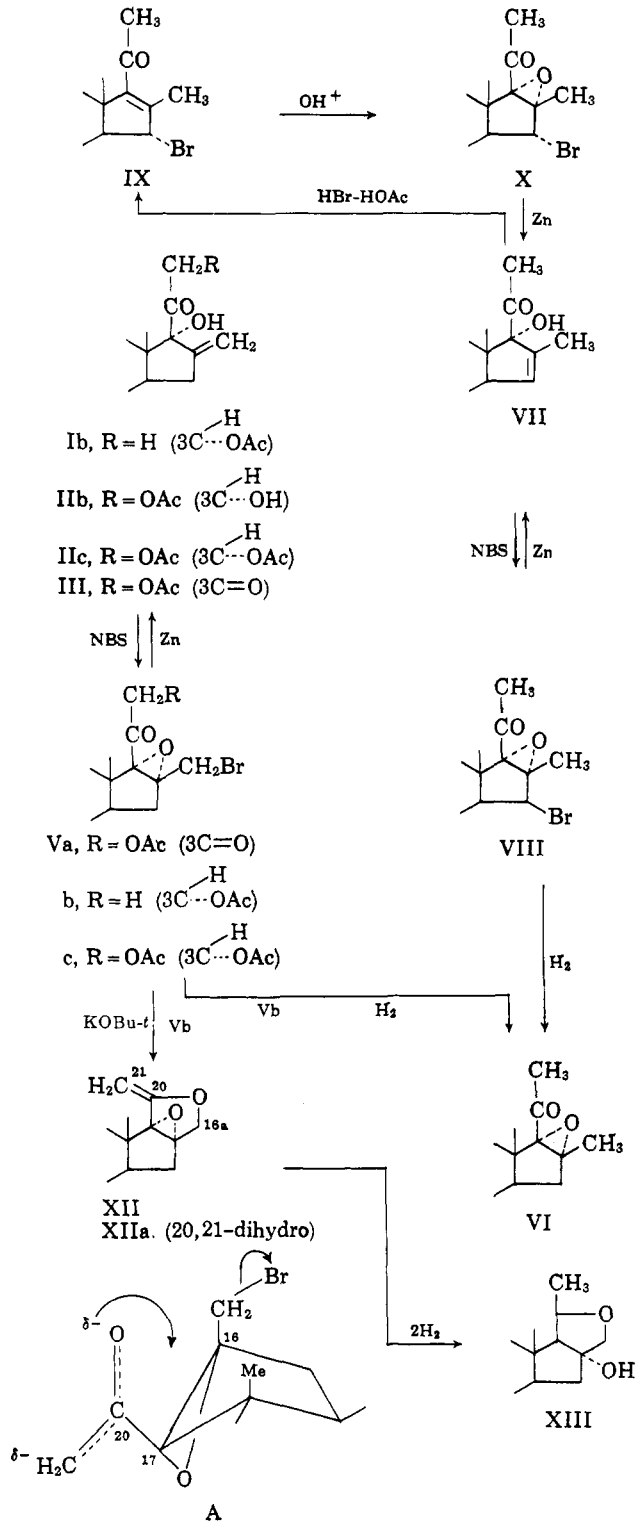
(11) For an analogous example in the atisine series, see W. Nagata, T. Sugasawa, M. Narisada, T. Wakabayashi, and Y. Hayase, *J. Am. Chem. Soc.*, **85**, 2342 (1963).

(12) The Syntex group (ref. 2b) has treated 17α-hydroxy-Δ^{15}-16-methylpregnen-20-ones (i) with N-bromoacetamide in dioxane–perchloric acid and formulated the products as 15-bromo-17α-hydroxy-Δ^{15}-16-methylpregnen-20-ones (ii) (*e.g.*, 15-bromo-Δ^{15}-16-methylprednisone 21-acetate). However, the n.m.r. and infrared data presented do not appear to offer positve evidence for the presence of the 17α-hydroxyl group or the Δ^{16}-double bond in ii. By analogy with our findings, the products ii are probably better formulated as 15β-bromo 16α,17a-oxides.



i ii

CHART I



tion of the operation of an SN2′-like process in its formation.[3] Both epimeric 15-bromo 16α,17α-oxides VIII and X were debrominated by zinc in acetic acid to re-form the Δ15-16-methyl-17α-hydroxy system VII. On hydrogenation of VIII and X, the debrominated oxide VI was formed in small yield. The major portion of the product consisted of the further hydrogenolysis products of VI, namely, a mixture of 3α-acetoxy-17α-hydroxy-16β-methylpregnane-11,20-dione and the corresponding 16α-methyl epimer,[3] shown by infrared and paper chromatographic evidence.

The bromo oxide Vb readily lost bromine under alkaline conditions. When treated with potassium *t*-butoxide in *t*-butyl alcohol–benzene, a bromine-free product was formed as a mixture of 3-alcohol and 3-acetate. Hydrolysis gave the crystalline 3-alcohol, m.p. 215–225°, best formulated as the 3-alcohol XII, the product of O-alkylation rather than the product of C-alkylation. This substance did not show cyclopentanone absorption (~5.75 μ) in the infrared, expected for C-alkylation, but did show moderate bands at 6.01 and 11.2 μ indicative of an *exo*-methylene group. This feature was also evident in the n.m.r. spectrum (doublet at τ 5.46 and 5.85). The compound reacted with osmium tetroxide (carbon–carbon double bond) but failed to give a Zimmerman test (α-methylene ketone). On hydrogenation, XII absorbed *ca.* 2.2 molar equiv. of hydrogen to give a nonpolar minor product tentatively formulated as the 20,21-dihydro compound XIIa and a polar major product. On acetylation, the latter yielded a monoacetate, the n.m.r. spectrum of which is in accord with XIII (or its 17-hydroxylated isomer). The occurrence of O-alkylation rather than C-alkylation in the formation of XII may be rationalized in terms of steric limitation of the side chain to the rotational conformation illustrated in the transitional intermediate A.[13]

For the preparation of 16-methylene-9α-fluoroprednisolone 21-acetate (XXVII) we wished to avoid an approach requiring ring A and ring C modification of a 16-methylenepregnane. We hoped rather to develop a shorter route from 9α-fluoroprednisolone 21-acetate (XIV) or 16α-methyl-9α-fluoroprednisolone 21-acetate (XVIII) involving introduction of the 16-methylene function at a final stage. To this end the intermediate 16-methyl-Δ1,4,16-pregnatriene XVII was our first objective, and it was obtained from XIV. The latter was converted into the Δ1,4,16-pregnatriene XVI by refluxing its 3,20-disemicarbazone XV in acetic anhydride–acetic acid[14] and subsequent reversal of the dehydrated semicarbazone in 1:1 aqueous acetic acid[3] (yield XIV → XVI, ~15–20%). The 16-methyl group was introduced into XVI by treatment with diazomethane followed by pyrolysis of the intermediate pyrazoline XVIa to give XVII (yield 70–80%).[15]

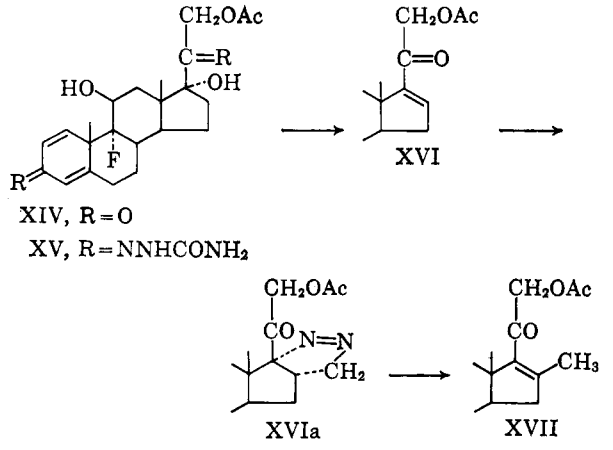
Dehydration of the 3,20-disemicarbazone of 16α-methyl-9α-fluoroprednisolone (XIX) was investigated in the hope of obtaining XVII by a shorter route. However, the 3,20-disemicarbazone XIX on extended treatment with hot acetic acid containing 5% acetic anhydride and reversal gave only traces of XVII and considerable amounts of recovered XVIII. Treatment of XIX with boron trifluoride–acetic acid–acetic anhydride followed by reversal gave only the 11-acetate of XVIII.

Model experiments on the dehydration of cortisone 3,20-disemicarbazone indicated that trifluoroacetic acid at 25° was more effective than hot acetic acid–acetic anhydride, the 16-dehydro product being produced in essentially quantitative yield following rever-

(13) See ref. 3 for a discussion on the effect of 16β-substituents on the preferred orientation of the side chain.

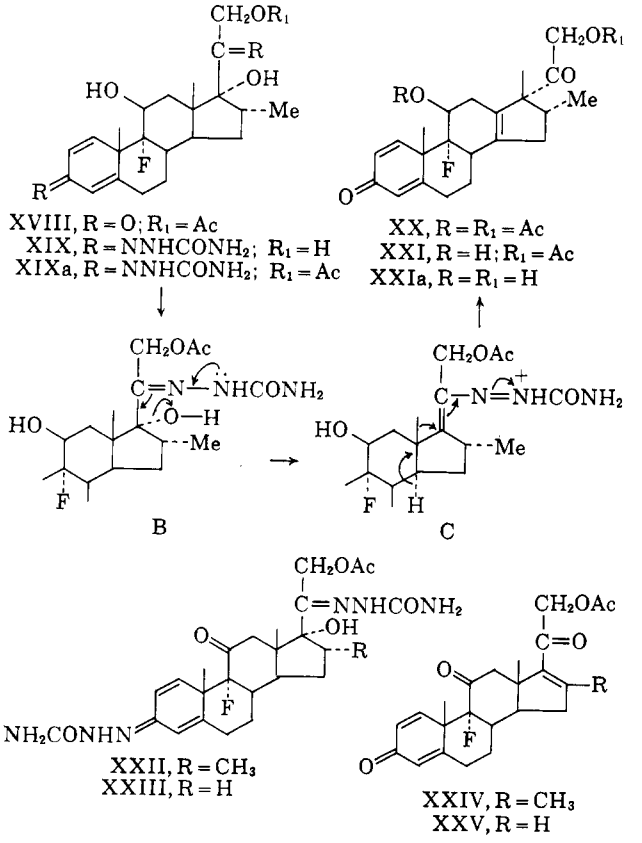
(14) Procedure of H. L. Slates and N. L. Wendler, *J. Org. Chem.*, **22**, 498 (1957).

(15) *Cf.* A. Wettstein, *Helv. Chim. Acta*, **27**, 1803 (1944); H. L. Slates and N. L. Wendler, U. S. Patent 3,121,078 (1964). The Δ1,4-dien-3-one system of XVI did not react with diazomethane although steroidal Δ1,4,6-trien-3-ones add diazomethane across the Δ1-double bond [R. Wiechert and E. Kaspar, *Chem. Ber.*, **93**, 1710 (1960)].



sal.[16] However, application of the room temperature trifluoroacetic acid procedure to XIXa led only to a trace of the desired Δ^{16}-compound. Two new substances were isolated in moderate yield.

The major product analyzed acceptably for $C_{26}H_{31}FO_6$ and had the following properties: m.p. 195–198°; λ_{max}^{MeOH} 235 mμ, $E_{1\%}^{cm}$ 260; $\lambda_{max}^{CHCl_3}$ 5.75, 5.82, 5.99, 6.11, 6.18, and 11.19 μ; no hydroxyl either by infrared or mobility on paper. The n.m.r. spectrum indicated the presence of *two* acetate methyl groups (τ 7.94) and the ultraviolet spectrum showed that the Δ^{16}-double bond had not been introduced. The evidence is in accord with structure XX arising by Kägi–Miescher rearrangement[17] as shown in formulations B and C. The Δ^{13}-position for the new double bond rather than Δ^{12} is in conformity with the n.m.r. evidence (no additional vinyl hydrogen). The second product isolated from the reaction proved to be the 11β-ol XXI since on acetylation (acetic anhydride–pyridine 25°) it was converted quantitatively to XX. Partial acetylation of the usually resistant 11β-hydroxyl group must have occurred during the concluding C-21 acetylation step to produce XX. The ease of this reaction is in accord with a more open environment for the axial 11β-hydroxyl group in XXI than in normal steroids in accord with migration of the C-13 methyl to C-17. In another run, the 11β,21-diol XXIa was isolated directly from the reversal reaction mixture.



9α-Fluoroprednisolone-3,20-disemicarbazone (XV) behaved similarly with trifluoroacetic acid, giving primarily a nonpolar rearrangement product and a minor quantity of the Δ^{16}-compound XVI.

In the 11-keto series (XXII and XXIII), rearrangement did not take place. Conversion of XXII to the 11-keto-16-methyl-1,4,16-pregnatriene XXIV occurred to a small extent, but the major product after the sequence was simply regenerated 9α-fluoro-16α-methylprednisone 21-acetate. In the absence of the 16α-methyl group (XXIII), the series of reactions went relatively smoothly to give the 16-dehydro compound XXV as the major product. The striking difference in migratory aptitude of the C-18 methyl group in the 11β-hydroxyl and 11-carbonyl series is noteworthy.

Sufficient 16-methyl-$\Delta^{1,4,16}$-pregnatriene XVII was prepared from XV by the hot acetic acid dehydration procedure followed by methylation to proceed further. Based on our experience with simpler 16-methyl-Δ^{16}-pregnenes,[3] we anticipated converting XVII to the 16α,17α-oxide XXVI and transforming the latter with acid to the 16-methylene and Δ^{15}-16-methyl isomers XXVII and XXVIII. The simple alkaline hydrogen peroxide epoxidation procedure[18] could not be applied to XVII because of the lability of the side chain to alkali. A milder, two-phase variant of Julian's method[19] worked reasonably well on the model compound, 3α-acetoxy-Δ^{16}-16-methylpregnane-11,20-dione (XXIX), and produced the 3α-acetoxy 16α,17α-oxide VI in good yield together with a small amount of the corresponding 3-alcohol. Application of this procedure to XVII, however, led rapidly to the corresponding 21-alcohol which did not react further at 0°. Warming the mixture to 25° led to a carboxylic acid, m.p. 170–180° (possibly XXX). Presumably the 16-methyl group inhibits reaction with hydroperoxide anion at the C-16 double bond and the side chain undergoes base-catalyzed rearrangement.[20] (See Chart II.)

Reaction of the model compound XXIX with peroxytrifluoracetic acid[21] in methylene chloride led rapidly to the oxide VI in quantitative yield. Similarly, the 16-methyl-1,4,16-pregnatriene XVII was converted in excellent yield to the desired 16α,17α-oxide XXVI, m.p. 227–230°, λ_{max}^{MeOH} 237 mμ (ε 15,100), without in-

(16) Since partial deactylation at C-21 was observed, the dehydration products were usually reacetylated.

(17) (a) H. Kägi and K. Miescher, *Helv. Chim. Acta*, **22**, 683 (1939); (b) for a recent review, see N. L. Wendler, "Molecular Rearrangements," P. de Mayo, Ed., Interscience Publishers, Inc., New York, N. Y., 1964, p. 1020 *et seq.*

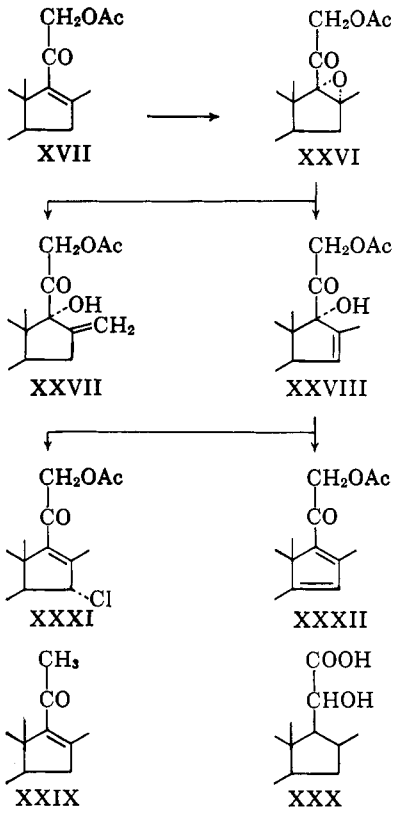
(18) P. L. Julian, E. W. Meyer, W. J. Karpel, and I. R. Walker, *J. Am. Chem. Soc.*, **72**, 5145 (1950).

(19) Procedure of C. Djerassi and C. T. Lenk, *ibid.*, **76**, 1722 (1954).

(20) See ref. 17b, p. 1068.

(21) *Cf.* W. D. Emmons and A. S. Pagano, *J. Am. Chem. Soc.*, **77**, 89 (1955).

CHART II



volvement of the ring A dienone system.[22] Although this substance did not depress the melting point of the starting material, the spectral properties leave no doubt that it is distinct and that the Δ^{16}-double bond is no longer present. Furthermore, the product characteristically gave a negative tetrazolium test,[23] although the infrared spectrum showed the presence of the ketol acetate part structure ($\lambda_{max}^{CHCl_3}$ 5.73, 5.79, and 8.10 μ).

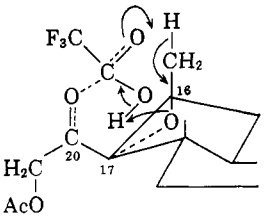
On treatment with hydrogen chloride in acetic acid at 25°, the 16β-methyl 16α,17α-oxide XXVI produced 16-methylene-9α-fluoroprednisolone 21-acetate (XXVII) which gave a strong blue tetrazolium test. The presence of the 16-methylene group was confirmed by the n.m.r. doublet at τ 4.74 and 4.91. The reaction was followed by paper chromatography of aliquots. Within 10 min. all starting oxide had disappeared and two polar spots of nearly equal mobility appeared. The more polar of these, XXVII, was invariant with time, whereas the second spot, formulated as the Δ^{15}-16-methyl compound XXVIII, became less intense as two nonpolar spots became more intense as the reaction progressed. The latter two substances (isolated by chromatography) are formulated as 9α-fluoro-15α-chloro-16-methyl-$\Delta^{1,4,16}$-pregnatriene-11β,21-diol-3,20-dione 21-acetate (XXXI), sintering at 200°, m.p. 272–275°dec.,[24] λ_{max}^{MeOH} 241 mμ (ϵ 20,800), and 9α-fluoro-16-methyl-$^{1,4}\Delta^{,14,16}$-pregnatetraene-11β,21-diol-3,20-dione 21-acetate (XXXII), m.p. 282–285° dec., λ_{max}^{MeOH} 307 mμ (ϵ 12,400) and 236 (16,200).

We had previously observed the conversion of the 16β-methyl 16α,17α-oxide VI into *exo* (Ib) and *endo* (VII) olefins and conversion of the latter into the corresponding 15α-halo-Δ^{16}-pregnen-20-one IX and $\Delta^{14,16}$-16-methylpregnadien-20-one.[3] For the initial isolation of the pure 16-methylene compound XXVII, crude crystalline XXVII was treated briefly with hydrogen bromide in acetic acid which completely converted *endo* isomer XXVIII present into easily separable more mobile entities.

Subsequent study showed the initial mixture of double bond isomers to be *ca.* 80–85% *exo* and *ca.* 15–20% *endo*. For isolation of the *endo* isomer XXVIII, the oxide XXVI was allowed to react with hydrogen chloride in acetic acid at 15° for 15 min. and the product mixture of XXVII and XXVIII was separated by preparative paper chromatography after column chromatography in a variety of systems failed to achieve complete resolution.

The oxide opening under other acidic conditions was investigated briefly with the intent of devising a procedure which would permit isolation of pure XXVII without chromatography. Hydrochloric acid in acetone and *p*-toluenesulfonic acid in hot benzene[4] gave mixtures containing XXVII and XXVIII, but with trifluoroacetic acid in benzene 16-methylene compound XXVII was produced considerably cleaner. The *endo* isomer XXVIII was absent and only minor amounts of two nonpolar impurities were formed. Crystallization of the total product gave pure XXVII in 80% yield. From the mother liquors a few per cent of pure $\Delta^{1,4,14,16}$-tetraene XXXII was obtained.

The trifluoroacetic acid result may be rationalized by invoking interaction of the carboxyl group of the latter with the C-20 carbonyl group, thereby favoring internal abstraction of a proton from the C-16 methyl group [*e.g.*, formulation D].



D

The oral antiinflammatory activity of several of the above compounds (hydrocortisone = 1) is summarized in Table I.[25]

The antiinflammatory activity in rats of XXVII and XXVIII closely paralleled that of the corresponding 16β-methyl and 16α-methyl analogs, respectively.[26] The Δ^{15}-16-methyl compound XXVIII appeared to be a

(22) The Δ^4-3-keto system of 16-dehydrocortisone acetate, however, did react with peroxytrifluoroacetic acid.

(23) R. E. Beyler and F. Hoffman [*J. Org. Chem.*, 572 (1956)] found that the alkaline blue tetrazolium assay indicative of the steroid ketol side chain is negative in the case of 16α,17α-oxido-20-keto 21-acetates. Alkaline degradation of this system appears to be more rapid than the oxidation-reduction reaction with tetrazolium reagent.

(24) On heating, XXXI evidently loses hydrogen chloride and is transformed to XXXII.

(25) Private communications from Dr. S. L. Steelman and E. R. Morgan, Merck Institute for Therapeutic Research. For references to the assay procedures, see S. L. Steelman, E. R. Morgan, and R. H. Silber, *Steroids*, **1**, 163 (1963). The electrolyte assays were performed by Dr. H. C. Stoerk and co-workers. Adrenalectomized rats were maintained for 24 hr. after operation on a low sodium and potassium diet, injected i.p. with 5 ml. of physiological saline solution and s.c. with 0.25 ml. of 30% ethanol containing 50 γ of steroid. Pooled urine (three rats) was collected and analyzed for sodium. Details of the biological results will be reported elsewhere.

(26) For a recent review of structure-antiinflammatory activity relationships in the cortical steroid field, see L. H. Sarett, A. A. Patchett, and S. L. Steelman, *Progr. Drug Res.*, 13 (1963). It is noteworthy that methylene groups at positions 2 and 6 strongly depress antiinflammatory activity.

TABLE I

ORAL ANTIINFLAMMATORY ACTIVITY

Compd.	Liver glycogen (mouse)	Systemic granuloma (rat)
16-Methyleneprednisone 21-acetate (IV)	2.5	8
9α-Fluoro-16-methyl-1,4,16-pregnatriene-11β,21-diol-3,20-dione 21-acetate (XVII)		<5
16α,17α-Oxido-9α-fluoro-16β-methyl-1,4-pregnadiene-11β,21-diol-3,20-dione 21-acetate (XXVI)		<1
16-Methylene-9α-fluoroprednisolone 21-acetate (XXVII)	15	58
Δ^{15}-9α-Fluoro-16-methylprednisolone 21-acetate (XXVIII)	29	156
15α-Chloro-9α-fluoro-16-methyl-1,4,-16-pregnatriene-11β,21-diol-3,20-dione 21-acetate (XXXI)	1	
9α-Fluoro-16-methyl-1,4,14,16-pregnatetraene-11β,21-diol-3,20-dione 21-acetate (XXXII)	<1	1

sodium retainer in rats in striking contrast with the 16-methylene compounds IV and XXVII as well as with the 16α- and 16β-methyl, 16α-hydroxyl, and 16α-fluoro corticoids which are sodium excreters.[26] The 16α,17α-oxide XXVI, although devoid of antiinflammatory activity, was a sodium excreter in rats.

Experimental[27]

21-Bromo-16-methylenepregnane-3α,17α-diol-11,20-dione (IIa).—To a stirred solution of 2.53 g. (7.00 mmoles) of 16-methylenepregnane-3α,17α-diol-11,20-dione (Ia) in 50 ml. of chloroform containing 3 drops of methanol was added 1.32 g. (8.38 mmoles) of bromine in 70 ml. of chloroform at 30° at such a rate as to keep the reaction mixture light yellow. Addition was complete in 6 hr. after which the reaction mixture was quenched by the addition of 50 ml. of water containing a small amount of sodium sulfite. The layers were separated and the chloroform solution was washed with 40 ml. of 5% potassium bicarbonate followed by 35 ml. of water, dried over sodium sulfate, and taken to dryness *in vacuo*. The residual foam on trituration with ether containing several drops of acetone, followed by aging overnight at 0°, yielded 2.32 g. (75.5%) of crystalline product, m.p. 190–198° dec. An analytical sample, recrystallized from acetone–ether, had the following properties: m.p. 200–204° dec.; $[\alpha]_D$ +33.5°; λ_{max}^{Nujol} 2.9–2.95, 5.76, and 5.91 μ.

Anal. Calcd. for $C_{22}H_{31}BrO_4$: C, 60.13; H, 7.11; Br, 18.18. Found: C, 60.31; H, 7.38; Br, 17.29.

Paper chromatography (benzene–formamide) showed the mother liquor to consist primarily of IIa and two minor mobile impurities.

16-Methylenepregnane-3α,17α,21-triol-11,20-dione 21-Acetate (IIb).—To a stirred solution of 2.22 g. of the 21-bromopregnane IIa in 23 ml. of acetone were added 2.19 g. of potassium acetate, 1.75 g. of potassium iodide, and 3 drops of glacial acetic acid. The reaction mixture was refluxed gently, with stirring, overnight. At the end of this time, the mixture was cooled to room temperature and filtered. The yellow filtrate was taken to dryness *in vacuo*. The residue was triturated with water, filtered, washed with water, and dried in air to yield 1.97 g. (93.4%) of crystalline product melting at 172–175°. The analytical sample (from acetone) had m.p. 173–175°; $[\alpha]_D$ +44°; $\lambda_{max}^{CHCl_3}$ 2.74, 2.85–3.0, 5.74, 5.78, 5.86, and 6.00–6.05 μ; n.m.r., τ 4.76 and 4.94 (C_{16}=CH_2).

Anal. Calcd. for $C_{24}H_{34}O_6$: C, 68.87; H, 8.18. Found: C, 68.47; H, 8.24.

16-Methylenepregnane-3α,17α,21-triol-11,20-dione 3,21-Diacetate (IIc).—Acetylation of 500 mg. of IIb in 10 ml. of pyridine and 0.5 ml. of acetic anhydride yielded the 3,21-diacetate (IIc), crystallized from acetone–ether: 395 mg. (first crop), m.p. 223–226°, $[\alpha]^{CHCl_3}{}_D$ +58°.

Anal. Calcd. for $C_{26}H_{36}O_7$: C, 67.80; H, 7.88. Found: C, 67.76; H, 7.84.

16-Methylenepregnane-17α,21-diol-3,11,20-trione 21-Acetate (III). A. Sodium Dichromate Oxidation of IIb.—To a stirred solution of 600 mg. (1.43 mmoles) of 16-methylenepregnane-3α,17α,21-triol-11,20-dione 21-acetate (IIb) in 16 ml. of glacial acetic acid was added 284 mg. (0.95 mmoles) of sodium dichromate in 13 ml. of glacial acetic acid at room temperature. The reaction mixture was stirred at room temperature for 3 hr., then diluted with water, and extracted with chloroform. The chloroform extract was washed successively with aqueous potassium bicarbonate and saturated salt solution, dried over magnesium sulfate, and taken to dryness *in vacuo*. The residual foam was triturated with ether containing a few drops of acetone and aged overnight at 0° to yield 384 mg. (64%) of crystalline product melting 195–210°. Paper chromatography (benzene–cyclohexane 4:1 saturated with formamide) showed this material to contain a more mobile component as an impurity which was not separable by either column chromatography or recrystallization. The total crude crystalline product as obtained, therefore, was carried through the subsequent steps to 16-methyleneprednisone 21-acetate IV.

Chromium trioxide–acetic acid and chromium trioxide–pyridine oxidation procedures when applied to IIb gave inferior results.

B. Zinc Debromination of Va.—To a stirred solution of 175 mg. of 16α,17α-oxido-16β-bromomethylpregnan-21-ol-3,11,20-trione 21-acetate (Va, below) in 10 ml. of acetic acid was added 120 mg. of zinc dust. Two additional 120-mg. portions of zinc dust were added, respectively, 10 min. and 40 min. after the first addition. After an additional hour, the mixture was filtered and the filtrate was diluted with water and extracted with chloroform. The chloroform extract was washed with aqueous potassium bicarbonate and saturated aqueous sodium chloride, dried over magnesium sulfate, and concentrated to dryness *in vacuo*. The residue, 130 mg. (89%), on paper chromatography (benzene–cyclohexane 4:1 saturated with formamide) was *ca.* 98% single-spot III, the only visible contaminant being starting material Va. Crystallization from a variety of solvents gave III as a gelatinous solid. The analytical sample was obtained from ethyl acetate–ether: double m.p. 175–185° and 205–215°; $[\alpha]_D$ +38°; $\lambda_{max}^{CHCl_3}$ 2.73, 2.80–2.94, 5.73, 5.76, 5.83, and 8.1 μ.

Anal. Calcd. for $C_{24}H_{32}O_6$: C, 69.20; H, 7.74. Found: C, 68.85; H, 7.72.

16-Methyleneprednisone 21-Acetate (IV).—To a stirred solution of 200 mg. (0.48 mmole) of crude 16-methylene 3-ketone III (prepared by above procedure A) in 4 ml. of chloroform containing 3 drops of glacial acetic acid at 0° was added 1 drop of a solution of 162 mg. (1.01 mmoles) of bromine in 0.53 ml. of glacial acetic acid and 0.47 ml. of chloroform. The reaction mixture was stirred at 0° until the reaction started (as indicated by decolorization), then chilled to −15°, and one-half of the bromine solution was added at such a rate that the reaction mixture remained colorless. The temperature was then raised to 3° and the remainder of the bromine solution was added in the same manner. After complete addition of the bromine, the reaction was immediately quenched by the addition of 94 mg. of sodium acetate in 0.4 ml. of water, and a few drops of 5% aqueous solution of sodium sulfite were added to decolorize the mixture. The mixture was then diluted with 15 ml. of chloroform and 5 ml. of water; the layers were separated: the chloroform solution was washed with 5 ml. of water, excess potassium bicarbonate, and 5 ml. of saturated salt solution, dried over magnesium sulfate, and taken to dryness *in vacuo* to yield 280 mg. of crude **2,4-dibromo-16-methylenepregnane-17α,21-diol-3,11,20-trione 21-acetate.** This material was dehydrobrominated without purification.

To a stirred solution of 275 mg. of the crude 2,4-dibromo-3-one in 3.3 ml. of dimethylformamide was added 53 mg. of sodium bromide. The mixture was stirred under nitrogen at room temperature for 1 hr. At the end of this period, 0.66 ml. of dimethylaniline was added and the reaction mixture was stirred at 135° for 2.25 hr. The mixture was cooled to 10° and added slowly to

(27) Melting points were taken on a micro hot-stage apparatus and are corrected. Unless otherwise specified, optical rotations were run in chloroform (*c* 1), ultraviolet spectra were run in methanol, and n.m.r. spectra were run in deuteriochloroform with a 60-Mc. Varian Associates Model 4300B spectrometer utilizing benzene as an external reference. Paper chromatograms were run on strips of Whatman No. 1 or No. 4 filter paper using the formamide systems of A. Zaffaroni, R. B. Burton, and E. H. Keutmann [*Science*, **111**, 6 (1950)].

a stirred solution of 0.46 ml. of concentrated hydrochloric acid in 19.4 ml. of water. The resulting precipitate was aged overnight at 0°, filtered, washed with dilute hydrochloric acid and water, and dried. The mother liquor yielded a small second crop on salting out to give a total of 135.3 mg. (69%) of crude IV. The crude product in ethyl acetate (10 ml.) was eluted through a column of 260 mg. of unground charcoal which was washed with ethyl acetate until the eluates were transparent in the ultraviolet. The combined eluates were taken to dryness and the residue (119 mg.) was chromatographed on 7 g. of neutral alumina. The crystalline material eluted by 30% chloroform–benzene to 50% chloroform–benzene (50 mg.) was crystallized from acetone–ether to give a first crop of 32 mg. of the 1,4-dien-3-one IV: m.p. 214–217°; $[\alpha]_D$ +123°; λ_{max} 238 mμ (ϵ 14,100); $\lambda_{max}^{CHCl_3}$ 2.74, 2.86–3.00, 5.73 sh, 5.76, 5.84, 6.00, 6.14, 6.20, and 11.19 μ; n.m.r., τ 4.71 and 4.88 (C-16 =CH_2); R_f −0.45 (benzene–formamide system) compared with that of 16β-methylprednisone 21-acetate, R_f −0.50.

Anal. Calcd. for $C_{24}H_{28}O_6$: C, 69.88; H, 6.84. Found: C, 69.96; H, 6.94.

In an attempt to apply the selenium dioxide dehydrogenation procedure[9] to III, a mixture of 60 mg. of III, 70 mg. of selenium dioxide, and 70 mg. of mercuric oxide in 4 ml. of *t*-amyl alcohol was refluxed for 20 hr. The reaction mixture was cooled, filtered the inorganic precipitate was washed with chloroform, and the filtrate was partitioned between water and chloroform. The chloroform extract was washed with aqueous potassium carbonate and salt solution, dried over magnesium sulfate, and concentrated to dryness. The residue was chromatographed on 3 g. of neutral alumina. From the 30% chloroform–benzene fractions a solid was obtained (13 mg.) which was crystallized from acetone–ether: 6 mg.; m.p. 206–210°; λ_{max} 238 mμ, $E_{1\%}^{cm}$ 341 λ_{max}^{Nujol} 2.96, 5.75 sh, 5.79, 5.84, 5.99, 6.11, 6.19, and 11.25 μ. This substance by paper chromatography (benzene–formamide) had R_f 0.66 compared with that of IV, R_f 0.45.

N-Bromosuccinimide Reactions. A. 16α,17α-Oxido-16β-bromomethylpregnan-3α-ol-11,20-dione 3-Acetate (Vb).—A stirred solution of 300 mg. of 16-methylenepregnane-3α,17α-diol-11,20-dione 3-acetate (Ib) and 265 mg. of N-bromosuccinimide in 8 ml. of *t*-butyl alcohol and 1.5 ml. of water was kept at 15° for 0.5 hr. and at 0° for 18 hr. Paper chromatography (ligroin–formamide) indicated the reaction to be incomplete; so it was continued for 4 hr. at 25° at which time Ib was consumed completely. The mixture was decolorized with 5% sodium sulfite solution, concentrated to dryness, and the product (single spot Vb) was precipitated by addition of water. It was filtered, washed with water, and dried in air: 332 mg. (93%); m.p. 154–156°; $[\alpha]_D$ 102.5°; $\lambda_{max}^{CHCl_3}$ 5.78, 5.84, and 7.97 μ; n.m.r., τ 6.40 (C-16 –CH_2Br).

Anal. Calcd. for $C_{24}H_{33}BrO_5$: C, 59.87; H, 6.90; Br, 16.60. Found: C, 60.00; H, 6.99; Br, 16.10.

B. 16α,17α-Oxido-16β-bromomethylpregnan-21-ol-3,11,20-trione 21-Acetate (Va).—In a similar manner, 200 mg. of 16-methylenepregnane-3α,17α,21-triol-11,20-dione 21-acetate (IIb) was treated with 300 mg. of N-bromosuccinimide in 5 ml. of *t*-butyl alcohol and 1 ml. of water to g ve the 3-ketobromo oxide Va: 185 mg. (80%); m.p. 190–196° (from acetone–ether); λ_{max}^{Nujol} 5.71, 5.76, 5.84, and 8.15 μ.

Anal. Calcd. for $C_{24}H_{31}BrO_6$: C, 58.18; H, 6.30; Br, 16.13. Found: C, 57.92; H, 6.55; Br, 15.96.

C. 16α,17α-Oxido-16β-bromomethyl-3α,21-diol-11,20-dione 3,21-Diacetate (Vc).—Similarly, 370 mg. of 16-methylenepregnane-3α,17α,21-triol-11,20-dione 3,21-diacetate (IIc) was treated with 260 mg. of N-bromosuccinimide in 9 ml. of *t*-butyl alcohol and 1 ml. of water at 25° overnight to give 370 mg. (94%) of the bromo oxide Vc: m.p. 153–155° (from acetone–ether); $[\alpha]_D$ +88°; $\lambda_{max}^{CHCl_3}$ 5.71, 5.77, 5.81, and 8.15 μ.

Anal. Calcd. for $C_{26}H_{35}BrO_7$: C, 57.88; H, 6.54; Br, 14.81. Found: C, 58.26; H, 6.42; Br, 14.17.

Zinc Debromination of Vb.—A solution of 100 mg. of the 16β-bromomethyl 16α,17α-oxide Vb in 5 ml. of acetic acid was debrominated with 200 mg. of zinc dust added in three portions as described above for Va to yield 90 mg. of Ib, m.p. 197–200° (from acetone–ether), identical with an authentic sample[3,4] by mixture melting point and infrared criteria.

Zinc Debromination of Vc.—Similarly, 75 mg. of Vc in 4 ml. of acetic acid was treated with 150 mg. of zinc to yield 50 mg. of 16-methylene compound IIc, m.p. 218–224° undepressed, and with identical infrared spectrum with that of an authentic sample.

Hydrogenolysis of Vb.—The 16β-bromomethyl 16α,17α-oxide Vb (200 mg.) in 40 ml. of methanol was treated with hydrogen at 1 atm. (25°) over 400 mg. of 25% palladium-on-calcium carbonate catalyst. When hydrogen uptake ceased, the catalyst was removed by filtration and the filtrate was taken to dryness. Paper chromatography of the residue (*n*-heptane–phenyl Cellosolve) showed it to consist mainly of 16α,17α-oxido-16β-methylpregnan-3α-ol-11,20-dione 3-acetate VI contaminated with polar impurities. Two crystallizations of the residue from ether–hexane gave VI, m.p. 160–164° undepressed with an authentic sample.[3,4] The respective infrared spectra were identical. A probe hydrogenolysis using 5% palladium on charcoal as catalyst and ethyl acetate as solvent was incomplete.

16α,17α-Oxido-15β-bromo-16β-methyl-5β-pregnan-3α-ol-11,20-dione 3-Acetate (VIII).—A solution of 115 mg. of Δ^{15}-16-methylpregnene-3α,17α-diol-11,20-dione 3-acetate (VII)[3,4] and 115 mg. of N-bromosuccinimide in 6 ml. of *t*-butyl alcohol and 0.75 ml. of water was stirred 4.5 hr. at 25°. The reaction was worked up as described for the preparation of Vb. Addition of water to the residue led to 110 mg. of VIII as plates, m.p. 150–153° dec. Crystallization from acetone–ether led to rectangular prisms: m.p. 132–140° dec.; $\lambda_{max}^{CHCl_3}$ 5.77, 5.83, and 7.96 μ; R_f −0.90 (ligroin–formamide) compared with that of VII, R_f −0.20.

Anal. Calcd. for $C_{24}H_{35}BrO_5$: C, 59.88; H, 6.91. Found: C, 59.98; H, 6.82.

16α,17α-Oxido-15α-bromo-16β-methylpregnan-3α-ol-11,20-dione 3-Acetate (X).—To a stirred solution of 1.00 g. (2.2 mmoles) of Δ^{16}-15α-bromo-16-methylpregnen-3α-ol-11,20-dione 3-acetate[3] in 20 ml. of methylene chloride at 0° was added 7.5 g. of disodium hydrogen phosphate followed by 2.5 ml. of 1.75 *M* peroxytrifluoracetic acid (prepared from 0.82 ml. of 90% hydrogen peroxide in 5 ml. of methylene chloride and 5.1 ml. of trifluoracetic anhydride by the procedure of Emmons and Pagano[21]). The reaction was followed by observing the disappearance of ultraviolet absorption of aliquots. After 5 hr. at 0°, it was judged to be complete. Water was added and the mixture was extracted with methylene chloride. The latter extract was washed with brine, dried over magnesium sulfate, and taken to dryness. Crystallization of the residue from ether–petroleum ether (b.p. 30–60°) gave X, 750 mg., m.p. 161–174° dec. Recrystallization gave 260 mg.: m.p. 178–181° dec.; analytical sample m.p. 182–183.5° dec.; $\lambda_{max}^{CHCl_3}$ 5.78, 5.84, and 7.95 μ, identical in the functional group region (but not the fingerprint region) with the spectrum of the epimeric bromo oxide VIII; R_f −0.90 (ligroin–formamide), the same as that of VIII.

Anal. Calcd. for $C_{24}H_{33}BrO_5$: C, 59.88; H, 6.91; Br, 16.60. Found: C, 59.62; H, 6.84; Br, 15.91.

Zinc Debromination of VIII.—The 15β-bromo-16β-methyl 16α,17α-oxide VIII (20 mg.) in 2 ml. of acetic acid, on stirring overnight at 25° with 100 mg. of zinc dust, gave 16 mg. of crude Δ^{15}-16-methylpregnene VII. Crystallization from acetone–ether gave 7 mg. of pure VII, m.p. 223–230° undepressed, and with an identical infrared spectrum as an authentic sample.[3]

Zinc Debromination of X.—A 200-mg. sample of X and 1 g. of zinc dust in 8 ml. of acetic acid were stirred overnight at 25° to give 125 mg. of VII, m.p. 219–229°.

Hydrogenolysis of VIII.—A stirred solution of 40 mg. of the 15β-bromo-16β-methyl 16α,17α-oxide VIII in 5 ml. of methanol was hydrogenated (1 atm., 25°) over 80 mg. of 25% palladium-on-calcium carbonate catalyst. After 2 hr. the mixture was filtered and the filtrate was taken to dryness. The residue was taken up in chloroform and the latter solution was washed with water and dried over magnesium sulfate. The chloroform was removed under vacuum and the bromine-free residue was crystallized from ether to give a first crop of 20 mg., m.p. 175–180°, and a partly crystalline mother liquor. The 175–180° melting material was shown to be a mixture (~2:1) of 16α-methyl- and 16β-methylpregnane-3α,17α-diol-11,20-dione 3-acetate by comparison of paper chromatographic mobilities (ligroin–formamide, 16β-methyl component, R_f −0.15; 16α-methyl component, R_f −0.37), infrared spectra ($\lambda_{max}^{CHCl_3}$ 2.85, 5.77, 5.85, and 7.95 μ), and n.m.r. spectra of known mixtures of the two components.

The mother liquor, by paper chromatography, in addition to the above two components, contained the 16β-methyl 16α,17α-oxide VI (ligroin–formamide, R_f −0.80).

Hydrogenolysis of X.——The 15α-bromo-16β-methyl 16α,17α-oxide X (100 mg.) in 10 ml. of ethyl acetate was hydrogenated at 25° and 1 atm. over 110 mg. of 25% palladium-on-calcium carbonate catalyst. After 4 hr., the mixture was worked up as in the previous experiment to give a first crop of 60 mg., m.p.

172–177°, of a mixture of 16α-methyl- and 16β-methylpregnane-3α,17α-diol-11,20-dione 3-acetate. Paper chromatography of the mother liquor (ligroin–formamide) showed the presence of the 16β-methyl 16α,17α-oxide VI.

Δ^{20}-16α,17α:16a,20-Dioxidopregnen-3α-ol-11-one (XII).—To a stirred solution of 1.16 g. of the 16β-bromomethyl 16α,17α-oxide Vb in 50 ml. of benzene kept under nitrogen at 25° was added 8.5 ml. of 0.85 *M* potassium *t*-butoxide in *t*-butyl alcohol. After 18 hr., 100 ml. of iced water was added and the mixture was extracted with chloroform. The combined extracts were washed with brine, dried over magnesium sulfate, and concentrated to dryness to yield a crystalline residue: 860 mg. (99%); m.p. 208–215°; single spot, R_f −0.60, benzene–cyclohexane 3:1 saturated with formamide. Crystallization from acetone–ether gave the analytical sample: m.p. 215–225°; $[\alpha]_D$ +95.2°; $\lambda_{max}^{CHCl_3}$ 2.72, 2.80–2.85 (OH), 5.85 (C-11 =O), 6.01, and 11.2 μ (C-20 $=CH_2$); n.m.r., τ 5.46 and 5.85 (C-20 $=CH_2$), 5.77 (d), and 6.09 (d) [C-16 CH_2—O].

Anal. Calcd. for $C_{22}H_{30}O_4$: C, 73.71; H, 8.43. Found: C, 73.87; H, 8.26.

The presence of an olefinic grouping in XII was indicated qualitatively by its reaction with osmium tetroxide in dioxane. The Zimmerman test for α-methylenic ketone functionality was negative.

Hydrogenation of XII.—A solution of 100 mg. of XII in 15 ml. of ethyl acetate was hydrogenated (1 atm., 25°) over 100 mg. of 10% palladium-on-Darco catalyst. After 18 hr., 2.2 molar equiv. of hydrogen had been absorbed. The catalyst was filtered and the filtrate was taken to dryness. Paper chromatography (benzene–cyclohexane 3:1 saturated with formamide) showed the product (100 mg.) to consist primarily of two substances, a major component more polar than XII and a minor component less polar than XII. These were separated by column chromatography on 3 g. of neutral alumina. The nonpolar minor component (7 mg.), m.p. 165–171°, had $\lambda_{max}^{CHCl_3}$ 2.75, 2.90–2.95, and 5.86 μ and was tentatively formulated as the 20,21-dihydro compound XIIa. The polar major component (44 mg.) had m.p. 221–224°; $\lambda_{max}^{CHCl_3}$ 2.7 5,2.90–2.95, and 5.85 μ, different from the mobile component in the functional group region. Acetylation (acetic anhydride–pyridine, 25°) yielded the corresponding monoacetate: m.p. 210–223°; n.m.r., τ 8.62 (d) (HC-20 $—CH_3$), 6.04 (d), 6.33 (d), (C-16 $—CH_2O—$), 7.82 (C-3 $—OCOCH_3$), and 5.9 (m) (C-20 —H). These properties are in accord with the hydrogenation resulting in saturation of the Δ^{20}-double bond and opening of the three-membered oxide ring to yield a tertiary alcohol (*e.g.*, XIII or its C-17 hydroxylated isomer).

3,20-Disemicarbazone of 9α-Fluoroprednisolone 21-Acetate (XV).—A mixture of 4.9 g. of 9α-fluoroprednisolone 21-acetate (XIV), 13.3 g. of semicarbazide hydrochloride, and 3.4 g. of semicarbazide free base in 29 ml. of dimethylformamide and 57 ml. of methanol was refluxed with stirring under nitrogen for 4 hr. The reaction mixture was cooled to 10° and 130 ml. of water was added slowly with stirring. The precipitated 3,20-disemicarbazone XV was filtered, washed with water, and dried in a vacuum oven at 50°: 4.93 g., m.p. >300°, λ_{max} 291 mμ (ε 26,000) and 241 (21,600). Addition of 150 ml. of saturated sodium chloride to the aqueous filtrate and chilling to 0° led to an additional 715 mg. of XV of comparable quality (total yield 91%).

9α-Fluoro-$\Delta^{1,4,16}$-pregnatriene-11β,21-diol-3,20-dione 21-Acetate (XVI).—A solution of 20 g. of 3,20-disemicarbazone XV in 1000 ml. of acetic acid and 0.6 ml. of acetic anhydride was heated on the steam bath (90–95°) under nitrogen for 4 hr. Water (1000 ml.) was then added and the resulting 50% aqueous acetic acid solution of dehydrated semicarbazone was heated on the steam bath for an additional 3 hr. to hydrolyze the semicarbazone linkages.[3] The reaction was concentrated under vacuum to 300 ml., 1 l. of water was added, and the mixture was extracted with chloroform. The chloroform extract was washed with dilute aqueous potassium carbonate and brine, and dried over magnesium sulfate. Removal of the solvent under vacuum gave 10.1 g. of a yellow foam. Combination of the crude product with 9.4 g. obtained in a parallel dehydration and reversal of 18.9 g. of XV gave 19.5 g. which was chromatographed on 600 g. of neutral alumina. Combination of the crystalline 30% chloroform–benzene fractions (5.00 g.) and crystallization from acetone–ether gave 3.86 g. of the $\Delta^{1,4,16}$-pregnatriene XVI: m.p. 220–223°; $[\alpha]_D$ +148°; λ_{max} 239 mμ (ε 25,100); $\lambda_{max}^{CHCl_3}$ 2.90, 5.73, 5.83, 6.0, 6.14, 6.19, and 6.26 μ.

Anal. Calcd. for $C_{23}H_{27}FO_5$: C, 68.63; H, 6.76. Found: C, 68.34; H, 7.10.

From the 50% benzene–chloroform to 100% chloroform eluates 4.14 g. of single-spot 9α-fluoroprednisolone 21-acetate (XIV) was recovered.

9α-Fluoro-16α,17α-methyleneazo-$\Delta^{1,4}$-pregnadiene-11β,21-diol-3,20-dione 21-Acetate (XVIa).—Diazomethane was generated by intermittently adding a filtered dimethylformamide solution of N,N-dimethyl-N,N-dinitrosoterephthalamide[28] to a warm mixture of aqueous potassium hydroxide and ether, and swept by means of nitrogen into a solution of 3.53 g. of the $\Delta^{1,4,16}$-pregnatriene XVI in 80 ml. of tetrahydrofuran and 120 ml. of ether. The diazomethane addition was continued intermittently until the steroid solution remained yellow for 4 hr. Crystallization of the product pyrazoline which had begun during the reaction was completed by cooling to 0°. The precipitate was filtered, washed with ether, and dried in air: 3.46 g.; m.p. 193–196°; $[\alpha]_D$ +55°; $\lambda_{max}^{CHCl_3}$ 2.7–2.9, 5.73, 5.76, 5.97, 6.00, 6.15, and 6.40 μ. Concentration of the filtrate to a small volume and addition of ether gave an additional 340 mg. of XVIa (total yield 97.5%).

Anal. Calcd. for $C_{24}H_{29}FN_2O_5$: C, 64.84; H, 6.57. Found: C, 65.33; H, 6.27.

9α-Fluoro-$\Delta^{1,4,16}$-16-methylpregnatriene-11β,21-diol-3,20-dione 21-Acetate (XVII). A.—The pyrazoline XVIa (3.75 g.) in a 100-ml., round-bottom flask was heated by an oil bath (0.4 mm.) from 100 to 190° at which point pyrolysis began. The mixture was heated to 200° until nitrogen evolution ceased (10 min.) and then cooled to room temperature. Crystallization of the residue from acetone–ether gave the $\Delta^{1,4,16}$-16-methylpregnatriene XVII in two crops: 2.62 g. (75%); m.p. 233–236°; $[\alpha]_D$ +92°; λ_{max} 243 mμ (ε 22,700); $\lambda_{max}^{CHCl_3}$ 2.85–2.90, 5.73, 5.98, 6.12; and 6.18 μ.

Anal. Calcd. for $C_{24}H_{29}FO_5$: C, 69.21; H, 7.01; F, 4.56. Found: C, 69.18; H, 7.05; F, 4.93.

B.—A solution of 1.00 g. of the 3,20-disemicarbazone XIX in 20 ml. of acetic acid and 1 ml. of acetic anhydride was refluxed under nitrogen for 23 hr. Water (20 ml.) was added, the mixture was refluxed 4 hr., and worked up as described for the preparation of XVI. Alumina chromatography gave from the benzene–30% chloroform eluates 20 mg. of XVII, m.p. 228–233°.

3,20-Disemicarbazone of 9α-Fluoro-16α-methylprednisolone (XIX).—A mixture of 7.2 g. of 9α-fluoro-16α-methylprednisolone, 2.1 g. of semicarbazide hydrochloride, and 5.4 g. of semicarbazide free base in 42 ml. of dimethylformamide and 84 ml. of methanol was refluxed for 3.5 hr. under nitrogen. Cooling and addition of 200 ml. of water gave the 3,20-disemicarbazone XIX: 10 g., m.p. >300°, λ_{max} 292 mμ (ε 25,500) and 240 (21,400).

A 2.0-g. sample of XIX was acetylated in 1.0 ml. of acetic anhydride, 20 ml. of collidine, and 10 ml. of dimethylformamide at room temperature overnight. Addition of 100 ml. of iced water containing 2 ml. of acetic acid led to precipitation of the 3,20-disemicarbazone 21-acetate XIXa which was filtered, washed with water and ether, and dried in air: 1.75 g. Reversal of a 50-mg. probe in hot 50% aqueous acetic acid followed by acetylation gave the parent steroid 21-monoacetate XVIII in good yield.

Attempted Dehydration of XIX in Acetic Acid–Boron Trifluoride Etherate–Acetic Anhydride.—The 3,20-disemicarbazone XIX (150 mg.) in 10 ml. of acetic acid, 0.6 ml. of boron trifluoride etherate, and 0.6 ml. of acetic anhydride was kept overnight at room temperature. Water (10 ml.) was added and the mixture was heated for 4 hr. on the steam bath. It was extracted with chloroform, and the latter extract was washed with aqueous potassium bicarbonate and brine, dried over magnesium sulfate, and concentrated to dryness. Paper chromatography (benzene–formamide) indicated the residue to consist primarily of the 21-acetate XVIII and a component with mobility similar to that of XVII. Isolation of this substance by alumina chromatography showed it to be identical in the infrared with the 11-acetate of XVIII. The isolated sample had m.p. 257–264°, λ_{max} 237 mμ (ε 14,800).

Rearrangement of Disemicarbazone XIXa in Trifluoroacetic Acid. 18-Nor-16α,17β-Dimethyl-$\Delta^{1,4,13}$-17α-pregnatriene-11β,21-diol-3,20-dione (XXIa), 11,21-Diacetate (XX), and 21-Acetate (XXI).—A solution of 1.55 g. of disemicarbazone XIXa in 15 ml. of trifluoroacetic acid was kept at 25° for 18 hr. The solvent was removed under vacuum and the residue was heated on the steam

(28) 70% N,N-dimethyl-N,N-dinitrosoterephthalamide–30% white mineral oil, Du Pont EXR-101.

bath in 50 ml. of 50% aqueous acetic acid for 5 hr. The reaction mixture was cooled to room temperature and 300 ml. of brine solution was added. The mixture was extracted with chloroform and the latter extract was washed with dilute potassium bicarbonate solution and brine, and was dried over magnesium sulfate. Removal of the solvent left a residue (870 mg.). This was acetylated in 0.5 ml. of acetic anhydride and 15 ml. of collidine at 25° for 2.5 hr. Iced water was added and the product was extracted into chloroform. The latter extract was washed with dilute hydrochloric acid and dilute aqueous potassium bicarbonate, dried over magnesium sulfate, and taken to dryness under vacuum. The residue (870 mg.) was chromatographed on 30 g. of neutral alumina. Combination of the benzene–chloroform (2–20%) fractions gave 300 mg. of single-spot XX (R_f −0.95 benzene-formamide). Crystallization from acetone–ether gave 232 mg.: m.p. 195–198°: λ_{max} 235 mμ (ε 11,800); $\lambda_{max}^{CHCl_3}$ 5.75, 5.82, 5.99, 6.11, 6.18, and 11.19 μ; n.m.r., τ 9.05 (d) (C-16 $-CH_3$), 8.91 (C-17 $-CH_3$), and 7.94 (11β,21-OCOCH_3). Compound XX gave a positive tetranitromethane test.

Anal. Calcd. for $C_{26}H_{34}FO_6$: C, 67.80; H, 7.22. Found: C, 67.82; H, 7.13.

From the benzene–chloroform (20–30%) fractions was obtained the monoacetate XXI (R_f −0.50, benzene–formamide): m.p. 248–250°; λ_{max} 236 mμ (ε 16,700); $\lambda_{max}^{CHCl_3}$ 2.95, 5.74, 5.81, 6.00, 6.11, 6.20, and 11.21 μ.

Anal. Calcd. for $C_{24}H_{29}FO_5$: C, 69.21; H, 7.02. Found: C, 69.23; H, 7.33.

Acetylation of 10 mg. of XXI in 0.2 ml. of acetic anhydride and 0.5 ml. of pyridine gave single spot 11,21-diacetate XX, m.p. 195–199°, undepressed on mixture melting point with the sample prepared above. The respective infrared spectra and mobilities on paper were identical.

In another run, disemicarbazone XIXa (1.00 g.) was treated with 10 ml. of trifluoroacetic acid at 25° overnight. Following work-up and reversal of the semicarbazide groups in 35 ml. of 50% aqueous acetic acid as described above, the reversal reaction mixture was concentrated to *ca.* 5 ml. Addition of water led to a crude solid which was filtered. The filtrate was extracted with chloroform and the latter extract was dried over magnesium sulfate and concentrated to dryness. Crystallization of the residue from acetone–ether gave the 11β,21-diol XXIa: m.p. 241–246°; λ_{max} 238 mμ (ε 15,100); λ_{max}^{Nujol} 3.03–3.08, 5.85, 6.04, 6.17, and 6.25 μ.

Anal. Calcd. for $C_{22}H_{27}FO_4$: C, 70.56; H, 7.27. Found: C, 70.38; H, 7.33.

Acetylation (acetic anhydride–pyridine, 25°) of XXIa led to the 11β,21-diacetate XX.

Rearrangement of Disemicarbazone XV in Trifluoroacetic Acid.—A solution of 100 mg. of disemicarbazone XV in 2 ml. of trifluoroacetic acid was kept overnight at room temperature and the semicarbazide residues were removed in hot 1:1 aqueous acetic acid as described above for XIXa. Acetylation (acetic anhydride–pyridine, 25°) of the product gave a solid, λ_{max} 235 mμ, $E_{1\%}^{cm}$ 320, that on paper chromatography (benzene–formamide) showed the presence of the 16-dehydro compound XVI, R_f −0.50 (minor), and a nonpolar (R_f −0.95) major component. On the basis of the similarity of its polarity and ultraviolet maximum at 235 mμ with the corresponding properties of XX, this material is probably the analogous rearrangement product (*e.g.*, 16-demethyl XX).

Treatment of Disemicarbazone XXIII with Trifluoroacetic Acid.—A solution of 600 mg. of the 3,20-disemicarbazone of 9α-fluoroprednisone 21-acetate (XXIII) prepared from 9α-fluoroprednisone 21-acetate by the procedure utilized for XV in 10 ml. of trifluoroacetic acid was kept overnight at 25°, the semicarbazide residues were removed in hot 1:1 aqueous acetic acid, and the residue was acetylated and chromatographed on 10 g. of neutral alumina as described in detail for XIXa. From the benzene–chloroform (5–15%) eluates there was obtained 160 mg. of crystalline **Δ1,4,16-pregnatriene-21-ol-3,11,20-trione 21-acetate (XXV)**: m.p. 170–173°; λ_{max} 236 mμ (ε 24,000); $\lambda_{max}^{CHCl_3}$ 5.73, 5.79, 5.91, 5.99, and 6.11 μ.

Anal. Calcd. for $C_{23}H_{25}FO_5$: C, 69.00; H, 6.29. Found: C, 68.76; H, 6.05.

Treatment of Disemicarbazone XXII with Trifluoroacetic Acid.—In a manner similar to the sequence XVIII → XIX → XIXa, 9α-fluoro-16α-methylprednisone was converted into the corresponding 3,20-disemicarbazone 21-acetate XXII. A solution of the latter (1.8 g.) in 20 ml. of trifluoroacetic acid was kept at 25° overnight, reversed and acetylated as above, and the product was chromatographed on 25 g. of neutral alumina. There was obtained 350 mg. of recovered 9α-fluoro-16α-methylprednisone 21-acetate and 4 mg. of the corresponding 16-dehydro compound XXIV, λ_{max} 240 mμ (ε 22,200).

16α,17α-Oxido-16β-methyl-1,4-pregnadiene-11β,21-diol-3,20-dione 21-Acetate (XXVI).—To a stirred solution of 2.5 g. of the Δ1,4,16-16-methylpregnatriene (XVII) in 40 ml. of methylene chloride at 0° was added 19 g. of disodium hydrogen phosphate followed by 6.2 ml. of 2 *M* peroxytrifluoroacetic acid reagent[21] prepared as described in the preparation of X. After 1 hr. at 0°, methylene chloride and water were added. The mixture was extracted with methylene chloride and the latter extract was washed with water and saturated sodium chloride solution. Removal of the solvent left a residue which was crystallized from acetone–ether to give three single-spot crops of the 16α,17α-oxide XXVI, 2.4 g. (92%). The analytical sample (from acetone–ether) had m.p. 227–230°; $[\alpha]_D$ +146°; λ_{max} 237 mμ (ε 15,100); $\lambda_{max}^{CHCl_3}$ 2.74, 2.90, 5.73, 5.79, 6.00, 6.13, 6.19, 8.10, 11.15, and 11.24 μ.

Anal. Calcd. for $C_{24}H_{29}FO_6$: C, 66.65; H, 6.76. Found: C, 66.58; H, 6.74.

In an unsuccessful probe experiment the Δ1,4,16-16-methylpregnatriene XVII (50 mg.) in 1 ml. of chloroform under nitrogen was added at 0° to a mixture of 6 ml. of ethanol, 3 ml. of water, 0.5 ml. of 7% potassium carbonate, 0.12 ml. of 1 *N* sodium hydroxide, and 0.5 ml. of 30% hydrogen peroxide under nitrogen.[19] The homogeneous mixture was kept under nitrogen at 0° and the reaction was followed by paper chromatography (benzene–formamide) of acidified 0.1-ml. aliquots. Within 1 hr., starting material was converted completely to a more polar tetrazolium positive substance (21-alcohol) with no further change in 90 hr. On warming to 25°, this intermediate was transformed in 48 hr. nearly completely to a more polar tetrazolium negative material. The reaction mixture was neutralized with 10% aqueous acetic acid and extracted with chloroform. The chloroform extract was dried over magnesium sulfate and concentrated to a crystalline acid (possibly XXX), soluble in 5% aqueous potassium bicarbonate and insoluble in water: m.p. 170–180°; λ_{max} 238 mμ, $E_{1\%}^{cm}$ 460; λ_{max}^{Nujol} 2.8–4.0, 5.85, 5.96, and 6.15 μ.

16-Methylene-9α-fluoroprednisolone 21-Acetate (XXVII). A. Trifluoroacetic Acid.—To a stirred solution of 9.00 g. of the 16α,17α-oxide XXVI in 180 ml. of benzene maintained at 10° was added (5 min.) 36 ml. of trifluoroacetic acid in 90 ml. of benzene. The mixture was kept at 25° for 18 hr. Ethyl acetate (200 ml.) was added followed by 300 ml. of cold water and the mixture was extracted with ethyl acetate. The organic extract was washed with excess cold 5% potassium bicarbonate and brine solution and dried over magnesium sulfate. Removal of the solvent left a solid residue, crystallization of which from ethyl acetate gave 7.15 g. (80%) of single-spot XXVII in two crops with considerable additional material in the mother liquors (analytical sample from ethyl acetate): m.p. 231–234°; $[\alpha]_D$ +43°; λ_{max} 238 mμ (ε 15,700); $\lambda_{max}^{CHCl_3}$ 2.73, 2.85–2.90, 5.73, 5.76, 5.99, 6.10, 6.18, and 11.2 μ; n.m.r., τ 4.74 and 4.94 (C-16 $=CH_2$).

Anal. Calcd. for $C_{24}H_{29}FO_6$: C, 66.65; H, 6.76. Found: C, 66.74; H, 6.71.

Further crystallization of the mother liquors from ethyl acetate–hexane led to **9α-fluoro-Δ1,4,14,16-16-methylpregnatetraene-11β,21-diol-3,20-dione 21-acetate (XXXII)**, 120 mg. (analytical sample from ethyl acetate–acetone): m.p. 282–285° dec.; $[\alpha]_D^{pyridine}$ +531°; λ_{max} 307 mμ (ε 12,400) and 236 (16,200); λ_{max}^{Nujol} 2.95, 5.70, 5.97, 6.13, 6.47, 8.15, and 11.2 μ.

Anal. Calcd. for $C_{24}H_{27}FO_5$: C, 69.55; H, 6.57. Found: C, 69.48; H, 6.88.

B. Hydrogen Chloride–Acetic Acid.—To a solution of 200 mg. of 16α,17α-oxide XXVI in 2 ml. of acetic acid was added 6 ml. of 5% hydrogen chloride in acetic acid. After 3.5 hr. at 25°, the mixture was concentrated to dryness. Paper chromatography (benzene–formamide) showed the residue to consist primarily of the 16-methylene compound XXVII contaminated with its Δ15-16-methyl isomer XXVIII and two nonpolar substances (XXXI and XXXII). Fractional crystallization did not materially improve the purity of the product. Chromatography on 5 g. of neutral alumina separated the two mobile from the two polar components. To the mixture of XXVII and XXVIII (100 mg.) from the alumina chromatography in 4 ml. of acetic acid at 12° was added 2 ml. of 10% hydrogen bromide in acetic acid (conversion of XXVIII to the mobile XXXII and 15-bromo analog of XXXI[3]). After 30 min. at 12°, the mixture was pumped to dryness under vacuum and the residue was chromatographed on 5 g. of neutral

alumina. From the crystalline benzene–20% chloroform fractions single-spot XXVII was obtained (50 mg.) which on crystallization from acetone–ether gave pure XXVII, m.p. 231–234°.

The mobile fractions from the original chromatogram (40 mg.) were separated by chromatography on Whatman No. 3 filter paper (benzene–cyclohexane 4:1, saturated with formamide, system). From the more polar band (9 mg.) was obtained on crystallization from acetone–ether nearly pure $\Delta^{1,4,14,16}$-tetraene XXXII (see above): m.p. 270–278° dec.; λ_{max} 306 mμ (ε 12,600) and 236 (16,800). Crystallization of material eluted from the more mobil band (17 mg.) from acetone–ether gave **15α-chloro-9α-fluoro-16-methyl-$\Delta^{1,4,16}$-pregnatriene-11β,21-diol-3,20-dione 21-acetate (XXXI)**: sintering at 200°, m.p. 272–275° dec.; λ_{max} 241 mμ (ε 20,800); $\lambda_{max}^{CHCl_3}$ 2.77, 2.90–2.95, 5.74, 6.00, 6.12, 6.18 and 11.16 μ.

9α-Fluoro-Δ^{15}-16-methylprednisolone 21-Acetate (XXVIII).—To a solution of 850 mg. of 16α, 17α-oxide XXVI in 10 ml. of acetic acid at 15° was added 10 ml. of 7% hydrogen chloride in acetic acid. After 15 min. at 15°, water was added and the mixture was extracted with chloroform. The chloroform extract was washed with water, 5% potassium bicarbonate solution, and brine, dried over magnesium sulfate, and concentrated to dryness to give a crystalline residue (850 mg.). Paper chromatography (benzene–chloroform 9:1 saturated with formamide) showed the latter to consist of two components of nearly similar mobility, the more polar XXVII (major) and the less polar XXVIII (minor) which by n.m.r. analysis was 80–85% XXVII and 15–20% XXVIII. The mixture could not be separated by column chromatography on alumina or by partition chromatography on celite. A 400-mg. portion was resolved, however, by preparative paper chromatography (40 mg. per 15 × 45 cm. sheet of Whatman No. 3 paper, benzene–chloroform 9:1, saturated with formamide). The desired Δ^{15}-16-methyl compound (XXVIII, 40 mg.) was obtained as single-spot material from the lower band and on crystallization from acetone–ether gave the analytical sample: m.p. 242–247°; $[\alpha]^{acetone}_D$ +45°; λ_{max} 238 mμ (ε 15,100); λ_{max}^{Nujol} 2.91, 3.05, 5.75, 5.81, 6.01, 6.15, 6.19, and 11.25 μ; n.m.r., τ 8.07 (C-16 $-CH_3$).

Anal. Calcd. for $C_{24}H_{29}FO_6$: C, 66.65; H, 6.76. Found: C, 66.72; H, 7.08.

From the upper band, 300 mg. of mixed fractions was recovered.

When 100 mg. of the 16α,17α-oxide XXVI in 3 ml. of acetone was treated with 1 ml. of concentrated hydrochloric acid at 0° for 1.5 hr., the product was a ~1:1 mixture of XXVII and XXVIII (n.m.r. and paper chromatography).

When 100 mg. of the 16α,17α-oxide XXVI was refluxed in 6 ml. of benzene and 7 mg. of *p*-toluenesulfonic acid for 1 hr., the product contained a ~5:1 mixture of XXVII and XXVIII.

Acknowledgment.—We wish to express our appreciation to Dr. N. R. Trenner and B. Arison for the n.m.r. spectra and their interpretation, to R. W. Walker and N. Allan for the infrared spectra, to A. Kalowsky for the ultraviolet spectra, and to Dr. R. N. Boos and associates for the elemental analyses.

The Reaction of Various Steroid α-Bromo Ketones with Dimethyl Sulfoxide[1]

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Received March 26, 1964

The reaction of methyl 4β-bromo-3-keto-5β-cholanate with dimethyl sulfoxide gave methyl 3,4-diketo-5β-cholanate and methyl-3-ketochol-4-enate, while the corresponding acid gave 3-ketochol-4-enic acid and 3-keto-5β-chol-1-enic acid. Similarly, 5-bromo-5α-cholestan-3β-ol-6-one acetate gave cholest-4-en-3β-ol-6-one acetate; 6β-bromo-5α-cholestan-3β-ol-7-one acetate gave cholest-5-en-3β-ol-7-one acetate and cholesta-3,5-dien-7-one; and 7α-bromo-5α-cholestan-3β-ol-6-one acetate gave cholest-5-ene-3β,6-diol-7-one 3-acetate.

In an accompanying paper[3] the reaction of 2α-bromo-5α-cholestan-3-one with dimethyl sulfoxide is described. The reaction gave a complex mixture of products, including the expected 3-hydroxy-5α-cholest-3-en-2-one and 5α-cholest-1-en-3-one, and was of little synthetic utility. In this paper reactions of other steroid α-bromo ketones (Chart I) are described which proceeded in a more straightforward manner and are of synthetic utility.

The first compound studied was methyl 4β-bromo-3-keto-5β-cholanate (Ia), which has the bromine atom in the equatorial conformation and an adjacent 5-axial hydrogen atom. When this compound was heated in dimethyl sulfoxide at 125–130°, starting material was recovered (32%) and methyl 3,4-diketo-5β-cholanate (II, 25%) and methyl 3-ketochol-4-enate (IIIa, 28%) were formed (the latter two yields are based on recovered starting material). The diketone gave a positive enol test with ferric chloride and therefore probably exists as a diosphenol, but no attempt was made to determine which isomer was present. It also gave a typical diosphenol ultraviolet absorption spectrum (λ_{max} 271 mμ). Although this bromo ketone had the same stereochemistry as 2α-bromo-5α-cholestan-3-one (bromine atom equatorial, hydrogen atom axial), its reaction with dimethyl sulfoxide was much less complex and the products were readily separable by column chromatography, thus providing a useful route to the previously unreported diosphenol.

When 4β-bromo-3-keto-5β-cholanic acid (Ib), instead of the methyl ester (Ia), was heated in dimethyl sulfoxide at 125–130° with sodium bicarbonate, the reaction, surprisingly and anomalously, resulted in elimination products only. Two olefins were formed, 3-ketochol-4-enic acid (IIIb, 80%) and what appeared to be 3-keto-5β-chol-1-enic acid (IV, 20%) (these yields are crude estimates from the ultraviolet spectrum), and no evidence could be obtained for the presence of any diosphenol. A possible explanation for this result is that the cholanic acid was present in the reaction mixture as the anion, owing to reaction with sodium bicarbonate. Thus, this anion, a stronger base than dimethyl sulfoxide or bicarbonate ion, was present to promote elimination at a more rapid rate than it took place with the methyl ester, where no base of comparable strength was present.

The next bromo ketone studied was 5-bromo-5α-cholestan-3β-ol-6-one acetate (VI). This compound

(1) A portion of this work was supported by Grant AM 05249-02 from the National Institutes of Health, U. S. Public Health Service.

(2) The major portion of this work is abstracted from the Ph.D. Thesis of R. N. I., Brown University, 1963. Brown University Fellow, 1959–1961. Holder of the Shell Oil Co. Fundamental Research Grant in Chemistry, 1961–1962.

(3) H. R. Nace and R. N. Iacona, *J. Org. Chem.*, **29**, 3498 (1964).