2 ml. of absolute ethanol was added 10 ml. of concentrated hydrochloric acid. After 24 hours of agitation at room temperature the mixture was extracted several times with methylene chloride, the combined extracts were washed with aqueous sodium bicarbonate solution, dried over anhydrous magnesium sulfate, and evaporated in vacuum. The residue weighed 10 mg. The aqueous reaction mixture was neutralized with sodium hydroxide solution and extracted three times with ethyl acetate, the combined extracts were washed with sodium bicarbonate solution, with brine, and then dried and evaporated in vacuum. The residue, weighing 125 mg., was combined with the previous residue isolated and chromatographed on Celite diatomaceous earth using a solvent system benzene–acetone–water (2.5:1:2). The appropriate fractions were combined and evaporated, yielding 30 mg. of crystals analyzing by paper chromatography as a mixture of a major component (product V) and a minor component (starting material IV). An additional 30 mg. of material was eluted, which analyzed as mainly unaltered starting material. The first fraction was recrystallized from aqueous alcohol and from alcohol, yielding the 16-dehydro amide, m.p. 228–232° dec., λ_{max} 238 mμ (ε 22,900); λ_{max}^{KBr} 2.87, 2.97, 6.03, 6.22, 6.32, 6.51 μ, etc.

Anal. Calcd. for $C_{23}H_{28}O_4NF$: C, 68.80; H, 7.03. Found: C, 68.25; H, 7.32.

21-Acetylamino-9α-fluoro-11β,17α,20β-trihydroxy-1,4-pregnadien-3-one (VI).—A solution of 100 mg. of 21-acetylamino-9α-fluoro-11β,17α-dihydroxy-1,4-pregnadiene-3,20-dione in 5 ml. of methanol and 5 ml. of dimethylformamide was cooled to 0°, and 13 mg. of sodium borohydride was added. After 90 minutes (occasional shaking, 0°) 0.5 ml. of glacial acetic acid was added. The reaction mixture was analyzed by paper chromatogram and shown to contain one non-reducing product at R_f 0.16 (system II), reactive toward isonicotinic acid hydrazide. No unaltered amide II (R_f 0.65) was detected.

9α-Fluoro-11β-hydroxy-1,4-androstadiene-3,17-dione (VII). A. From 21-Acetylamino-9α-fluoro-11β,17α,20β-trihydroxy-1,4-pregnadien-3-one.—The reaction mixture from the previous experiment, containing VI as the only detectable steroid, was mixed with 50 ml. of a solution containing 4% by weight of trichloroacetic acid in 75% aqueous ethanol. To this was added 1.7 g. of sodium bismuthate and the mixture was agitated for 75 minutes at room temperature. The reaction mixture was adjusted to near neutrality by careful addition of strong sodium hydroxide solution. The solids which precipitated were filtered and washed with three portions of hot acetone, and the combined filtrates and washes were concentrated in vacuum until the organic solvent had evaporated. Two drops of concentrated hydrochloric acid was added to ensure an acid reaction and the solution was held at 4° overnight. Paper-gram examination of the solution indicated that no reaction had occurred and that the starting material VI was the major component in the preparation. The solution was extracted with methylene chloride, the extracts washed with saturated aqueous sodium bicarbonate solution, dried over magnesium sulfate, and evaporated in vacuum, and the residue again treated with sodium bismuthate in the same proportions as used before, except the reaction ran for 5 hours. Work-up of the reaction mixture in the same way as before yielded a residue which analyzed by paper chromatography as containing starting material VI and a more mobile component. The residue was chromatographed on Florisil; elution with methylene chloride–5% acetone gave 28 mg. of a material which, on recrystallization from acetone–petroleum ether, gave 16 mg. of 9α-fluoro-11β-hydroxy-1,4-androstadiene-3,17-dione, m.p. 244–246°, identified by comparison with the authentic sample prepared under B below.

B. From 9α-Fluoro-11β,17α,21-trihydroxy-1,4-pregnadiene-3,20-dione.—To a solution of 600 mg. of 9α-fluoro-11β,17α,21-trihydroxy-1,4-pregnadiene-3,20-dione in 350 ml. of a 4% solution of trichloroacetic acid in 75% aqueous ethanol was added 17 g. of sodium bismuthate. The resulting slurry was shaken for 90 minutes, at which time a sample withdrawn from the mixture failed to give a positive test with alkaline tetrazolium blue. The reaction mixture was adjusted to near neutrality with strong sodium hydroxide solution, the solids filtered, the filter cake extracted thoroughly with hot acetone, and the combined filtrates and acetone washes concentrated in vacuum to remove the organic solvent. The aqueous solution was acidified with 4 drops of concentrated hydrochloric acid and cooled at 4°. The product crystals were collected in two crops, 90 mg., m.p. 246–249.5°, and 135 mg., m.p. 244.5–249°. Extraction of the mother liquor with methylene chloride after making alkaline gave an additional 148 mg., m.p. 248–250°. Recrystallization from acetone–petroleum ether several times gave the pure 9α-fluoro-11β-hydroxy-1,4-androstadiene-3,17-dione, λ_{max} 236 mμ (ε 14,720); λ_{max}^{KBr} 2.88, 5.75, 6.01, 6.20, 9.73, 11.17 μ, etc.

Anal. Calcd. for $C_{19}H_{23}O_3F$: C, 71.68; H, 7.28; F, 5.97. Found: C, 71.41; H, 7.49; F, 6.10.

Both samples were identical with another sample, m.p. 247–251° (capillary), prepared by R. H. Lenhard of these laboratories by selenium dioxide dehydrogenation of 9α-fluoro-11β-hydroxy-4-androstene-3,17-dione. Identity of all three samples was established by comparisons of infrared spectra, melting point behavior, paper chromatographic mobility and color test behavior (positive Zimmermann test).[28]

The mobility of the 17-ketone VII was: system IV, R_f 0.86; system V, R_f 0.56; system VI, R_f 0.29.

(28) A. Nobile, U. S. Patent 2,955,118, October 14, 1960, describes 9α-fluoro-11β-hydroxy-1,4-androstadiene-3,17-dione, m.p. 252–253°, $[\alpha]_D$ +113.6° (dioxane).

[CONTRIBUTION FROM THE MERCK SHARP & DOHME RESEARCH LABORATORIES, DIVISION OF MERCK & CO., INC., RAHWAY N. J.]

A General Synthesis of 4,5-Unsaturated 2-Oxasteroids. A Synthesis of 2-Oxacortisol[1]

BY RALPH HIRSCHMANN, N. G. STEINBERG AND ROBERT WALKER

RECEIVED OCTOBER 2, 1961

The synthesis of 2-oxacortisol and its 9α-chloro-16α-methyl analog is described. Osmylation of 17α,20;20,21-bismethylenedioxy-1,4-pregnadiene-3,11-dione (prednisone BMD) followed by lead tetraacetate cleavage gave the required tricyclic steroid derivative III. Saponification led to the sodium salt of the aldehydic acid which was reduced with hydride under carefully controlled conditions to afford the BMD of 2-oxacortisol. In the 9α-fluoro series osmylation took place primarily at the 4,5-double bond.

The decade after the discovery of the therapeutic effects of cortisone in the treatment of rheumatoid arthritis has witnessed a great effort to prepare analogs which are superior to the hormone, cortisol. The syntheses of the very potent 16-epimeric 9α-fluoro-11β,17,21-trihydroxy-16-methyl-pregna-1,4-dien-3,20-diones[2] are examples of recent advances

(1) Presented in part at the 140th Meeting of the American Chemical Society, Chicago, Ill., September, 1961.

(2) G. E. Arth, J. Fried, D. B. R. Johnston, D. R. Hoff, L. H. Sarett, R. H. Silber, H. C. Stoerk and C. A. Winter, *J. Am. Chem. Soc.*, **80**, 3161 (1958); D. Taub, R. D. Hoffsommer, H. L. Slates and N. L.

in the field. On the other hand, compounds such as D-homocortisol,[3] 19-norcortisol,[4] A-norcortisol,[5] and homologs of cortisol methylated at C-4[6] C-7α, C-7β,[7] C-9α[8] and C-11α,[9] as well as the 2-[10] or 16β[11]-halo derivatives of cortisol, all of which have shown little or no activity, have served to emphasize the fact that the structural requirements for anti-inflammatory activity are very specific.

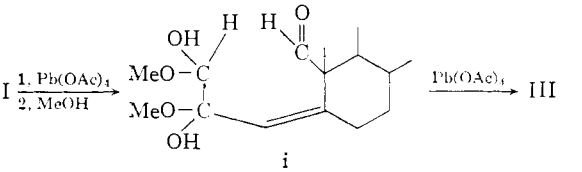
This paper describes the synthesis of 2-oxacortisol acetate (X) and of its 9α-chloro-16α-methyl analog XXVIIIa. We undertook the preparation of these compounds in the hope that this modification of the cyclopentanophenanthrene skeleton would be consistent with the requirements for anti-inflammatory activity. It was hoped, moreover, that the hetero atom would simulate the C_1–C_2 double bond in prednisolone and thus similarly retard the *in vivo* reduction of the A-ring unsaturated carbonyl system.[12]

We employed 1,2-dihydroxy-17α,20;20,21-bis-methylene-dioxy-4-pregnene-3,11-dione (1,2-dihydroxycortisone-BMD) (I), which we had described previously,[5] as the starting material. Treatment with sodium metaperiodate in aqueous alcohol eliminated carbon-2 and gave a neutral product which showed an absorption maximum at 224 mμ[13] in the ultraviolet (ϵ 14,500) and at 2.9–3.0, 5.79, 5.87, 6.1 to 6.2 μ in the infrared.[14] On the basis of these results and the analytical data, the oxidation product was formulated as the lactol II which contains the desired hetero-ring system. The assigned structure is consistent also with the n.m.r. spectrum which showed the olefinic proton (C-4) at 4.12 τ and a proton at 3.68 τ (C-1).[15]

The lactol was smoothly converted into the sodium salt (IV) of the tautomeric acid aldehyde on brief treatment with a slight excess of sodium methoxide in methanol at room temperature. The infrared spectrum of IV showed a maximum at 6.33 μ confirming the presence of a carboxylate anion and n.m.r. spectroscopy revealed an aldehydic proton at -0.052 τ.[13] The conversion of I into an aldehyde-acid IV rather than a keto-acid supports our previous conclusion[5] that the starting material I is hydroxylated at C-1, C-2 and not at C4, C-5 (V). Hydrolysis of II with aqueous formic acid gave 1β-hydroxy-2-oxacortisone (VII). The lactol II proved to be surprisingly[16] resistant toward oxidation at C-1 with pyridine–chromium trioxide or even chromic acid in acetic acid.

We investigated also the action of lead tetraacetate upon I. The starting material was nearly insoluble in methanol or benzene but dissolved readily in a mixture of these solvents. The lead tetraacetate oxidation product obtained under these anhydrous conditions was not identical with the periodate cleavage product but gave correct carbon, hydrogen and methoxyl analyses for either structure III or VI. The compound showed a maximum at 222 mμ (ϵ 9,450) and a single intense peak in the infrared at 5.84 μ. On mechanistic grounds[17] alone, structure III is to be preferred over the isomeric structure VI. Furthermore, the compound could be converted into a 1-thio ether XII on treatment with ethyl mercaptan in the presence of sodium methoxide as described below and this again favors structure III. Moreover, n.m.r. spectroscopy[15] fully corroborated these conclusions, since the lead tetraacetate cleavage product revealed an aldehydic proton at -0.05 τ but not a C-1 proton of the type shown in the spectrum of II or XII. Finally its marked negative rotation, contrasted with the positive rotation of II and XII and XI, is consistent with the assigned ester-aldehyde structure.

The ester aldehyde was easily converted into II either by saponification followed by acidification or under acidic conditions by heating with a 50% aqueous solution of acetic acid at 100° for thirty minutes. The latter procedure did not result in extensive loss of the bismethylenedioxy protecting group. While precipitation of II from a solution of its sodium salt with mineral acid might give rise to a kinetic product, this is not the case in the formation of the lactol either from the lead tetraacetate cleavage product with hot aqueous acid or from the treatment of I with periodate in ethyl



i

Wendler, *J. Am. Chem. Soc.*, **80**, 4435 (1958); **82**, 4012 (1960); E. P. Oliveto, R. Rausser, L. Weber, A. L. Nussbaum, W. Gebert, C. T. Coniglio, E. B. Hershberg, S. Tolksdorf, M. Eisler, P. L. Perlman and M. M. Pechet, *ibid.*, **80**, 4431 (1958).

(3) R. O. Clinton, H. C. Neumann, A. J. Mason, S. C. Laskowski and R. G. Christiansen, *ibid.*, **80**, 3395 (1958).

(4) A. Zaffaroni, H. J. Ringold, G. Rosenkranz, F. Sondheimer, G. H. Thomas and C. Djerassi, *ibid.*, **76**, 6210 (1954); B. J. Magerlein and J. A. Hogg, *ibid.*, **79**, 1508 (1957).

(5) R. Hirschmann, G. A. Bailey, R. Walker and J. M. Chemerda, *ibid.*, **81**, 2822 (1959).

(6) N. G. Steinberg, R. Hirschmann and J. M. Chemerda, *Chemistry & Industry*, 975 (1958).

(7) C. H. Robinson, O. Gnoj and E. P. Oliveto, *J. Org. Chem.*, **24**, 121 (1959); J. A. Zderic, H. Carpio and H. J. Ringold, *J. Am. Chem. Soc.*, **81**, 432 (1959); R. E. Beyler, A. E. Oberster, F. Hoffman and L. H. Sarett, *ibid.*, **82**, 170 (1960).

(8) F. Hoffman, R. E. Beyler and M. Tishler, *ibid.*, **80**, 5322 (1958).

(9) G. S. Fonken, J. A. Hogg and A. V. McIntosh, Jr., *J. Org. Chem.*, **24**, 1600 (1959); R. E. Beyler, F. Hoffman and L. H. Sarett, *J. Am. Chem. Soc.*, **82**, 178 (1960).

(10) A. H. Nathan, B. J. Magerlein and J. A. Hogg, *J. Org. Chem.*, **24**, 1517 (1959).

(11) D. E. Ayer and W. P. Schneider, *J. Am. Chem. Soc.*, **82**, 1250 (1960).

(12) C. A. Nugent, K. Eik-Nes and F. H. Tyler, *J. Clin. Endocrinol. and Metabolism*, **17**, 502 (1957).

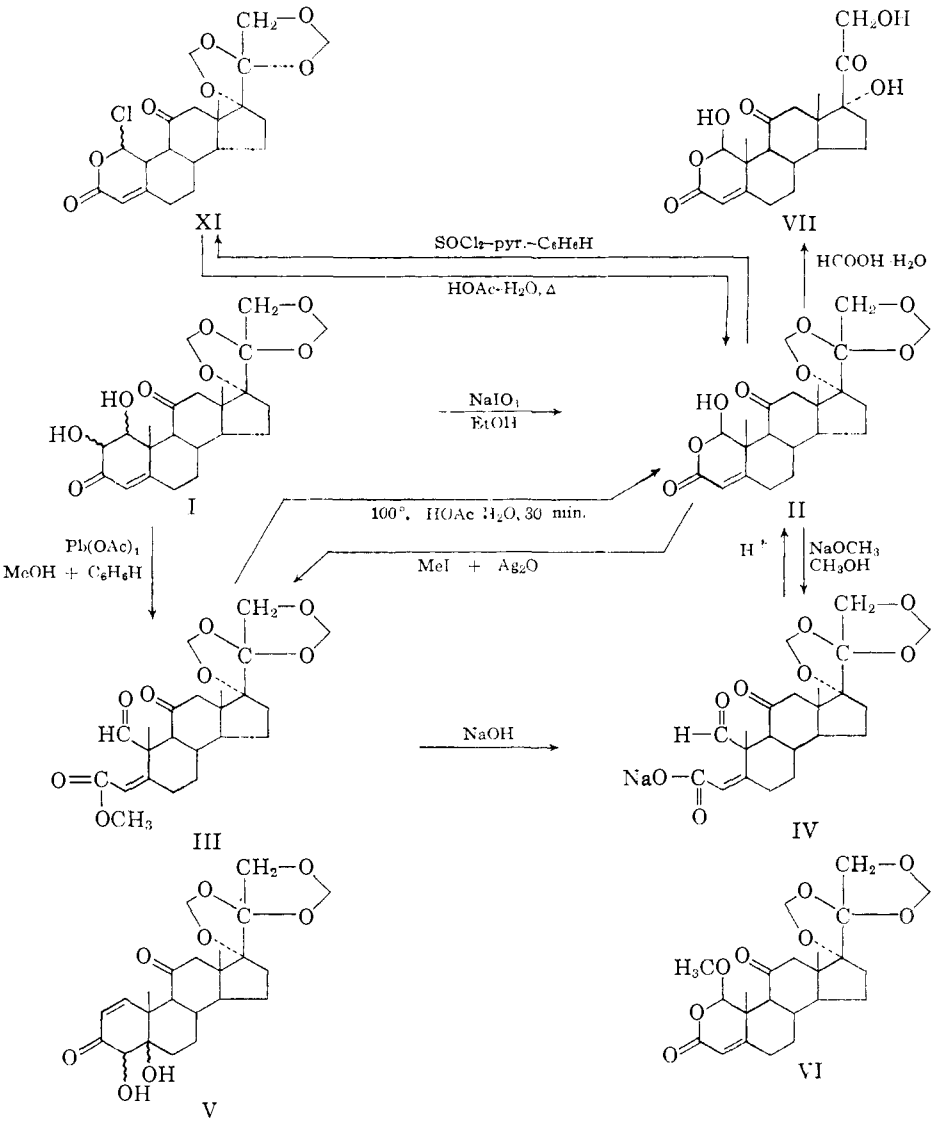
(13) α,β-Unsaturated lactones and acids are known to display the absorption maximum at shorter wave length than the corresponding ketones. See, *e.g.*, L. J. Haynes and E. R. H. Jones [*J. Chem. Soc.*, 954 (1946)]; T. L. Jacobs and N. Takahashi [*J. Am. Chem. Soc.*, **80**, 4865 (1956)].

(14) The infrared spectra of steroid lactones were reviewed recently by R. N. Jones and B. S. Gallagher [*ibid.*, **81**, 5242 (1959)].

(15) The nuclear magnetic spectrum was carried out with a 60 megacycle Varian model 4300-B spectrometer with benzene as an external reference. The proton resonances are given in frequency independent τ-units. For details see B. G. Christensen, R. G. Strachan, N. R. Trenner, B. H. Arison, R. Hirschmann and J. M. Chemerda [*ibid.*, **82**, 3995 (1960)]. The authors are greatly indebted to Dr. N. R. Trenner and Mr. B. Arison for the determination and interpretation of the spectra.

(16) Both of the 1-epimeric 1-hydroxycholestanes have been oxidized to the ketone by P. Striebel and Ch. Tamm [*Helv. Chim. Acta*, **37**, 1094 (1954)].

(17) E. Baer [*J. Am. Chem. Soc.*, **62**, 1597 (1940)] discussed the oxidation cleavage of α-keto acids and α-keto alcohols by means of lead tetraacetate. In the case at hand (i) is a plausible intermediate.

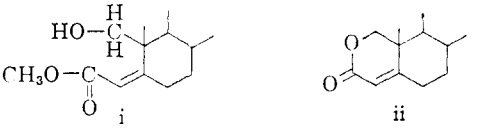


alcohol. Accordingly, the hydroxyl group at C-1 in compounds II and VII is believed to be in the more stable β-configuration.

The lactol and the ester-aldehyde could be interrelated also by alkylating II with methyl iodide in the presence of silver oxide.

The conversion of III into the bismethylenedioxy derivative of 2-oxacortisol (IX) required only selective reduction of the aldehyde and 11-keto groups with retention of an unsaturated ester function. We sought to effect this transformation with sodium borohydride in aqueous tetrahydrofuran. The non-crystalline reaction product showed, however, only low extinction in the ultraviolet and only weak carbonyl absorption in the infrared. This reduction product could not be converted into IX on treatment with manganese dioxide. The crude reduction product[18] was therefore not investigated in detail. Other unsuccessful attempts to utilize the ester aldehyde III directly in the synthesis of 2-oxacortisol such as Meerwein–Ponndorf reduction or reduction with one-half mole of $LiAlH_4$ did not give promising results. When III was reduced over platinum oxide in ethanol in the presence of iron(II) chloride and zinc acetate—conditions which favor the conversion of citral to geraniol and of cinnamic aldehyde to cinnamyl alcohol[19]—only

(18) It is possible that reduction with sodium borohydride effected reduction of the aldehyde and C-11 carbonyl groups to give i and that the latter was transformed into a lactone (ii) by internal ester exchange. It is known that lactonic carbonyl functions can be reduced by sodium borohydride: (a) N. G. Gaylord, "Reduction with Complex Metal Hydrides," Interscience Publishers, Inc., New York, N. Y., 1956, p. 531. In a very recent paper N. W. Atwater [*J. Am. Chem. Soc.*, **83**, 3071 (1961)] described the reduction of saturated B-ring lactones with this reducing agent. (b) Moreover, the reduction of a double bond conjugated with a carbonyl group by sodium borohydride has been observed before. See, *e.g.*, C. Djerassi, P. Sengupta, J. Herran and F. Walls [*ibid.*, **76**, 2966 (1954)] or F. Sondheimer, M. Velasco, E. Batres and G. Rosenkranz [*Chemistry & Industry*, 1482 (1954)]. An interesting recent example was provided by T. L. Jacobs and R. B. Brownfield [*J. Am. Chem. Soc.*, **82**, 4033 (1960)]. See also Ch. Tamm [*Helv. Chim. Acta*, **43**, 338 (1960)].

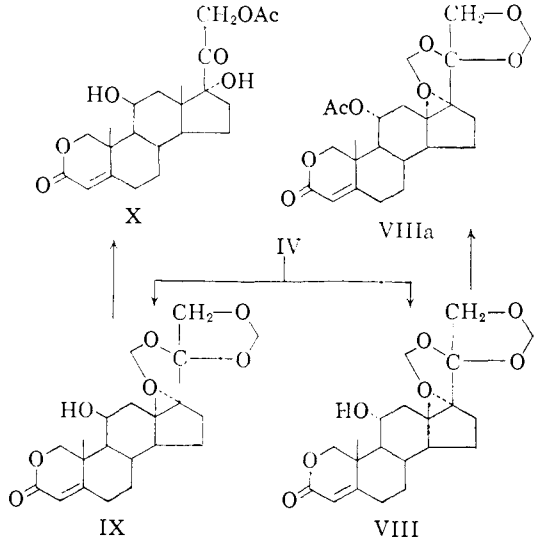


i ii

(19) W. F. Tuley and R. Adams, *J. Am. Chem. Soc.*, **47**, 3061 (1925); R. Adams and B. S. Garvey, *ibid.*, **48**, 477 (1926).

the olefinic double bond was reduced. The resulting saturated ester aldehyde XVI showed an aldehydic proton resonance[15] at 0.41 τ and, like its precursor, methoxy proton resonances at 6.25 τ, but—as expected—the C-4 olefin proton absorption at 4.23 τ was absent.

Under carefully controlled conditions it was, however, possible to utilize the sodium salt (IV) of the aldehydic acid for the preparation of 2-oxacortisol. Treatment of an aqueous solution of IV at a *p*H of about 9 with sodium borohydride at room temperature overnight resulted in the separation of a precipitate which afforded a mixture of the bismethylenedioxy derivatives of 2-oxacortisol (IX) and of its C-11 epimer VIII. The configurational assignment at C-11, based on the relative mobilities on paper chromatography,[5] was confirmed by the observation that VIII, but not IX, could be converted into the C-11 acetate VIIIa under mild conditions.



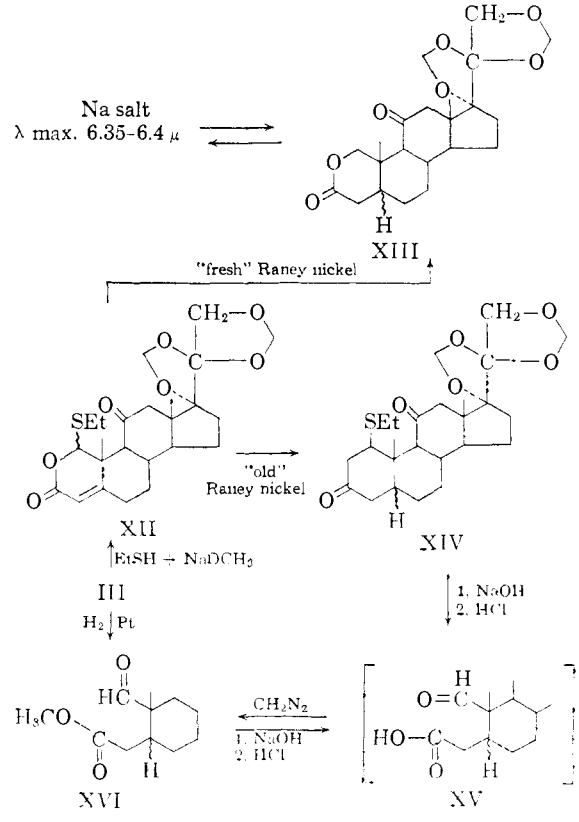
Solution spectra in chloroform of both VIII and IX showed carbonyl absorption at 5.81 μ (strong) and at longer wave lengths (shoulder at 5.88 in IX and λ_{max} at 5.91 μ for VIII). The extinction in the ultraviolet at 223 mμ (ϵ 13,700) and at 225 mμ (13,500) for VIII and IX, respectively, showed that the *major peak* (5.81 μ) cannot be attributed to gross contamination of VIII and IX with the corresponding saturated lactones. It must be concluded, therefore, that the carbonyl absorptions at 5.81 and at 5.88–5.91 μ originate with a single carbonyl group. The presence of two absorption maxima in the carbonyl region assignable to a single carbonyl stretching vibration has been observed before[5,20,14] and has been ascribed to Fermi resonance between the undisturbed carbonyl vibration and an overtone of the out-of-plane bending vibration of an olefinic hydrogen.[14,20] The lactones IX and VIII showed absorption maxima at approximately half of the frequency of the carbonyl band at 11.72 and 11.67 μ, respectively, but we are not certain that these maxima are associated with the out-of-plane bending of the C-4 hydrogen.

(20) P. Yates and L. L. Williams, *J. Am. Chem. Soc.*, **80**, 5896 (1958).

Treatment of the bismethylenedioxy derivative of 2-oxacortisol with dilute formic acid gave 2-oxacortisol which was characterized as the 21-acetate X (λ_{max} 223 mμ, ϵ 14,700).

While the above synthesis of IX was in progress, we explored alternate methods to remove the hydroxyl substituent at C-1. When the lactol II was allowed to react with thionyl chloride in benzene in the presence of pyridine we obtained the 1-chlorosteroid (XI), which showed an absorption maximum at 228 mμ (ϵ 13,500). We were unable to remove the halogen substituent reductively under a variety of conditions including the use of deactivated Raney nickel, chromous chloride at room temperature, zinc and aqueous ethanol or sodium iodide in refluxing acetone, or chromous acetate in aqueous acetic acid at room temperature. At elevated temperatures the last named reagent effected hydrolysis of the halosteroid to give II.

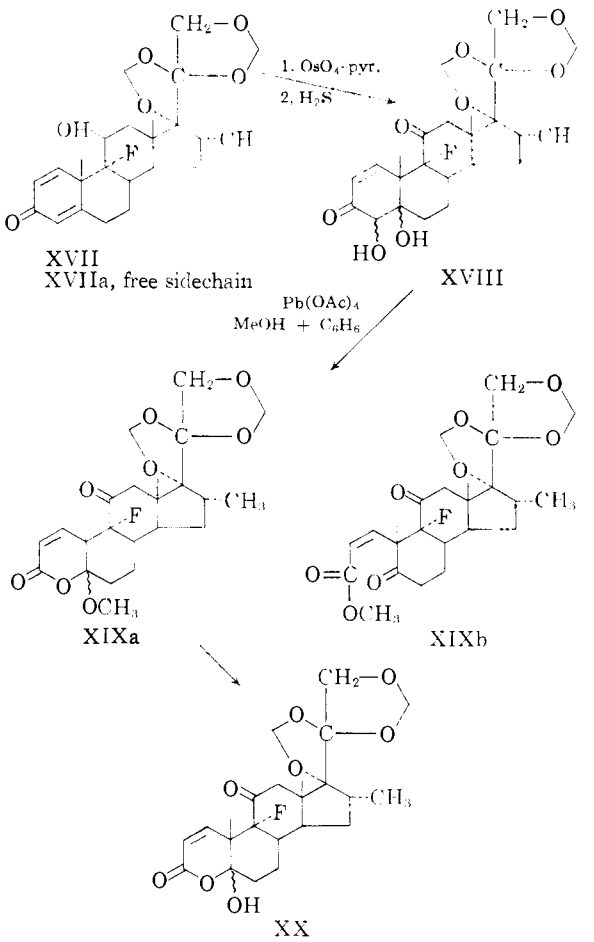
As mentioned above, the ester aldehyde III, when allowed to react with ethyl mercaptan in the presence of sodium methoxide, afforded a sulfur-containing product which gave analytical values and showed ultraviolet and infrared maxima consistent with structure XII; n.m.r. spectroscopy showed a proton (C-1) at 3.64 τ, an olefinic proton (C-4) at 4.15 τ as well as the thioether function (7.17 τ (quartet) and 8.65 τ (triplet)).[15] Compound XII appeared to be an excellent intermediate for the preparation of 2-oxacortisol. Treatment of XII with Raney nickel did indeed effect reduction at C-1, but not without concomitant reduction of the 4,5-double bond. The resulting lactone XIII could be saponified to give a water-soluble salt which regenerated XIII upon acidification. That



reduction of the double bond occurred more readily than cleavage of the carbon–sulfur bond was suggested by the fact that Raney nickel, which had aged for several months, converted XII into a sulfur-containing lactone which was devoid of selective absorption in the ultraviolet and which is formulated as XIV. The infrared spectrum of XIV resembled that of the 4,5-dehydro-analog XII in many respects, notably in the presence of strong absorption maxima at 7.35, 8.5 and at 9.95 μ. Saponification of XIV followed by acidification unexpectedly gave an acidic product (XV) rather than a lactone. The acid was converted into the methyl ester XVI with diazomethane. The ester was shown to contain an aldehydic hydrogen by n.m.r. This compound proved to be identical with the hydrogenation product XVI derived from the ester aldehyde III referred to above. The catalytic hydrogenation product, upon saponification and acidification, also afforded an acid (XV).

Having completed the synthesis of 2-oxacortisol acetate (X), we attempted to prepare an analog containing activity-enhancing groups at C-9 (halogen) and at C-16 (α-methyl). The bismethylenedioxy derivative of dexamethasone (XVII), first prepared by Dr. R. E. Beyler and Miss F. Hoffman of these laboratories, was allowed to react with osmium tetroxide in pyridine solution, and the resulting osmate ester was decomposed with hydrogen sulfide in dioxane. Crystallization of the crude reaction mixture afforded a product, λ_{max} 226 mμ, indicative of the 4,5-dihydroxy-Δ^1-structure XVIII. In addition we found that the 11β-hydroxy group had undergone oxidation to the ketone.[21] The other reaction product was 16α-methyl-9α-fluoroprednisone BMD. Compound XVIII was readily cleaved by lead tetraacetate to give XIX.[22] The latter failed to exhibit a selective absorption in the ultraviolet but displayed strong end absorption (ϵ 6,000 at 220 mμ); n.m.r. confirmed the presence of the two olefinic protons and of the methoxy group. Similar ultraviolet spectral characteristics were exhibited by the lactol XX which was obtained by treatment of XIX with sodium hydroxide in refluxing aqueous methanol for several hours, followed by acidification.

Since the hydroxylation of the fluorohydrin XVII had not taken the desired course, we studied also the hydroxylation of the corresponding 9,11-epoxide XXIII,[23] obtained from XXI in two steps according to the general method of Hoffman, Beyler and Tishler.[8] The hydroxylation afforded both the 1,2- (XXIV) and the 4,5-dihydroxy compound XXV. The former showed an absorption maximum at 242.5 mμ (ϵ 12,500), whereas the latter, the more mobile isomer, as expected absorbed at lower wave length (228 mμ) and had a lower molecular extinction (9,400). Furthermore, compound XXIV showed a stronger carbon–carbon double



bond peak than XXV in the infrared which is also in accord with the assigned structures. Compound XXIV, on treatment with sodium metaperiodate, gave the lactol XXVI.

Conversion of XXVI into the sodium salt of the corresponding aldehydic acid and subsequent reduction with sodium borohydride gave the epoxylactone XXVII. In order to minimize reduction of the α,β-unsaturated system, sodium chloride was added to the reaction mixture to cause the desired reduction product to separate from the reaction mixture as the reaction progressed. It is noteworthy that the 9,11-epoxide was not reductively converted into an 11β-hydroxy group, whereas a 14β,15β-epoxide[24] apparently did not survive treatment with sodium borohydride.

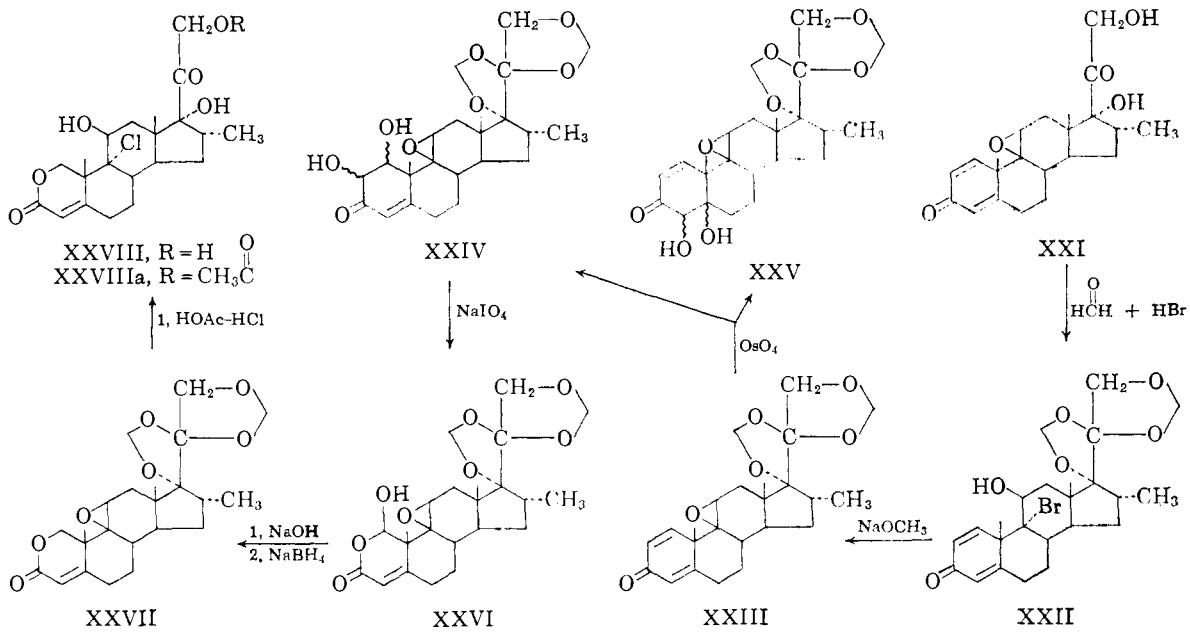
Beyler, Hoffman and Sarett[9] have recently described the preparation of 9β,11β-epoxy-17,21-dihydroxy - 11α - methylpregn - 4 - en - 3,20-dione from the corresponding 3-ketal-BMD with acetic acid in the presence of hydrochloric acid. Under these conditions our epoxy-BMD (XXVII) gave, however, the chlorohydrin XXVIII which was converted into the 21-acetate XXVIIIa. In order to leave as much as possible of this material for animal assay, the acetate was characterized

(21) A similar observation has been made in the osmylation of prednisolone-BMD to 1,2-dihydroxyprednisone-BMD (R. Hirschmann and G. Bailey, unpublished observation).

(22) On mechanistic grounds[17] we prefer structure XIXb, but the infrared spectrum did not provide clearcut evidence for the presence of *two* saturated carbonyl peaks.

(23) This compound was first prepared from 16α-methylprednisolone acetate as an intermediate in a synthesis of dexamethasone (R. Hirschmann, unpublished observation).

(24) See ref. 18a, p. 673. It is known however, that 9α,11α-epoxides are resistant to cleavage by borohydride [C. Djerassi, E. Batres, M. Velasco and G. Rosenkranz, *J. Am. Chem. Soc.*, **74**, 1712 (1952)]. D. J. Collins [*J. Chem. Soc.*, 3919 (1959)] found a 4α,5α-epoxide to be stable to this reagent.



only by a chlorine analysis. The structure was, however, fully confirmed by spectral data, paper-strip mobility and a quantitative tetrazolium assay.

Compound X was about one-fourth as effective as cortisol in reducing the eosinophile count, in the liver glycogen deposition assay and in the local and systemic granuloma inhibition tests. Compound XXVIIIa was approximately equi-potent to cortisol in the systemic granuloma inhibition test and in the liver glycogen deposition assay. It is clear, therefore, that while the replacement of the methylene group by oxygen resulted in diminished potency, the new ring system was compatible with anti-inflammatory activity.

Acknowledgment.—The authors are greatly indebted to Dr. L. H. Sarett for his interest and for many helpful discussions. The authors wish to thank Messrs. N. R. Trenner and B. Arison for the determination and interpretation of the n.m.r. spectra, Mr. N. Allen for certain of the infrared spectra, Dr. D. Williams for rotation data, Mr. R. N. Boos and his associates for the elemental analyses and Mr. A. Kalowsky for ultraviolet absorption spectra. We are greatly indebted to Drs. S. Steelman and H. Stoerk for the animal assays.

Experimental[25]

Cleavage of 17α,20;20,21-Bismethylenedioxy-1,2-dihydroxy-4-pregnene-3,11-dione (I) with Lead Tetraacetate.—A solution of 4.00 g. of 1,2-dihydroxycortisone BMD (I) in 262 ml. of benzene and 523 ml. of methanol was treated with 11.6 g. of lead tetraacetate for 18 hours at room temperature. After the addition of the oxidizing agent, the mixture acquired a red color which disappeared on standing. An equal volume of benzene was added and the mixture was washed several times with water. Removal of the solvent followed by crystallization from methanol afforded 2.48 g. of the ester-aldehyde III, m.p. 227–228°, R_f (benzene) 0.9. An analytical sample, m.p. 231–236°, λ_{max} 222 mμ (ε 9,450), $[\alpha]_D$ −51° ($CHCl_3$), was obtained by recrystallization from methanol. N.m.r.[16] revealed an aldehydic proton at −0.05τ, and olefinic proton at 4.23τ and the methyl resonance at 6.25τ.

Anal. Calcd. for $C_{23}H_{30}O_8$: C, 63.58; H, 6.96; OCH_3, 7.2. Found: C, 63.22; H, 6.77; OCH_3, 7.07.

Cleavage of I with Sodium Metaperiodate.—A solution of 434 mg. of I in 100 ml. of ethanol was treated with 1.72 g. of sodium metaperiodate dissolved in 10 ml. of water and was allowed to stand at room temperature for about 60 hours. After removal of the solvents the residue was distributed between ether and water. The organic layer was washed with an aqueous solution of sodium thiosulfate and again with water, and dried over magnesium sulfate. The crude product, amounting to 300 mg., was dissolved in 60 ml. of a mixture of benzene and ether (5:1), adsorbed on 15 g. of acid-washed alumina and eluted successively with benzene–ether (5:1, 1:1), with ether and then with ether–acetone (9:1). The last-named system afforded, after crystallization from methanol, 77 mg. of II, m.p. 230–233°. An analytical sample, obtained by recrystallization from methanol, melted at 232–234°, λ_{max} 224 mμ (ε 14,500), $[\alpha]_D$ +73.5° ($CHCl_3$); $\lambda_{max}^{CHCl_3}$ 2.9–3.0, 5.79, 5.87, 6.1–6.2 (weak), 9–9.2 μ. This material was far less mobile by paper chromatography than the ester aldehyde III, showing an R_f (benzene) 0.17.

Anal. Calcd. for $C_{22}H_{28}O_8$: C, 62.84; H, 6.71. Found: C, 62.95; H, 6.59.

Interconversions of the Periodate and Lead Tetraacetate Cleavage Products and of the Sodium Salt (IV). (a) Acid Hydrolysis of III.—A 1.71-g. sample of III (m.p. 228–231°) was suspended in 32.4 ml. of 50% (v./v.) acetic acid and heated on a steam-bath for 1.5 hours. The resulting solution was cooled and poured into 300 ml. of water. The mixture was chilled in an ice-bath and the product (1.435 g.) was isolated by filtration. The material, m.p. 227–229°, was identical with the product from the periodate oxidation described above.

(b) **Saponification of III.**—A 125-mg. sample of III was dissolved in 10 ml. of methanol with heating. Addition of 4 ml. of 0.11 *N* sodium hydroxide gave a precipitate which redissolved on heating. The homogeneous mixture was kept at room temperature overnight. After removal of the bulk of the methanol *in vacuo* at room temperature the aqueous solution of the sodio salt IV was made acid with cold 2.5 *N* hydrochloric acid. The resulting lactol, m.p. 219–221°, λ_{max} 223 mμ (ε 13,000), was removed by filtration. The product was single spot material by paper chromatography. One single recrystallization from methanol gave 80 mg., m.p. 226–229°. The infrared and ultraviolet spectra were identical with that of material prepared by periodate cleavage of I.

(c) **Conversion of II → III.**—A mixture of 100 mg. of the 1-hydroxy-2-oxasteroid II, m.p. 224–226°, and 500 mg. of

(25) All melting points are uncorrected. All R_f-values were determined by descending paper chromatography, on Whatman paper No. 4, using methanol–formamide (2:1) as the stationary phase and the indicated solvents as the mobile phase.

silver oxide was refluxed in methyl iodide with constant stirring for 6 hours. The mixture was filtered and the filtrate was taken to dryness. The crude material was found to be single spot material by paper chromatography (benzene). The mobility of the crude product was the same as that of the ester aldehyde III. Crystallization from methanol gave 65.5 mg., m.p. 228–230°, λ_{max}^{MeOH} 220 mμ (ε 9,300). The infrared spectrum of the crystalline product was the same as that of the ester aldehyde III.

(d) **Treatment of II with Alkoxide.**—A solution of 41 mg. of II in methanol was treated with a stoichiometric amount of sodium methoxide in methanol. The solvent was removed *in vacuo* and the residue was triturated with anhydrous ether. The crystalline product showed an absorption maximum at 6.33 μ in the infrared (COO^-). Nuclear magnetic resonance revealed on aldehydic hydrogen at 0.33τ in D_2O.[15] Treatment of IV with aqueous acid gave II.

1ξ-Chloro-2-oxacortisone BMD (XI).—A suspension of 0.700 g. of II in 4.18 ml. of dry pyridine and 97.2 ml. of dry benzene was chilled in an ice-bath and treated with 16.15 ml. of purified thionyl chloride. After standing at room temperature for about 30 minutes, the solution was taken to dryness, ice-water was added and the product was removed by filtration. The crude product was dissolved in a mixture of formamide and methanol and extracted six times with benzene. The combined extracts were back-extracted successively with formamide, water and with a saturated solution of sodium chloride. Removal of the solvent gave substantially pure XI (557 mg.), m.p. *ca.* 225–228°. Admixture of either II or III depressed the melting point of this material. An analytical sample, m.p. 225–227°, $[\alpha]_D^{CHCl_3}$ +104°, λ_{max} 228 mμ (ε 13,500), was prepared by recrystallization from acetone–water, using Nuchar C-190-N to remove traces of colored impurities.

Anal. Calcd. for $C_{22}H_{27}O_7Cl$: C, 60.20; H, 6.20. Found: C, 60.57; H, 6.19.

Acid Hydrolysis of XI.—A mixture of 38.0 mg. of the above chloro compound, 0.78 ml. of acetic acid and 0.39 ml. of water was heated on a steam-bath under nitrogen with 67.5 mg. of chromous acetate with constant stirring. The mixture was cooled, diluted with water, and extracted with chloroform. The product was identical with II, obtained by periodate cleavage of I.

1β-Hydroxy-2-oxacortisone (VII).—A 500-mg. sample of II, m.p. 227–229°, was suspended in 50 ml. of 60% aqueous formic acid and heated on a steam-bath for 1 hour. The mixture was cooled and extracted three times with ethyl acetate. The extracts were washed with a solution of sodium carbonate and with a saturated solution of sodium chloride. Removal of the solvent from the dried solution gave an amorphous solid (290 mg.) which was crystallized from methanol to afford VII, m.p. 225–227° (micro-hot-stage). Paper chromatography showed the crude and the crystalline product to be essentially pure VII contaminated by a small amount of a more mobile impurity, presumably a 21-formate. An analytical sample of VII was obtained by descending paper chromatography on Whatman paper No. 4, using formamide–methanol (1:2) as the stationary phase and chloroform as the mobile phase. The product was eluted from the dried sheets with methanol. After distillation of the solvent, the residue was taken up in ethyl acetate and washed repeatedly with water. Crystallization of the residue from acetone–Skellysolve B with the aid of Nuchar C-1000-N gave the triol, m.p. 242–244°, λ_{max} 223 mμ (ε 14,500).

Anal. Calcd. for $C_{20}H_{26}O_7$: C, 63.48; H, 6.93. Found: C, 63.81; H, 7.01.

Saponification and Hydride Reduction of III.—A suspension of 268 mg. of III in 6.75 ml. of 0.0922 *N* sodium hydroxide was heated on a steam-bath under nitrogen for 30 minutes with occasional shaking. The resulting solution of the sodium salt IV was cooled, diluted with 5 ml. of water and treated with 290 mg. of sodium borohydride at room temperature overnight. A precipitate separated in the course of the reduction. The mixture was cooled and acidified with hydrochloric acid. The product was removed by filtration and washed free of acid to give 200 mg. of a mixture of the C-11 epimeric diols VIII and IX. The mixture was separated by descending paper chromatography using 20 sheets of Whatman paper No. 4 with formamide–methanol (1:2) as the stationary phase and benzene–Skellysolve B (1:1) as the mobile phase. The products were isolated essentially as described for VII. The more mobile zone was eluted with methanol and the extracts were taken to dryness. Water was added, the product was removed by filtration and washed with water to give 68.0 mg. of **2-oxacortisol BMD (IX).** A 58-mg. aliquot was crystallized from acetone–Skellysolve B to afford 38 mg., m.p. 251–255°. One further recrystallization gave 30.2 mg., m.p. 253–255°, λ_{max}^{MeOH} 225 mμ (ε 13,500). The melting point was not improved on one further recrystallization from the same solvent pair.

Anal. Calcd. for $C_{22}H_{30}O_7$: C, 65.01; H, 7.44. Found: C, 65.00; H, 7.20.

Isolation of the less mobile equatorial isomer VIII (**2-oxa-11-epicortisol BMD**), essentially as described above, gave 38.4 mg. The product was combined with an additional 120 mg. of crude VIII obtained in the same manner. Crystallization from methanol gave 102 mg. of product, m.p. 269–279.8°, λ_{max}^{MeOH} 223 mμ (ε 13,500). Two further recrystallizations from methanol gave an analytical specimen, m.p. 282–285°, λ_{max}^{MeOH} 223 mμ (ε 13,700).

Anal. Calcd. for $C_{22}H_{30}O_7$: C, 65.01; H, 7.44. Found: C, 64.75; H, 7.64.

Acetylation of the Equatorial Isomer VIII.—A 15.4 mg. sample of VIII, m.p. 282–285°, was treated with 0.3 ml. each of pyridine and acetic anhydride at room temperature overnight. The reagents were removed *in vacuo* and 1 ml. of water was added. The crude product was removed by filtration and crystallized twice from acetone–Skellysolve B using decolorizing charcoal in the final recrystallization. The 11α-acetate VIIIa (9.2 mg.) melted at 220–222.8°. The compound showed carbonyl absorption at 5.81 and 5.88 μ (lactone and 11-acetate) and at 8.04 μ (acetate) ($CHCl_3$).

Anal. Calcd. for $C_{24}H_{32}O_8$: C, 64.27; H, 7.19. Found: C, 64.58; H, 7.44.

Under the same conditions, compound IX was recovered unchanged.

2-Oxacortisol 21-Acetate (X).—A 54.5-mg. sample of the 11β-hydroxy compound IX was heated in 60% aqueous formic acid on a steam-bath for about 6 minutes. The mixture was cooled and the solvents were removed *in vacuo*. Addition of water gave a solid which was crystallized from water to afford 28.8 mg. of 2-oxacortisol, m.p. 212–215°. The compound was characterized as its 21-monoacetate which was prepared by dissolving 18 mg. of the triol in 0.3 ml. of pyridine and 0.3 ml. of acetic anhydride. The mixture was kept at room temperature overnight, solvents were removed *in vacuo*, the residue was treated with water and the product was removed by filtration. Crystallization from acetone–Skellysolve B gave well defined needles (17. 6 mg.), m.p. 194–196°. One further recrystallization from the same solvent pair gave a m.p. of 189–190°, λ_{max}^{MeOH} 223 mμ (ε 14,700).

Anal. Calcd. for $C_{22}H_{30}O_7$: C, 65.01; H, 7.44. Found: C, 64.90; H, 7.29.

1ξ-Thioethyl-2-oxacortisone BMD (XII).—The ester-aldehyde III (600 mg.) was added to a solution of 13.3 ml. of 0.1 *N* methanolic sodium methoxide in 50 ml. of ethyl mercaptan and the mixture was stirred at room temperature overnight. The *p*H of the solution was then adjusted to about 6 with acetic acid and the solvents were removed *in vacuo*. Residual mercaptan was largely removed by the repeated addition of petroleum ether and removal of the solvent. The crude product was distributed between chloroform and water, the organic layer was dried and taken to dryness. Crystallization of the residual oil from acetone–Skellysolve B gave 500 mg. of prisms, m.p. 262–265.3°. The thioether was shown to be an acetone solvate but one single recrystallization from methanol–water gave the desired compound, m.p. 261.5–265°, $[\alpha]_D$ +121° ($CHCl_3$); $\lambda_{max}^{CHCl_3}$ 5.80, 5.88, 6.10, 9.05–9.20, 7.37, 8.5 and 9.92 μ. N.m.r.[15] revealed the C-1 proton at 3.64τ and the olefinic C-4 proton at 4.15τ. The peaks at 7.17τ (quartet) and at 8.65τ (triplet) indicated the thioether function.

Anal. Calcd. for $C_{24}H_{32}O_7S$: C, 62.05; H, 6.94; S, 6.90. Found: C, 62.45; H, 7.23; S, 6.82.

4,5ξ-Dihydro-2-oxacortisone BMD (XIII).—An ethanolic solution of 435 mg. of the thioether XII, m.p. 259–262°, was stirred at room temperature with 3 teaspoons of freshly

prepared Raney nickel for 1.5 hours. The mixture was filtered and the residue was extracted repeatedly with hot ethyl acetate. The combined filtrate and washes afforded only 164 mg. of crude product. Crystallization from acetone–Skellysolve B gave prisms, m.p. 273–275°, which showed a $\lambda_{max}^{CHCl_3}$ at 5.76 μ and a pronounced shoulder at 5.83 μ, and in Nujol λ_{max} 5.76, 5.90 μ. An analytical specimen, m.p. 276–279.8°, $[\alpha]_D$ −68° ($CHCl_3$), was prepared by repeated recrystallization from the same solvent pair.

Anal. Calcd. for $C_{22}H_{36}O_7$: C, 65.01; H, 7.44. Found: C, 64.76; H, 7.67.

Saponification of XIII.—A 10-mg. aliquot of the saturated lactone XIII was suspended in 0.16 ml. of 0.1 *N* aqueous sodium hydroxide and diluted with 3 ml. of water. The mixture was heated on a steam-bath for about 30 minutes. The resulting solution was freeze-dried. The product showed a strong absorption maximum at 6.35–6.4 μ indicative of the carboxylate anion. Acidification of an aqueous solution of the salt regenerated XIII.

Saturated Esteraldehyde (XVI). (a) By Catalytic Hydrogenation of III.—A solution of 436 mg. of the esteraldehyde III, m.p. 230.8–233°, in 32 ml. of ethanol and 40 ml. of benzene was reduced over 300 mg. of platinum oxide at room temperature and atmospheric pressure until the hydrogen uptake was complete. The product (490 mg.) was crystallized from acetone–Skellysolve B to afford 259 mg. of the saturated esteraldehyde, m.p. 165–169°. An analytical specimen,[26] m.p. 172–175°, was obtained by recrystallization from the ether–petroleum ether.

Anal. Calcd. for $C_{23}H_{32}O_8$: C, 62.28; H, 7.39. Found: C, 62.55; H, 7.49.

The infrared spectrum was free of hydroxyl absorption but showed a maximum at 5.78 μ and a shoulder at 5.85 μ. The material was devoid of selective absorption in the ultraviolet and showed no olefinic protons by n.m.r.[15] An aldehydic proton was indicated at 0.41τ and methoxy protons at 6.25τ. Saponification of the catalytic reduction product afforded after acidification only a bicarbonate soluble product which melted unsharp between 201–215° (micro-hot-stage). The infrared spectrum of this product was identical with the acid derived from XIV.

(b) *Via* the Saturated Thioether XIV.—A sample of Raney nickel, which had been prepared several months earlier, was washed repeatedly with water until the washings were neutral and then with ethyl acetate. The resulting reducing agent was suspended in refluxing ethyl acetate for 2 hours. One-half teaspoon of the catalyst was then added to a solution of 50 mg. of the thioether XII in ethanol and the mixture was stirred at room temperature for 10 minutes. The catalyst was removed by filtration and the filtrate was taken to dryness. The crude product (39 mg.) was devoid of selective absorption in the ultraviolet, but showed strong absorption maxima in chloroform at 7.35, 8.5 and 9.95 μ, reminiscent of compound XII. Crystallization from methanol–water afforded XIV, m.p. 200–207°,[26] $[\alpha]_D$ −61° ($CHCl_3$).

Anal. Calcd. for $C_{24}H_{34}O_7S$: S, 6.9. Found: S, 6.71.

A 20-mg. aliquot of the saturated thioether XIV prepared as described above was heated with 4 ml. of 0.1 *N* sodium hydroxide on a steam-bath for 10 minutes, but this procedure failed to effect solution of the ester. Addition of 2–3 drops of 2.5 *N* sodium hydroxide also did not bring the steroid into solution. The insolubles were therefore removed by filtration and dissolved in 3 ml. of methanol. After the addition of about 6 drops of 1.25 *N* aqueous sodium hydroxide the mixture was briefly heated on a steam-bath. Removal of the methanol *in vacuo* followed by the addition of water gave a solution of the sodium salt of the acid XV. Acidification with an excess of hydrochloric acid afforded an acid which showed strong hydrogen bonding at 3–4 μ. Treatment of the acid with diazomethane afforded the same methyl ester[26] obtained by the hydrogenation of III.

Osmylation of Dexamethasone BMD.—A solution of 14.95 g. of XVII in 290 ml. of pyridine was cooled to 5° and treated with a solution of 9.6 g. of osmium tetroxide in 96 ml. of pyridine for 4 days. The crude osmate ester was isolated and decomposed as previously described[5] in the prednisone series to afford, after crystallization from acetone, 3.75 g. of XVIII, m.p. *ca.* 292–296°, λ_{max} 227.5 mμ (log ϵ 9,300). The compound gave a positive tetrazolium test[5] and a negative ferric chloride test.[5] The molecular extinction of the former was only about 12% of that given by 1,2-dihydroxycortisone BMD. Further recrystallization from pyridine–water and from methylene chloride–ether did not substantially change the m.p. (297–300°) nor the ultraviolet spectrum. This material failed to give an acceptable C and H analysis (Calcd. for $C_{24}H_{29}FO_8$: F, 4.07. Found: F, 4.03), but even the crude crystalline product was satisfactory for use in the subsequent step. The solid state infrared spectrum of the osmylation product showed hydroxyl absorption (2.85–3.0 μ), an unsaturated carbonyl system (5.94 and 6.15 μ) and a saturated carbonyl peak at 5.82 μ. The mother liquors contained 16α-methyl-9α-fluoroprednisone BMD.

Lead Tetraacetate Oxidation of XVIII.—A solution of 300 mg. of the crude, crystalline diol XVIII in about 100 ml. of benzene–methanol (4:1) was treated with 1.2 g. of lead tetraacetate and the crude product (280 mg.) was isolated essentially as described for the preparation of III. The product showed no absorption maximum between 215 and 280 mμ, but the molecular extinction at 215 mμ was about 6,700. One crystallization from acetone–Skellysolve B gave prisms (155 mg.), m.p. 270–277° dec. An analytical specimen, obtained by recrystallization from acetone–methaeol, melted at 281–284° dec.

Anal. Calcd. for $C_{24}H_{31}O_8F$: C, 61.79; H, 6.70; F, 4.07. Found: C, 62.16; H, 6.95; F, 4.12.

A sample, m.p. 275–283°, obtained by recrystallization from acetone–Skellysolve B confirmed the presence of a methoxy group. (Calcd.: OCH_3, 6.6. Found: OCH_3, 6.65). N.m.r. spectroscopy revealed no aldehydic protons but two olefinic protons (doublets) at 3.59, 3.81τ and at 3.86, 4.08τ[15] and the methoxy proton resonance at 6.29τ. The infrared spectrum showed $\lambda_{max}^{CHCl_3}$ 5.79, 6.06 μ; λ_{max}^{Nujol} 5.82, 6.06 μ; shoulders at 5.78 μ and 5.99 Nujol.

Saponification of XIX.—To a suspension of 220 mg. of XIX, m.p. 274–281° dec., in 45 ml. of methanol was added 2.6 ml. of a solution of 1 *N* aqueous sodium hydroxide. The mixture was refluxed in an inert atmosphere for 45 minutes. The resulting solution was diluted with water and concentrated to remove the bulk of the methanol. Because a solid separated in the course of the concentration step, the saponification was judged to have been incomplete. The alkaline mixture was again made homogeneous by the addition of methanol and refluxing was resumed for about 2 hours. The solution was kept at room temperature overnight. The bulk of the alcohol was again removed *in vacuo* and the resulting aqueous solution was extracted twice with ether, cooled and acidified with a cold solution of hydrochloric acid to afford 200 mg. of product, $\lambda_{max}^{Pyridine}$ 2.95, 5.79 μ; λ_{max}^{Nujol} 3.04, 5.81, 6.10 μ. One crystallization from acetone–Skellysolve B gave a sample, m.p. 294–295° dec., and the m.p. was not improved (293–295.5°) by a further recrystallization from acetone–methanol.

Anal. Calcd. for $C_{23}H_{29}O_8F$: C, 61.05; H, 6.46. Found: C, 61.29; H, 6.44.

BMD of 9β,11β-Epoxy-16α-methyl-17,21-dihydroxy-1,4-pregnadiene-3,20-dione (XXIII).—A cold solution of 25 g. of XXI in a mixture of 850 ml. of chloroform and 125 ml. of methylene chloride was treated successively with 250 ml. each of formaldehyde (Merck, reagent) and 48% aqueous hydrobromic acid. The mixture was stirred at room temperature for 24 hours. The crude product was isolated in the usual manner. A 13.3-g. aliquot of crude XXII (Calcd.: Br, 16.3. Found: Br, 16.56) was suspended in 50 ml. of methanol and allowed to react with 29.8 ml. of a 1.01 *N* methanolic solution of sodium methoxide for 45 minutes. The mixture became homogeneous after about 30 minutes, but a precipitate separated later on. The *p*H of the mixture was adjusted to 6 with acetic acid and the precipitate was removed by filtration and washed with methanol to give 7.4 g. of XXIII, m.p. 205–207°, which was devoid of hydroxyl or saturated carbonyl. The filtrate afforded a second crop (2.75 g.), m.p. 197–201°. An analytical sample, m.p. 220–221°, λ_{max} 249.5 mμ (ϵ 15,500), was obtained by chromatography on alumina and subsequent recrystallization from acetone–Skellysolve B.

Anal. Calcd. $C_{24}H_{30}O_6$: C, 69.54; H, 7.30. Found: C, 69.62; H, 7.48.

(26) It is possible that the product may contain the C-5 epimer as a contaminant.

Osmylation of XXIII.—A solution of 7.5 g. of crude, unchromatographed XXIII in 150 ml. of pyridine was treated with a solution of 5.0 g. of osmium tetroxide in 50 ml. of pyridine with external cooling. The solution was kept at room temperature for one day and the mixture of osmate esters was precipitated with Skellysolve B and removed by filtration. The product was dissolved in 700 ml. of dioxane and reduced with hydrogen sulfide at 5° for 0.5 hour. The osmium dioxide was precipitated by addition of salt water and the steroid was extracted into chloroform until the organic extracts gave a negative tetrazolium test.[5] The crude product, obtained after removal of solvents, was dissolved in ether and filtered to remove additional amounts of inorganic material. The product was then taken up in pyridine, and water was added to afford 1.425 g. of a mixture of the isomeric diols.

A 200-mg. aliquot was put on 20 sheets of Whatman paper No. 4 and was chromatographed using methanol–formamide (2:1) as the stationary phase and benzene–Skellysolve B (1:1) as the mobile descending phase. **The more mobile 4,5-dihydroxy compound XXV** (59.5 mg.) was isolated from the dry paper essentially as described for VII above. Crystallization from acetone–petroleum ether gave 20.9 mg., m.p. *ca.* 230°, λ_{max}^{MeOH} 228 mμ (ε 9,400). In the infrared, the compound showed maxima ($CHCl_3$) at 2.79 μ (OH), 2.86 (OH), 5.92 (3-ketone) and only a weak band at 6.16 μ characteristic of Δ^1-3-ketones. One further recrystallization from the same solvent system gave a different crystalline modification, m.p. 211–215°, λ_{max}^{MeOH} 228 mμ (ε 9,600).

Anal. Calcd. for $C_{24}H_{32}O_8$: C, 64.27; H, 7.19. Found: C, 64.80; H, 7.32.

The less mobile isomeric **1,2-dihydroxy compound XXIV** was obtained from an osmylation of 15 g. of XXIII which was allowed to proceed for 3 days but which was otherwise carried out essentially as described above. The crude mixture isolated as above by crystallization from pyridine–water amounted to 3.8 g. and a second crop of 2.55 g. Recrystallization of the combined fractions from acetone–Skellysolve B gave 2.71 g. which was chromatographed on 20 sheets of Whatman paper No. 3 to give 220 mg. of XXIV, m.p. *ca.* 227–232°. An analytical sample melted at 230–232°, λ_{max} 242.5 mμ (ε 12,500), $[\alpha]_D$ − 38° ($CHCl_3$).

Anal. Calcd. for $C_{24}H_{32}O_8$: C, 64.27; H, 7.19. Found: C, 64.37; H, 7.29.

Periodate Cleavage of XXIV.—A solution of 220 mg. of XXIV in 32 ml. of methanol was allowed to react with stirring with a solution of 760 mg. of sodium metaperiodate in 12 ml. of water at room temperature overnight. The bulk of the methanol was removed *in vacuo* and the residue was distributed between water and a mixture of chloroform and ether. The organic layer afforded 215 mg. of crude XXVI, λ_{max} 227.5 mμ (ε 11,230). The product was purified by paper chromatography in the usual manner using formamide as the stationary phase and benzene–Skellysolve B as the mobile component. A weak spot at the point of application was not examined further. The major component (R_f 0.12) was isolated from paper as described for VII to give 54.0 mg. Crystallization from acetone–Skellysolve B yielded 40 mg. of XXVI, m.p. 264–266° dec.

Anal. Calcd. for $C_{23}H_{30}O_8$: C, 63.58; H, 6.96. Found: C, 63.35; H, 6.91.

In another experiment (220-mg. scale) the crude reaction product was crystallized directly from acetone–Skellysolve B to afford 101.0 mg. of XXVI, m.p. 265–266°, and a second crop (11.5 mg.), m.p. 263–265°.

BMD of 9β,11β-Epoxy-17,21-dihydroxy-16α-methyl-2-oxa-4-pregnene-3-one (XXVII).—A 100-mg. sample of XXVI, m.p. 265–266°, was dissolved in 15 ml. of methanol with heating. The solution was cooled and treated with 2.18 ml. of 0.1020 *N* aqueous solution of sodium hydroxide. The *p*H of the solution was adjusted to 9 by the addition of several drops of the aqueous base and the bulk of the methanol was then removed *in vacuo* and the residual solution (*p*H *ca.* 9) was treated with 1 ml. of a saturated solution of sodium chloride. The resulting precipitate was just redissolved with water and 110 mg. of sodium borohydride was added. The mixture was kept at room temperature overnight. A solid separated in the course of the reduction. The mixture (*p*H 10) was made acid to congo red with 2.5 *N* hydrochloric acid and the product was isolated by filtration. The product, 90 mg., R_f 0.84, was crystallized from acetone–Skellysolve B to give 51.0 mg., m.p. *ca.* 225–228°, λ_{max} 225 mμ (ε 14,000). An analytical specimen, obtained after two further recrystallizations from the same solvent pair, melted at 225–228°.

Anal. Calcd. for $C_{23}H_{30}O_7$: C, 66.01; H, 7.23. Found: C, 65.97; H, 7.32.

9α-Chloro-11β,17,21-trihydroxy-16α-methyl-2-oxa-4-pregnene-3,20-dione 21-Acetate (XXVIIIa).—A solution of 120 mg. of XXVII in a mixture of 28.8 ml. of 50% aqueous acetic acid and 2.4 ml. of concentrated hydrochloric acid was heated on a steam-bath under nitrogen for 4 minutes. The mixture was poured into water and extracted with chloroform and with ethyl acetate. The combined organic layers were washed with water, and with a 5% solution of sodium bicarbonate. The mixture was again washed with water and taken to dryness to give 85.1 mg. of a mixture. The major component, which had the expected mobility on paper, was isolated by paper chromatography using formamide as the stationary phase and chloroform as the mobile component to afford 21.3 mg. of XXVIII which was acetylated with 0.2 ml. of pyridine and 0.2 ml. of acetic anhydride at room temperature overnight. The product was purified by paper chromatography using the formamide–benzene system. The product was crystallized from acetone–Skellysolve B to give 5.4 mg. of XXVIIIa, m.p. 178–182° dec., λ_{max} 223 mμ (ε 13,400).

Anal. Calcd. for $C_{23}H_{31}O_7Cl$: Cl, 7.5; Found: Cl, 8.0.

A quantitative assay for the 20-keto-21-acetoxy system with tetrazolium reagent gave 96% of the extinction of 16α-methyl-9α-chloroprednisolone acetate.