state. Reasoning from the fact that the valence shell orbitals of sulfur are quite extended and pursuant upon the idea advanced by Pauling[14a] that high hydration properties accompany only relatively contracted orbitals, the very contrary could have been expected. However, the most recent studies on hydrogen bonding in analogous sulfur and oxygen models[15] strongly suggest that sulfur is a much better proton acceptor than oxygen. When this is taken in conjunction with the well recognized fact that sulfur tolerates positive charge much better than oxygen in comparable onium ion substrates, a plausible explanation for the high negative w-values for acid-catalyzed ring opening of episulfides becomes evident. That is to say, the greater degree of onium ion character must be associated with a greater extent of hydration of the protonated episulfide reagent as compared to thiol product. The attainment of the transition state and consequent loss of onium ion character could correspond to the stripping away of water molecules of hydration in greater number than are participating as nucleophiles on the (opposite) back side of the rupturing carbon–sulfur bond.

On the other hand, we may also be encountering "hydration theory" deviations[5c] that can arise in cases where the substrate is exceedingly different in chemical nature from the indicator bases used in determining the H_0 scale. Under such circumstances, where there may be experienced considerable dislocation in comparing the hydration properties of the indicator base and conjugate acid with those of the corresponding substrate species, negative w-values are not unexpected.[5c] Indeed, the acid–base centers of the indicators are usually (second row) nitrogen atoms, whereas the corresponding functional center in our substrate is a (third row) sulfur atom with attendant differences in hydration properties to be anticipated.[14] Despite the occurrence of linear relationships (Fig. 2 and 3) in applying both the Zucker–Hammett and Bunnett criteria, some residual uncertainty may still exist concerning the validity of this application until it can be demonstrated by an independent method that the degree of protonation of the sulfur atom of our substrate correlates with H_0.

Whatever may prove to be the correct explanation for the apparent disparity in the results obtained, we believe that the simultaneous application of both (S.–C. and w) criteria as tests of mechanism can be recommended. The S.–C. criterion at this writing appears to be a sensitive (but negative) test[1a] by use of which one may learn whether there is any solvent involvement in the transition state. The w criterion, on the other hand, appears to possess the potential, thus far lacking in the S.–C. criterion, of identifying the extent and the role of H_2O participation in the transition state, where unusual hydration properties of the substrate, medium sensitivity of the reaction mechanism or other factors do not obfuscate the result. When used concurrently, as in the present instance, interpretations can be ventured with somewhat greater confidence.

(14) L. Pauling, "The Nature of the Chemical Bond," 3rd Ed., Cornell Univ. Press, Ithaca, N. Y., Chap. 12, 1960.

(15) P. von R. Schleyer and R. West, *J. Am. Chem. Soc.*, **81**, 3164 (1959); and private communication from P. von R. Schleyer, Dec. 27, 1962.

[CONTRIBUTION FROM THE RESEARCH INSTITUTE FOR MEDICINE AND CHEMISTRY, CAMBRIDGE, MASS.]

The Synthesis of Substituted Aldosterone[1]

BY M. AKHTAR, D. H. R. BARTON, J. M. BEATON AND A. G. HORTMANN

RECEIVED NOVEMBER 30, 1962

A number of substituted aldosterones have been synthesized. In each case the angular 18-aldehyde grouping has been inserted by nitrite photolysis. The best procedure for the synthesis of 17α-hydroxyaldosterones involves protection of the side chain as the 17,20:20,21-bismethylenedioxy grouping. One of the methylenedioxy groups is hydrolyzed when an 18-oxime is treated with nitrous acid. The other has been removed under acidic hydrolytic conditions which afford, in general, 18,21-anhydro compounds. By special acid-catalyzed acetylation procedures the 18,21-anhydro ring has been opened to give 17,18-triacetates which on mild alkaline hydrolysis afford the desired 17α-hydroxyaldosterones.

In recent papers from this Institute[2] we have described convenient syntheses of aldosterone and 19-noraldosterone acetates. In spite of the potential biological interest of substituted aldosterones, especially those bearing 17α-hydroxyl groups, very few compounds of this type have hitherto been described. Racemic 16α-methyl- and 17α-hydroxyaldosterone have been obtained recently by total synthesis.[3] The present paper records the synthesis of a number of substituted aldosterones. The success of the work was made possible by the photolytic rearrangement of nitrites discovered earlier in this Institute.[4]

Dehydrogenation of aldosterone acetate (II) with selenium dioxide[5] gave 1-dehydroaldosterone acetate (IIa).[6] This compound was, however, more conveniently prepared by photolysis of the 11-nitrite (Ia) of 1-dehydrocorticosterone acetate (Ib) followed by treatment with nitrous acid as detailed earlier.[2,4] 1-Dehydroaldosterone acetate was supplied to Dr. Marcel Gut of the Worcester Foundation and used by him in a synthesis of tritium labeled aldosterone acetate.[7]

In similar experiments, corticosterone acetate (I) was dehydrogenated with chloranil[8] to the 6-dehydro compound Ic which was converted to the nitrite Id, photolyzed and further processed with nitrous acid to furnish 6-dehydroaldosterone acetate (IIb). Addition of thiolacetate ion to the latter gave the interesting[9] 7α-thiolacetoxy derivative IIc. We also examined the addition of thiolacetic acid to 6-dehydrocorticosterone acetate (Ic) and thus obtained the 7α-thiolacetoxy derivative Ie. Conversion of the latter to its nitrite and

(1) This paper is Communication No. 22 from the Research Institute for Medicine and Chemistry. For No. 21 see M. M. Pechet, Fifth Pan-American Congress of Endocrinology, in press.

(2) D. H. R. Barton and J. M. Beaton, *J. Am. Chem. Soc.*, (a) **82**, 2641 (1960); **83**, 4083 (1961); (b) **83**, 750 (1961); **84**, 199 (1962).

(3) P. Wieland, K. Heusler and A. Wettstein, *Helv. Chim. Acta*, **43**, 617 (1960); **43**, 2066 (1960).

(4) D. H. R. Barton, J. M. Beaton, L. E. Geller and M. M. Pechet, *J. Am. Chem. Soc.*, **82**, 2640 (1960); **83**, 4076 (1961); A. L. Nussbaum and C. H. Robinson, *Tetrahedron*, **17**, 35 (1962).

(5) Ch. Meystre, H. Frey, W. Voser and A. Wettstein, *Helv. Chim. Acta*, **39**, 734 (1956); S. A. Szpilfogel, T. A. P. Posthumus, M. S. de Winter and D. A. van Dorp, *Rec. trav. chim.*, **75**, 475 (1956); H. Ringold and G. Rosenkranz, U. S. Patent 2,957,895.

(6) E. Vischer, J. Schmidlin and A. Wettstein, *Experientia*, **12**, 50 (1956), record a m.p. (182–185°) for this compound which was prepared microbiologically from a racemic intermediate.

(7) K. R. Laumus and M. Gut, *J. Org. Chem.*, **27**, 314 (1962).

(8) E. J. Agnello and G. D. Laubach, *J. Am. Chem. Soc.*, **82**, 4293 (1960).

(9) R. M. Dodson and R. C. Tweit, *ibid.*, **81**, 1224 (1959); J. A. Cella and R. C. Tweit, *J. Org. Chem.*, **24**, 1109 (1959); R. C. Tweit, *ibid.*, **27**, 2693 (1962); R. C. Tweit, F. B. Colton, N. L. McNiven and W. Klyne, *ibid.*, **27**, 3325 (1962).

photolysis followed by the usual processing did not give tractable products.

Synthesis of 17α-hydroxy derivatives of aldosterone proved to be far more challenging. For example, prednisolone acetate (III) gave a highly crystalline nitrite (IIIa) which on photolysis and treatment with nitrous acid, gave, as the only isolable product, the nitrone IV, analogous to a compound obtained in our earlier work.[2] It became clear from this and related experiments that some protection of the cortical side chain was needed if 17α-hydroxy derivatives of aldosterone were to be made generally available. The bismethylenedioxy group[10] has been found satisfactory. The bismethylenedioxy derivative V of prednisolone[10] gave a nitrite (Va) which, on photolysis, afforded in good yield the 18-oxime VI. On treatment with nitrous acid this furnished the interesting monomethylenedioxy derivative VII. The constitution of the latter is based upon the appropriate analytical data, the presence of a 20-carbonyl band in the infrared spectrum and the formation of a monobenzylidene derivative on base-catalyzed condensation with benzaldehyde. In the infrared spectrum hydroxyl absorption was present. This must have been due to tertiary OH because the compound resisted acetylation and mild chromic acid oxidation. On further treatment with dioxane–sulfuric acid under gentle conditions 18,21-anhydro-1-dehydro-17α-hydroxyaldosterone (VIII) resulted. The formation of the monomethylenedioxy derivative VII probably proceeds through the oxonium ion IX which permits (IX, X; see arrows) an intramolecular rupture of the bismethylenedioxy grouping. The conversion of the 18,21-anhydro compound to 1-dehydro-17α-hydroxyaldosterone (XI) was not very easy, but by acid-catalyzed acetylation under carefully defined conditions the triacetate XIa could be obtained in good yield. Mild alkaline hydrolysis then afforded the desired compound XI. In order to prove that D-homoannulation had not occurred, the latter was oxidized by chromium trioxide in pyridine to the lactone XII. The latter had the correct analytical composition and showed the expected γ-lactone and cyclopentanone carbonyl absorption in the infrared spectrum.

The synthesis of 9α-fluoro-17α-hydroxy derivatives of aldosterone was easier in that the formation of 18,21-anhydro compounds as intermediates could be avoided. 17,20;20,21-Bismethylenedioxy-9α-fluorocortisol[10] (Vb) was converted to the nitrite, photolyzed, and the total product treated with nitrous acid in the usual way. This gave the monomethylenedioxy derivative VIIa which, on mild acid treatment in a stream of nitrogen to remove the formaldehde as it was generated, gave the desired 9α-fluoro-17α-hydroxyaldosterone (XIb). The constitution of this compound was proved by oxidation with chromium trioxide in pyridine to the γ-lactone XIIa. Selenium dioxide oxidation of the monomethylenedioxy derivative VIIa gave the 1-dehydro compound VIIb which on mild acidic hydrolysis as above afforded 1-dehydro-9α-fluoroaldosterone (XIc). The rather easy synthesis of these 9α-fluoro compounds must depend on the relative difficulty of formation of an 11(18)-oxonium ion when a 9α-fluoro-substituent is present. Intramolecular cyclization of the 21-hydroxyl onto position 18 is thus relatively precluded.

We now turn to the synthesis of 17α-hydroxyaldosterone (XId) itself. Cortisol, treated with paraformaldehyde and acid, gave the known[10] 20,21-bismethylenedioxy derivative Vc and a new compound identified as the tris-derivative XIII (R = CH_2OH). On melting, the latter evolved formaldehyde and gave the usual bis-derivative Vc. Chromic acid oxidation furnished the formate XIII (R = CHO) which, on alkaline hydrolysis, gave again the bis-derivative Vc. Heating the formate XIII (R = CHO) with formic acid gave cortisol 11-formate.[11] The tris derivative XIII (R = CH_2OH) afforded a crystalline nitrite which on photolysis also gave the 11-formate XIII (R = CHO).

In the meantime the bis-derivative Vc was converted to the crystalline nitrite Vd and photolyzed in the usual way. Chromatography of the product gave the desired 18-oxime VIa as well as the *syn*-XIV and *anti*-XV-oximino-ketones resulting[2] from radical attack upon C-19. The formulation of these compounds is based upon extensive evidence adduced earlier[2] in a comparable example. Additional chemical evidence for the formulation of the *anti*-oximino-ketones XV was secured in the following way.[12] Treatment with phosphorus oxychloride in pyridine gave the lactone XVI. Alkaline hydrolysis of the latter afforded the expected hydroxy-acid XVII which with diazomethane gave the methyl ester XVIIa. Chromic acid oxidation of the latter afforded the expected methyl ester ketone.

Reverting to the 18-oxime VIa, treatment of this compound with nitrous acid gave the monomethylenedioxy derivative VIIc which on mild hydrolysis afforded the 18,21-anhydro-17α-hydroxyaldosterone (VIIIa) that we had obtained earlier[2] by an alternative and less efficient route from cortisol 3,20-bisethylene ketal. On acid-catalyzed acetylation under carefully defined conditions the anhydro compound VIIIa gave the 17,18,21-triacetate XIe, which on mild alkaline hydrolysis furnished 17α-hydroxyaldosterone (XIf).[13]

We next turned our attention to the synthesis of 1-dehydro-9α-fluoro-17α-hydroxy-16α-methylaldosterone (XIg), the aldosterone analog of dexamethasone.[14] The 17,20;20,21-bismethylenedioxy derivative Ve of dexamethasone was converted to the nitrite Vf and photolyzed to furnish in good yield the 18-oxime VIb. Treatment with nitrous acid in the usual way gave the monomethylenedioxy derivative VIId.[15] Treatment of the latter with acetic acid–acetic anhydride–47% hydriodic acid gave in adequate yield the 18,21-anhydro compound VIIIb. Perchloric acid-catalyzed acetylation of the anhydro derivative afforded the 17α,18,21-triacetate XIh, which on mild alkaline hydrolysis gave the desired aldosterone derivative XIg. For proof of constitution this compound was oxidized with chromium trioxide in pyridine to the γ-lactone XIIb.

The use of hydrogen iodide in the sequence of reactions described above is mandatory. Experiments with other acids did not give, at least in our hands, the required 18,21-anhydro compound. For example, when the monomethylenedioxy derivative VIId was treated with acetic acid–hydrogen bromide it gave in poor yield the 16ξ-bromodiacetate XVIII. Its formulation as a 16-bromo ketone is substantiated by facile

(10) R. E. Beyler, R. M. Moriarty, F. Hoffman and L. H. Sarett, *J. Am. Chem. Soc.*, **80**, 1517 (1958).

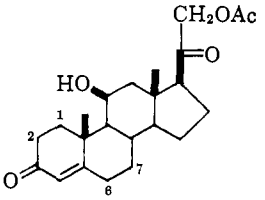
(11) E. P. Oliveto, C. Gerold, R. Rausser and E. B. Hershberg, *ibid.*, **77**, 3564 (1955).

(12) We acknowledge with gratitude prior information from Drs. E. P. Oliveto and H. Riemann and their collaborators of the Schering Corporation on comparable reactions carried out in a different series of compounds.

(13) The partial synthesis of 17α-hydroxyaldosterone has also been claimed by P. Wieland, K. Heusler and A. Wettstein (*Helv. Chim. Acta*, **44**, 2121 (1961)). However, no rotation, ultraviolet spectrum or analytical data are given. Our own synthesis was first reported at the I.U.P.A.C. Meeting in Montreal, Canada, in August, 1961.

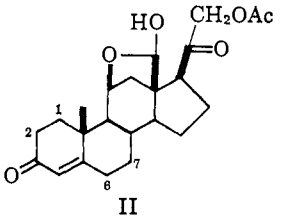
(14) G. E. Arth, D. B. R. Johnson, J. Fried, W. W. Spooncer, D. R. Hoff and L. H. Sarett, *J. Am. Chem. Soc.*, **80**, 3160 (1958); E. P. Oliveto, R. Rausser, A. L. Nussbaum, W. Gebert, E. B. Hershberg, S. Tolksdorf, M. Eisler, P. L. Perlman and M. M. Pechet, *ibid.*, **80**, 4428 (1958).

(15) The four last-named compounds were first prepared and characterized by Drs. E. P. Oliveto and C. H. Robinson and their colleagues of the Schering Corporation.



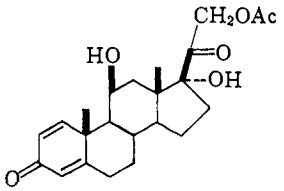
I

Ia, 11-nitrite of 1-dehydro
b, 1-dehydro
c, 6-dehydro
d, 11-nitrite of 6-dehydro
e, 7α-thiolacetoxy



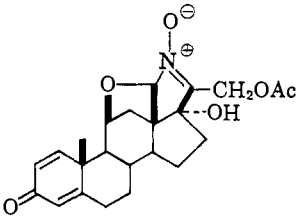
II

IIa, 1-dehydro
b, 6-dehydro
c, 7α-thiolacetoxy

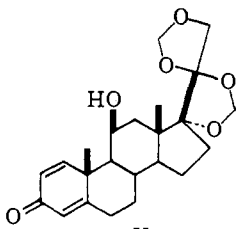


III

IIIa, 11-nitrite

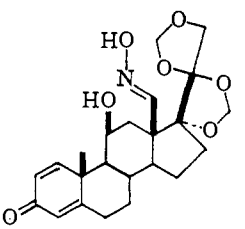


IV



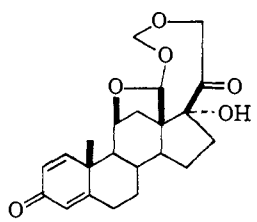
V

Va, 11-nitrite
b, 1,2-dihydro-9α-fluoro
c, 1,2-dihydro
d, 11-nitrite of 1,2-dihydro
e, 9α-fluoro-16α-methyl
f, 11-nitrite of 9α-fluoro-16α-methyl
g, 9α-bromo



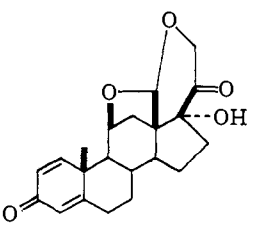
VI

VIa, 1,2-dihydro
b, 9α-bromo-1,2-dihydro



VII

VIIa, 1,2-dihydro-9α-fluoro
b, 9α-fluoro
c, 1,2-dihydro
d, 9α-fluoro-16α-methyl
e, 9α-bromo-1,2-dihydro

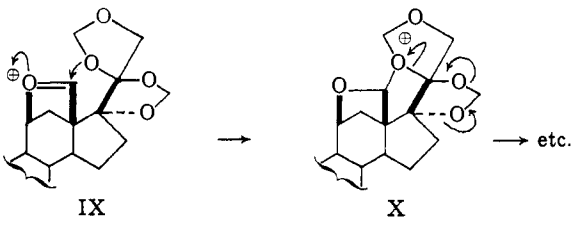


VIII

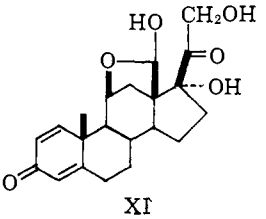
VIIIa, 1,2-dihydro
b, 9α-fluoro-16α-methyl

loss of hydrogen bromide on digestion with pyridine to give a compound with an extra α,β-unsaturated ketone grouping. The formulation is also supported by the following experiments on model compounds. Cortisone (XIXa) with acetic acid–hydrogen bromide gave the 16ξ-bromo derivative XXa, which on digestion with pyridine furnished 21-acetoxypregna-4,16-diene-3,11,20-trione (XXIa).[16] Treatment of the latter with acetic acid–hydrogen bromide re-formed the 16ξ-bromo compound XXa in good yield. The enone XXIa is probably an intermediate in the formation of XXa. Treatment of the 16ξ-bromo compound with Raney nickel gave 21-acetoxypregn-4-ene-3,11,20-trione. In similar experiments cortisol (XIXb) furnished in small yield 21-acetoxy-16ξ-bromo-pregna-4,9(11)diene-3,20-dione (XXb). On digestion with pyridine this afforded the known[16] enone XXIb.

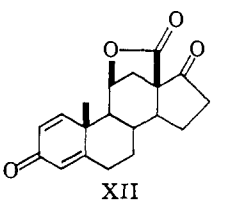
(16) W. S. Allen and S. Bernstein. *J. Am. Chem. Soc.*, **77**, 1031 (1955).



IX X

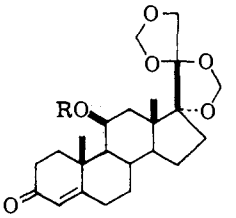


XI

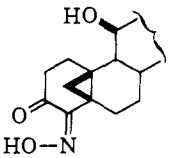


XII

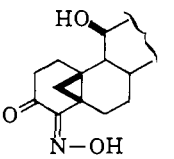
XIa, 17,18,21-triacetate
b, 1,2-dihydro-9α-fluoro
c, 9α-fluoro
d, 1,2-dihydro
e, 17,18,21-triacetate of 1,2-dihydro
f, 1,2-dihydro
g, 9α-fluoro-16α-methyl
h, 17,18,21-triacetate of 9α-fluoro-16α-methyl
XIIa, 1,2-dihydro-9α-fluoro
b, 9α-fluoro-16α-methyl



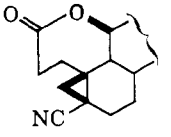
XIII

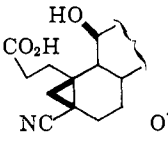


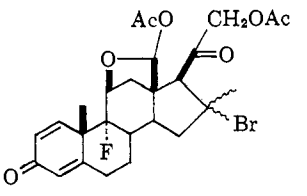
XIV



XV







XVI XVII XVIII

XVIIa, Me ester

In recent work[17] we have shown that the nitrites of chloro- and bromohydrins can be photolyzed smoothly and the halohydrin grouping then used later to synthetic advantage.[18] We have carried out preliminary experiments of a similar nature directed toward the synthesis of substituted aldosterones.

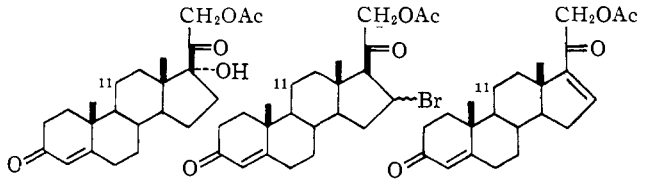
11-Epicortisol (XIXc) was converted to its 17,20;20,21-bismethylenedioxy derivative which, on dehydration in the usual way,[19] gave the 9(11)-olefin. Addition of hypobromous acid to the latter furnished the 9α-bromo-11β-hydroxy compound Vg. This was nitrosated and photolyzed as before[17] to give, as major isolated product, the desired 18-oxime VIb. With nitrous acid this afforded the monomethylenedioxy compound VIIe and the oximino-lactone XXIIa. The latter is a type of compound that we have encountered on several occasions from the action of nitrous acid on 11β-hydroxy-18-oximino compounds. For example, the oximino-lactone XXII is a by-product in the action of nitrous acid on the oxime VIa (see above). In the specific case of the 9α-bromo derivative XXIIa we proved the

(17) M. Akhtar and D. H. R. Barton. *ibid.*, **84**, 1496 (1962).

(18) See also T. Jen and M. E. Wolff. *J. Med. Pharm. Chem.*, **5**, 876 (1962); A. Bowers, R. Villotti, J. A. Edwards, E. Denot and O. Halpern. *J. Am. Chem. Soc.*, **84**, 3204 (1962).

(19) J. Fried and E. F. Sabo. *ibid.*, **75**, 2273 (1953).

structure by reduction with zinc dust to the hydroxamic acid XXIII (characteristic ferric reaction). Reduction of the monomethylenedioxy compound VIIe in the same way did not give tractable compounds, but with a

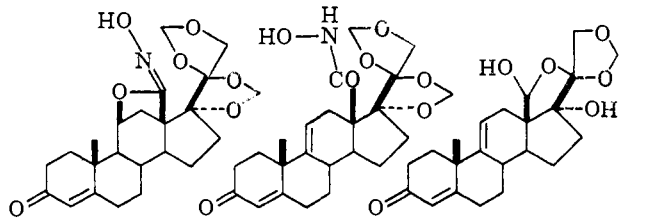


XIX XX XXI

XIXa, 11-(C=O) b, 11β-OH c, 11α-OH

XXa, 11-(C=O) b, 9(11)-dehydro

XXIa, 11-(C=O) b, 9(11)-dehydro



XXII XXIII XXIV

XXIIa, 9α-bromo

zinc–copper couple a product was obtained which lacked the 20-carbonyl group and may be formulated as XXIV.

A report on the biological activities of the substituted aldosterones described in this paper will be given later from this Institute by Dr. M. M. Pechet and his colleagues.

Experimental

Microanalyses were performed by Dr. Alfred Bernhardt, Max Planck Institute, Mulheim (Ruhr), Germany. Infrared spectra were determined using an Infracord model 137 spectrophotometer. Unless stated otherwise ultraviolet spectra were determined in methanol and optical rotations in chloroform. M.p.'s were taken on a Kofler-type hot-stage. Mercks acid-washed alumina was used for all chromatograms.

1-Dehydroaldosterone 21-Acetate (IIa). (a) From Aldosterone 21-Acetate.—Aldosterone 21-acetate[2] (252 mg.) and selenium dioxide (131 mg.) in *tert*-butyl alcohol (12.5 ml.) containing pyridine (0.05 ml.)[5] was refluxed for 76 hr. The reaction mixture was diluted with methylene dichloride (10 ml.) and heated with pptd. silver for 15 min. on the steam-bath. Removal of the silver by filtration, dilution with water, extraction into methylene dichloride and washing successively with small portions of saturated aqueous sodium bicarbonate, aqueous ammonium sulfide (4 times), dilute aqueous ammonia, water, 2 *N* hydrochloric acid and saturated aqueous sodium chloride, gave, on crystallization from ethyl acetate, 1-dehydroaldosterone 21-acetate (IIa) as prisms (117 mg.), m.p. 183–186°. Crystallization from ethyl acetate–hexane gave the analytical specimen, m.p. 186–191°, $[\alpha]_D$ +65° (*c* 1.20), λ_{max} 243 mμ (ε 14,100); $\gamma_{max}^{CHCl_3}$ 3650, 3450, 1745, 1660 and 1620 cm.$^{-1}$.

Anal. Calcd. for $C_{23}H_{28}O_6$: C, 68.98; H, 7.05; O, 23.97. Found: C, 68.89; H, 6.75; O, 24.18.

(b) From 1-Dehydrocorticosterone Acetate (Ib).—The acetate (4.0 g.) was converted to the nitrite (not isolated) which was photolyzed in benzene as for corticosterone acetate.[2] The total material was treated with nitrous acid as before[2] and the product chromatographed over alumina to give 1-dehydroaldosterone acetate (780 mg.). In minor amount the corresponding nitrone was also obtained. This had m.p. 208–216°, $[\alpha]_D$ +93° (*c* 0.80), λ_{max} 242 mμ (ε 26,000); γ_{max}^{KBr} 1745, 1660, 1625, 1600, 1580 and 1220 cm.$^{-1}$.

Anal. Calcd. for $C_{23}H_{27}O_5N$: C, 69.50; H, 6.85; O, 20.13; N, 3.42. Found: C, 69.59; H, 6.94; O, 19.92; N, 3.72.

6-Dehydrocorticosterone 21-Acetate (Ic).—Corticosterone 21-acetate (25.9 g.) and chloranil (57.2 g.)[3] in *tert*-butyl alcohol (1500 ml.) were refluxed with vigorous stirring for 1.5 hr. The excess of chloranil was removed by filtration of the hot solution and the solvent removed *in vacuo*. The residue in methylene dichloride was washed successively with hydrochloric acid (0.5 *N*), aqueous sodium hydroxide (1%), water and then dried (Na_2SO_4). Crystallization of the product from ethyl acetate–hexane gave 6-dehydrocorticosterone 21-acetate (Ic) (15.75 g.) as triangular plates, m.p. 160–165°. The analytical specimen had m.p. 161–165°, $[\alpha]_D$ +237° (*c* 1.00), λ_{max} 284 mμ (ε 24,800); γ_{max}^{KBr} 3650, 3400, 1755, 1730, 1660, 1620 and 1590; $\gamma_{max}^{CHCl_3}$ 3710, 3600, 1750, 1730, 1655, 1620 and 1585 cm.$^{-1}$.

Anal. Calcd. for $C_{23}H_{30}O_5$: C, 71.48; H, 7.82; O, 20.70. Found: C, 71.46; H, 7.72; O, 20.92.

6-Dehydrocorticosterone 11-Nitrite 21-Acetate (Id).—6-Dehydrocorticosterone 21-acetate (Ic) (4.95 g.) in pyridine (Karl Fischer reagent grade; 150 ml.) was treated with excess of nitrosyl chloride at 0° until the solution became reddish brown.[4] Dilution with ice-water, extraction into methylene dichloride and crystallization from ethyl acetate–hexane gave 6-dehydrocorticosterone 11-nitrite 21-acetate (Id) (4.66 g.), m.p. 150–154°. The analytical sample had m.p. 152–155°, $[\alpha]_D$ +319° (*c* 1.20); γ_{max}^{KBr} 1755, 1715, 1650, 1620 and 1585; $\gamma_{max}^{CHCl_3}$ 1750, 1730, 1670, 1650, 1630 and 1590 cm.$^{-1}$.

Anal. Calcd. for $C_{23}H_{29}O_6N$: C, 66.49; H, 7.04; O, 23.11; N, 3.37. Found: C, 66.48; H, 6.95; O, 23.23; N, 3.36.

6-Dehydroaldosterone 21-Acetate (IIb).—The 11-nitrite described above (2.25 g.) in toluene (75 ml.) was irradiated at 10° for 45 min. according to our general procedure.[2,4] After addition of methylene dichloride to dissolve pptd. material, the whole solution was evaporated to dryness *in vacuo*. The residue in acetic acid (20 ml.) was treated with aqueous sodium nitrite (5%, 10 ml.) at 5° for 1 hour. Dilution with water, then extraction with methylene dichloride gave, after working up in the usual way, a residue which was chromatographed over alumina (65 g.) in methylene dichloride. Elution with methylene dichloride containing 0.5% of methanol afforded, after crystallization from ethyl acetate, 6-dehydroaldosterone 21-acetate (IIb) (575 mg.) as small needles, m.p. 204–208°. The analytical specimen had m.p. 204–207°, $[\alpha]_D$ +86° (*c* 0.60), λ_{max} 284 mμ (ε 25,200); γ_{max}^{KBr} 3600, 1740, 1660, 1620 and 1585; $\gamma_{max}^{CHCl_3}$ 3700, 3550, 1750, 1660, 1620 and 1585 cm.$^{-1}$.

Anal. Calcd. for $C_{23}H_{28}O_6$: C, 68.97; H, 7.05. Found: C, 68.78; H, 7.03.

In a repeat preparation a less polar material was eluted first. This had m.p. 152–157°, $[\alpha]_D$ +325°, (*c* 1.20), λ_{max}^{MeOH} 281 mμ (ε 26,300); γ_{max}^{KBr} 1755, 1740, 1710, 1660, 1625 and 1590 cm.$^{-1}$. It is formulated as the 11-ketone corresponding to 6-dehydrocorticosterone 21-acetate.

Anal. Calcd. for $C_{23}H_{28}O_5$: C, 71.85; H, 7.34; O, 20.81. Found: C, 71.56; H, 7.10; O, 21.12.

7α-Thiolacetoxycorticosterone 21-Acetate (Ie).—6-Dehydrocorticosterone 21-acetate (Ic) (3.5 g.) in thiolacetic acid (3.5 ml.) was heated on the steam-bath under nitrogen for 1 hr. Most of the excess of thiolacetic acid was removed *in vacuo*. Crystallization of the residue from methanol furnished 7α-thiolacetoxycorticosterone 21-acetate (Ie) (2.60 g.) as needles, m.p. 200–202°. The analytical specimen had m.p. 202–204°, $[\alpha]_D$ +108° (*c* 1.40), λ_{max}^{MeOH} 238 mμ (ε 19,000); $\gamma_{max}^{CHCl_3}$ 3700, 3550, 1745, 1725, 1680, 1670 and 1620 cm.$^{-1}$.

Anal. Calcd. for $C_{25}H_{34}O_6S$: C, 64.91; H, 7.41; S, 6.93. Found: C, 65.10; H, 7.25; S, 6.40.

7α-Thiolacetoxyaldosterone 21-Acetate (IIc).—6-Dehydroaldosterone 21-acetate (IIb) (2.25 g.) in thiolacetic acid (5.0 ml.) was heated on the steam-bath under nitrogen for 45 min. Dilution with methylene chloride, washing successively with water, aqueous sodium hydroxide (1%) and saturated sodium chloride solution and drying (sodium sulfate), gave, on chromatography over alumina (eluting with methylene dichloride containing 0.5% methanol), 7α-thiolacetoxyaldosterone 21-acetate (IIc). Crystallized from ethyl acetate–ether this (1.60 g.) had m.p. 105–115°. The analytical specimen had m.p. 116–120°, $[\alpha]_D$ +37° (*c* 1.50), λ_{max} 238 mμ (ε 19,600); γ_{max}^{KBr} 3500, 1740, 1685, 1670 and 1620; $\gamma_{max}^{CHCl_3}$ 3740, 1750, 1690, 1680 and 1625 cm.$^{-1}$.

Anal. Calcd. for $C_{25}H_{32}O_7S$: C, 63.00; H, 6.77; O, 23.50; S, 6.73. Found: C, 62.25, 63.84; H, 6.93, 6.98; O, 23.73; S, 7.12, 6.62.

Prednisolone 21-Acetate 11-Nitrite (IIIa).—Prednisolone acetate (III) (5 g.) in pyridine (100 ml.) was treated with nitrosyl chloride (gas) at 0° until an orange color persisted. The solution was warmed to room temperature, diluted with water and extracted with methylene dichloride. After washing with water and drying (sodium sulfate) the solvent was removed *in vacuo* and the residue crystallized from methanol to furnish prednisolone 21-acetate 11-nitrite (IIIa) (4.5 g.) as plates, m.p. 185–187°, $[\alpha]_D$ +20° (*c* 1.0); γ_{max}^{KBr} 3400, 1760, 1745, 1675, 1656, 1635 and 1620 cm.$^{-1}$.

Anal. Calcd. for $C_{23}H_{29}O_7N$: C, 64.00; H, 6.77; N, 3.25. Found: C, 63.75; H, 6.85; N, 3.45.

Photolysis of Prednisolone 21-Acetate 11-Nitrite (IIIa).—The nitrite (2.5 g.) in toluene (700 ml.) was irradiated at 20° as described before.[2,4] After 1 hour the solid that had separated (700 mg.) was collected and refluxed in methanol (30 ml.) for

30 min. After removal of the methanol the residue in methylene dichloride was chromatographed over alumina (20 g.), eluting with methylene dichloride containing increasing amounts of methanol. The first fraction, crystallized from methanol, afforded prednisolone 21-acetate (III) (375 mg.). Later fractions furnished the nitrone IV (150 mg.). Crystallized from methanol this had m.p. 238–242°, $[\alpha]_D$ +183° (*c* 1.2), λ_{max} 243 mμ (ε 26,000); γ_{max}^{KBr} 3300, 1745, 1665, 1625, 1600 and 1570 cm.$^{-1}$.

Anal. Calcd. for $C_{23}H_{27}O_6N$: C, 66.80; H, 6.60; O, 23.20; N, 3.40. Found: C, 66.50; H, 6.80; O, 23.30; N, 3.45.

17,20;20,21-Bismethylenedioxyprednisolone 11-Nitrite (Va).—The prednisolone derivative[10] (3.8 g.) in pyridine (100 ml.) was treated at −20° with an excess of nitrosyl chloride and further processed as above. Crystallization of the product from methylene dichloride–methanol gave 17,20;20,21-bismethylenedioxyprednisolone 11-nitrite (Va) (2.8 g.) as plates, m.p. 188–190°, $[\alpha]_D$ +20° (*c* 1.0); γ_{max}^{Nujol} 1660, 1640, 1620 and 1600 cm.$^{-1}$.

Anal. Calcd. for $C_{23}H_{29}O_7N$: C, 64.00; H, 6.75; N, 3.25. Found: C, 63.75; H, 6.60; N, 3.55.

Photolysis of 17,20;20,21-Bismethylenedioxyprednisolone 11-Nitrite (Va).—The nitrite (5.0 g.) in toluene (200 ml.) was photolyzed for 2 hours at 20° as described previously.[2,4] Without further treatment the solution was chromatographed over alumina (100 g.) eluting with methylene dichloride containing increasing proportions of methanol. The first fractions gave 17,20;20,21-bismethylenedioxyprednisolone (V) (600 mg.). The later fractions afforded the desired 18-oxime VI (3.0 g.) which, after crystallization from ethyl acetate–hexane, had m.p. 270–274°, $[\alpha]_D$ 0° (*c* 1.00), λ_{max} 244 mμ (ε 14,300); γ_{max}^{KBr} 3600, 3400, 1660, 1620 and 1600 cm.$^{-1}$.

Anal. Calcd. for $C_{23}H_{29}O_7N$: C, 64.00; H, 6.75; O, 25.95; N, 3.25. Found: C, 63.80; H, 6.85; O, 26.00; N, 3.25.

Treatment of the 18-Oxime VI with Nitrous Acid.—The oxime (1.0 g.) in acetic acid (34 ml.) at 50° was treated with 5% aqueous sodium nitrite (24 ml.) and the solution left at ambient temperature for 1.5 min. (color change: yellow-blue-green-yellow). The reaction mixture was poured into water and extracted several times with methylene dichloride. The combined methylene dichloride extracts were washed with aqueous sodium bicarbonate, dried (sodium sulfate) and evaporated *in vacuo*. The residue was chromatographed over alumina (20 g.) in methylene dichloride containing increasing proportions of methanol. Crystallization of combined fractions from acetone–hexane gave the monomethylenedioxy derivative VII (650 mg.). An analytical sample crystallized from methylene dichloride–methanol had m.p. 211–216°, $[\alpha]_D$ +150° (*c* 0.85), λ_{max} 240 mμ (ε 14,000); γ_{max}^{KBr} 3500, 1710, 1665, 1620 and 1600 cm.$^{-1}$.

Anal. Calcd. for $C_{22}H_{26}O_6$: C, 68.55; H, 6.80; O, 24.85. Found: C, 68.55; H, 6.90; O, 24.60.

This monomethylenedioxy derivative VII (200 mg.) in methanol (10 ml.) and freshly redistilled benzaldehyde (1.5 ml.) was treated with methanolic potassium hydroxide (5%, 1.5 ml.) for 3 days at room temperature. Chromatography of the product over alumina and crystallization from acetone–hexane gave the 21-benzylidene derivative (160 mg.), m.p. 245–251°, $[\alpha]_D$ +383° (*c* 1.77); λ_{max} 230 mμ (ε 18,800), 241 mμ (ε 18,500) and 290 mμ (ε 22,300); $\gamma_{max}^{CHCl_3}$ 3600, 1665 and 1625 cm.$^{-1}$.

Anal. Calcd. for $C_{29}H_{30}O_6$: C, 73.40; H, 6.36; O, 20.23. Found: C, 73.25; H, 6.25; O, 20.35.

18,21-Anhydro-1-dehydro-17α-hydroxyaldosterone (VIII).—The monomethylenedioxy derivative VII (50 mg.) in dioxane (3 ml.) and water (7 ml.) was treated at 0° with concd. sulfuric acid (0.6 ml.) (good agitation). The solution was allowed to warm to room temperature and then heated on the steam-bath under nitrogen for 2 hours. Dilution with water and extraction into methylene dichloride gave, after crystallization from acetone–hexane, 18,21-anhydro-1-dehydro-17α-hydroxyaldosterone (VIII) (32 mg.), m.p. 222–225°. The analytical specimen had m.p. 235–244°, $[\alpha]_D$ +144° (*c* 0.77), λ_{max} 242 mμ (ε 16,000); γ_{max}^{KBr} 3500, 1740, 1665 and 1600 cm.$^{-1}$.

Anal. Calcd. for $C_{21}H_{24}O_5$: C, 70.75; H, 6.80. Found: C, 70.50; H, 6.60.

1-Dehydro-17α-hydroxyaldosterone (XI).—The monomethylenedioxy derivative VII (1.0 g.) was processed as above and the total product taken up in acetic acid (100 ml.) and acetic anhydride (60 ml.), cooled to 5°, and treated dropwise (good agitation) with aqueous perchloric acid (70%, 12 ml.). The solution was left at 5° for 2 hr. and then poured into ice-water. Neutralization with aqueous ammonia, extraction into methylene dichloride and crystallization of the product from ethyl acetate–hexane, gave 1-dehydro-17α-hydroxyaldosterone triacetate (XIa) (760 mg.), m.p. 226–236°. The analytical sample had m.p. 235–240°, $[\alpha]_D$ +83° (*c* 1.68), λ_{max} 241 mμ (ε 14,500); γ_{max}^{KBr} 1745, 1710, 1665, 1620 and 1600 cm.$^{-1}$.

Anal. Calcd. for $C_{27}H_{32}O_9$: C, 64.80; H, 6.45; O, 28.75. Found: C, 65.10; H, 6.55; O, 28.50.

This triacetate (126 mg.) in methanol (30 ml.) at 0° was treated with 0.1 *N* aqueous sodium hydroxide (2.8 ml.) and the solution stirred at the same temperature under nitrogen for 1 hr. Dilution with water (100 ml.) containing acetic acid (2 drops), thorough (25 ml. × 10) extraction with methylene dichloride and crystallization of the product from ethyl acetate–methanol gave 1-dehydro-17α-hydroxyaldosterone (XI) (40 mg.), m.p. 205–210°. Recrystallization from the same solvent mixture gave the analytical specimen in two forms, m.p. 204–207° and 215–219°, $[\alpha]_D$ +72° (*c* 1.04), λ_{max} 241 mμ (ε 14,000); γ_{max}^{KBr} 3500, 3300, 1665, 1620 and 1600 cm.$^{-1}$.

Anal. Calcd. for $C_{21}H_{26}O_6$: C, 67.35; H, 7.00; O, 25.65. Found: C, 67.25; H, 6.95; O, 25.60.

Oxidation of 17α-Hydroxy-1-dehydroaldosterone to the 18 → 11-Lactone (XII).—17α-Hydroxy-1-dehydroaldosterone (XI) (80 mg.) in pyridine (4 ml.) was treated with chromium trioxide (500 mg.) suspended in pyridine (7 ml.) and left at room temperature for overnight. Dilution with water and working up in the usual way gave, after crystallization from acetone–hexane, the γ-lactone XII (15 mg.). The analytical specimen had m.p. 308–311°, $[\alpha]_D$ +173° (*c* 0.56); γ_{max}^{KBr} 1780, 1735, 1650, 1625 and 1600 cm.$^{-1}$.

Anal. Calcd. for $C_{19}H_{20}O_4$: C, 73.05; H, 6.45. Found: C, 72.99; H, 6.45.

9α-Fluoro-17α-hydroxyaldosterone (XIb).—17,20;20,21-Bismethylenedioxy-9α-fluorocortisol[10] (Vb) (25 g.) was converted to the nitrite in the usual way and the total product taken up in toluene (1.3 l.) containing a trace of pyridine. The solution was photolyzed (650-ml. portions) for 1.5 hr. at 5–10° using a 500-w. Hanovia lamp under nitrogen in the usual way.[2,4] The solution after photolysis was chromatographed over Florisil (650 g.) eluting with (4:5) benzene–methylene dichloride to give the crystalline 18-oxime (10 g.) which showed the expected ultraviolet and infrared spectra. Without further characterization this material (2.5 g.) in 75% aqueous acetic acid (200 ml.) was treated at −2° with water (25 ml.) containing sodium nitrite (3.75 g.). After leaving for 20 min. at room temperature the product was extracted into methylene dichloride in the usual way and chromatographed over Florisil (75 g.) in methylene dichloride to furnish, after crystallization from ethyl acetate–hexane, the monomethylenedioxy derivative VIIa as needles (810 mg.), m.p. 234–260°. The analytical specimen had m.p. 252–265°, $[\alpha]_D$ +131° (*c* 0.80), λ_{max} 237 mμ (ε 17,400); γ_{max}^{KBr} 3575, 1705–1695, 1670 and 1620 cm.$^{-1}$.

Anal. Calcd. for $C_{22}H_{27}O_6F$: C, 65.01; H, 6.70. Found: C, 64.96; H, 6.59.

The monomethylenedioxy compound VIIa (140 mg.) in dioxane (9 ml.) and water (20 ml.) containing concd. sulfuric acid (1.8 ml.) was heated in a stream of nitrogen for 1 hr. at 75–80°. Crystallization of the product from ethyl acetate–methanol gave 9α-fluoro-17α-hydroxyaldosterone (XIb) as needles (67 mg.), m.p. 210–218°. The analytical specimen had m.p. 216–222°, $[\alpha]_D$ +63° (*c* 0.80 in dioxane), λ_{max} 237 mμ (ε 18,400); γ_{max}^{KBr} 3500, 1660 and 1620 cm.$^{-1}$.

Anal. Calcd. for $C_{21}H_{27}O_6F$: C, 63.94; H, 6.90; F, 4.82. Found: C, 64.38, 64.31; H, 7.39, 7.01; F, 4.83.

9α-Fluoro-17α-hydroxyaldosterone (XIb) (122 mg.) in pyridine (5 ml.) was treated with chromium trioxide (500 mg.) suspended in pyridine (10 ml.) and left at room temperature for 20 hr. Dilution with water and working up in the usual way gave, after crystallization from ethyl acetate-hexane, the lactone XIIa as prisms, m.p. 225–252° (27 mg.). The analytical specimen had m.p. 251–255°, λ_{max} 235 mμ (ε 18,300); γ_{max}^{KBr} 1780, 1745, 1665 and 1620 cm.$^{-1}$.

Anal. Calcd. for $C_{19}H_{21}O_4F$: C, 68.66; H, 6.37. Found: C, 68.86; H, 6.60.

1-Dehydro-9α-fluoro-17α-hydroxyaldosterone (XIc).—9α-Fluoro-17α-hydroxy-18,21-monomethylenedioxyaldosterone (VIIa) (2.0 g.) in *tert*-butyl alcohol (100 ml.) containing pyridine (0.24 ml.) and selenium dioxide (810 mg.) was refluxed under nitrogen for 72 hr. The solvent was removed *in vacuo* and the residue taken up in methylene dichloride and filtered through Supercel. The solution was washed with aqueous sodium hydrogen carbonate, ammonium sulfide, 2 *N* aqueous ammonia, water and saturated sodium chloride solution. Chromatography over alumina (50 g.) in methylene dichloride containing increasing amounts of methanol gave starting material (510 mg.) and 1-dehydro-9α-fluoro-17α-hydroxy-18,21-monomethylenedioxyaldosterone (VIIb) (600 mg.). Purified by further chromatography and by crystallization from ethyl acetate–hexane this formed needles (380 mg.), m.p. 239–253°, $[\alpha]_D$ +105° (*c* 0.90), λ_{max} 238 mμ (ε 15,600); γ_{max}^{KBr} 3600, 1700, 1660 and 1625 cm.$^{-1}$.

Anal. Calcd. for $C_{22}H_{25}O_6F$: C, 65.33; H, 6.23. Found: C, 64.96; H, 6.59.

This derivative (180 mg.) in dioxane (9 ml.) and water (20 ml.) containing concd. sulfuric acid (1.8 ml.) was heated in a stream of nitrogen at 80° for 1.8 hr. Crystallization of the product from acetone–methanol afforded 1-dehydro-9α-fluoro-17α-hydroxyaldosterone (XIc) as needles, m.p. 203–216°. The analytical specimen had m.p. 205–213°, $[\alpha]_D$ +33° (*c* 0.80 in dioxane), λ_{max} 238 mμ (ε 16,500); γ_{max}^{KBr} 3450, 1660 and 1615 cm.$^{-1}$.

Anal. Calcd. for $C_{21}H_{25}O_6F$: C, 64.27; H, 6.42. Found: C, 64.36; H, 6.77.

Methylenedioxy Derivatives of Cortisol.—Finely powdered cortisol (100 g.) suspended in chloroform (4 l.) and 37% formalin (1 l.) was treated at room temperature (stirring) with concd. hydrochloric acid (1 l.). The temperature rose to *ca.* 30° and the steroid rapidly dissolved. After 40 min. the chloroform layer was separated, washed with water, dried (Na_2SO_4) and chromatographed over alumina (2 kg.). Elution with methylene dichloride containing increasing amounts of methanol gave two compounds. The less polar (48.5 g.) gave, on crystallization from ethyl acetate, 17,20;20,21-bismethylenedioxycortisol (Vc).[10] The more polar compound (17.2 g.), crystallized from ethyl acetate, had m.p. 184–186° and 217°. Further crystallization gave the analytical specimen of 11;17,20;20,21-trismethylenedioxycortisol (XIII, R = CH_2OH), m.p. 192–195° and 215–220°, $[\alpha]_D$ +55° (*c* 1.00), λ_{max} 242 mμ (ε 17,300); γ_{max}^{KBr} 3450, 1660 and 1610; $\gamma_{max}^{CHCl_3}$ 3700, 3500, 1660 and 1615 cm.$^{-1}$.

Anal. Calcd. for $C_{24}H_{31}O_7$: C, 66.34; H, 7.89; O, 25.77. Found: C, 66.45; H, 7.76; O, 26.05.

11;17,20;20,21-Trismethylenedioxycortisol (XIII, R = CH_2-OH) (50 mg.) was heated at 200° in an open tube for 2 min. during which time the compound melted with effervescence (smell of formaldehyde) and then resolidified. Crystallization from ethyl acetate gave 17,20;20,21-bismethylenedioxycortisol (Vc) (40 mg.), identified by m.p., mixture m.p., $[\alpha]_D$ and infrared spectrum. The conversion of the trismethylenedioxy- to the bis-derivative was also effected by refluxing in acetic acid under nitrogen for 5 min.

11;17,20;20,21-Trismethylenedioxycortisol (XIII, R = CH_2-OH) (500 mg.) in acetone (50 ml.) was treated at room temperature with an excess of 8 *N* chromium trioxide (persistent brown color). Crystallization of the product from methylene dichloride–ethyl acetate gave 17,20;20,21-bismethylenedioxy-cortisol 11-formate (XIII, R = CHO) (450 mg.) as prisms, m.p. 220–226°, $[\alpha]_D$ +39° (*c* 1.10): γ_{max}^{KBr} 1715, 1675 and 1615 cm.$^{-1}$.

Anal. Calcd. for $C_{24}H_{32}O_7$: C, 66.64; H, 7.46; O, 25.90. Found: C, 66.57; H, 7.46; O, 25.89.

This formate (XIII, R = CHO) (100 mg.) in 1% methanolic sodium hydroxide (50 ml.) was refluxed for 15 min. Crystallization of the product from methylene dichloride–hexane gave 17,20;20,21-bismethylenedioxycortisol (Vc).

The formate XIII (R = CHO) (100 mg.) in 60% formic acid (30 ml.) was heated in the steam-bath for 10 min. and the formic acid removed *in vacuo*. Crystallization of the product from ethyl acetate–hexane gave cortisol 11-formate (45 mg.).[11]

11;17,20;20,21-Trismethylenedioxycortisol (XIII, R = CH_2-OH) (750 mg.) in pyridine (10 ml.) was cooled to −20° and treated with an excess of nitrosyl chloride (gas) in the usual way. Addition of water gave the crystalline nitrite XIII (R = CH_2O–NO) (680 mg.). Recrystallized from methylene dichloride–hexane this had m.p. 164–170°, $[\alpha]_D$ +48° (*c* 1.00); λ_{max} 240, 359, 373 and 386 mμ (ε 17,700, 64, 69 and 43, respectively); γ_{max}^{KBr} 1670, 1650 and 1620 cm.$^{-1}$.

Anal. Calcd. for $C_{24}H_{33}O_8N$: C, 62.19; H, 7.18; O, 27.62; N, 3.02. Found: C, 61.20; H, 7.13; O, 26.94; N, 2.92.

This nitrite (prepared from 5.0 g. of 11;17,20;20,21-trismethylenedioxycortisol) in toluene (700 ml.) was photolyzed for 90 min. at 20° in the usual way. Chromatography of the product in methylene dichloride over alumina, eluting with increasing preparations of methanol, furnished 17,20;20,21-bismethylenedioxycortisol 11-formate (XIII, R = CHO; see above) (2.08 g.) and 17,20;20,21-bismethylenedioxycortisol (Vc) (1.2 g.).

17,20;20,21-Bismethylenedioxycortisol 11-Nitrite (Vd).—17,20;20,21-Bismethylenedioxycortisol (Vc) (27.5 g.) in pyridine (200 ml.) was treated at room temperature with an excess of nitrosyl chloride (gas). Cautious dilution with water, filtration and crystallization from methylene dichloride–hexane gave the 11-nitrite Vd as prisms, m.p. 170–172° (24.6 g.). A second crop (3.3 g.) had m.p. 164–168°. Recrystallization from methylene dichloride–methanol containing a trace of pyridine and then from methylene dichloride–hexane afforded the analytical specimen, m.p. 171–173°, $[\alpha]_D$ +59° (*c* 0.90); λ_{max} 239, 344, 357, 370 and 385 mμ (ε 15,300, 79, 78, 69 and 42, respectively); γ_{max}^{KBr} 3250, 1665 and 1625 cm.$^{-1}$.

Anal. Calcd. for $C_{23}H_{31}O_7N$: C, 63.72; H, 7.21; O, 25.84; N, 3.23. Found: C, 63.82; H, 7.16; O, 25.67; N, 3.51.

Photolysis of 17,20;20,21-Bismethylenedioxycortisol 11-Nitrite (Vd).—The nitrite Vd (6.4 g.) in toluene (200 ml.) was irradiated for 90 min. at 5° as previously described.[2,4] After standing at 5° overnight the solution was chromatographed over alumina (200 g.). Elution with methylene dichloride containing increasing proportions of methanol followed by crystallization from ethyl acetate–methylene dichloride gave the following compounds in order of ease of elution: (i) 17,20;20,21-Bismethylenedioxycortisone (200 mg.), (ii) the same derivative (20 mg.) and the *syn*-oximino-ketone XIV (150 mg.), (iii) the *syn*-oximino-ketone XIV (290 mg.). Recrystallized from ethyl acetate this formed prisms, m.p. 236–245°, $[\alpha]_D$ −20° (*c* 1.00), λ_{max} 276 mμ (ε 2,400); λ_{max}^{MeOH} (addition of 1% methanolic sodium hydroxide) 276 mμ (ε 6,800); $\gamma_{max}^{CHCl_3}$ 3700, 1730, 1660 and 1540; γ_{max}^{KBr} 3550, 1710 and 1605 cm.$^{-1}$.

Anal. Calcd. for $C_{23}H_{31}O_7N$: C, 63.72; H, 7.21; O, 25.84; N, 3.23. Found: C, 63.69; H, 6.98; O, 26.02; N, 3.23.

(iv) 17,20;20,21-Bismethylenedioxy-18-oximinocortisol (VIa) (2.18 g.) formed tenacious solvates. From ethyl acetate it crystallized as prisms, m.p. 220–229°, $[\alpha]_D$ +50° (*c* 0.90), λ_{max} 241 mμ (ε 17,000); $\gamma_{max}^{CHCl_3}$ 3650, 3250, 1735 (ethyl acetate), 1660 and 1620 cm.$^{-1}$.

Anal. Calcd. for $C_{23}H_{31}O_7N$: C, 63.72; H, 7.21; O, 25.84; N, 3.23. Found: C, 62.93, 63.28; H, 6.99, 6.63; O, 26.30, 26.49; N, 3.61, 3.32.

After recrystallization from methylene dichloride–hexane and drying at 120° (0.1 mm.) for 16 hours it had m.p. 223–227°.

Anal. Calcd. for $C_{23}H_{31}O_7N \cdot {}^1/_2CH_2Cl_2$: C, 59.30; H, 6.78; O, 23.53; N, 2.94; Cl, 7.45. Found: C, 59.88, 60.05; H, 6.81, 7.01; O, 23.92; N, 3.77, 3.17; Cl, 7.37.

(v) The *anti*-oximino-ketone XV (330 mg.): recrystallized from ethyl acetate–methylene dichloride this formed prisms, m.p. 246–257°, $[\alpha]_D$ +130° (*c* 0.80), λ_{max}^{MeOH} 246 mμ (ε 5,700), λ_{max} (addition of 1% sodium hydroxide) 297 mμ (ε 11,800); γ_{max}^{KBr} 3650, 3300, 1720 and 1600 cm.$^{-1}$.

Anal. Calcd. for $C_{23}H_{31}O_7N$: C, 63.72; H, 7.21; O, 25.84; N, 3.23. Found: C, 63.56; H, 7.33; O, 26.05; N, 3.40.

Treatment of 17,20;20,21-Bismethylenedioxy-18-oximinocortisol (VIa) with Nitrous Acid.—The 18-oximino compound VIa (6.33 g.) in acetic acid (180 ml.) was treated at room temperature with 5% aqueous sodium nitrite (60 ml.). During 5 min. the color changed blue → green → yellow. After working up in the usual way the product was chromatographed over alumina (380 g.) in methylene dichloride containing increasing proportions of methanol. Elution with up to 1% methanol and crystallization from ethyl acetate gave the 18,21-methylenedioxy derivative VIIc as needles (2.97 g.), m.p. 194–216°. The analytical specimen, recrystallized from ethyl acetate–hexane, had m.p. 220–236°, $[\alpha]_D$ +182° (*c* 1.00), λ_{max} 240 mμ (ε 14,700); γ_{max}^{KBr} 3550, 1700, 1670 and 1620; $\gamma_{max}^{CHCl_3}$ 3600, 1700, 1670 and 1620 cm.$^{-1}$.

Anal. Calcd. for $C_{22}H_{28}O_6$: C, 68.02; H, 7.26; O, 24.71. Found: C, 67.77; H, 7.13; O, 24.94.

Further elution gave the oximino-lactone XXII (960 mg.) as prisms from ethyl acetate; m.p. 280–290°. The analytical specimen had m.p. 288–306°, λ_{max} 239 mμ (ε 16,200); γ_{max}^{KBr} 3350, 1705, 1665 and 1620 cm.$^{-1}$.

Anal. Calcd. for $C_{23}H_{29}O_7N$: C, 64.02; H, 6.77; O, 25.96; N, 3.25. Found: C, 64.27, 64.06; H, 6.79, 6.92; O, 26.17.

The monomethylenedioxy compound VIIc (500 mg.) in dioxane (6 ml.) and water (14 ml.) was treated in a stream of nitrogen (*ca.* 5 l. per hr.) at 0° with concd. sulfuric acid (1.2 ml.) and then heated on the steam-bath for 90 min. Addition of water and extraction into methylene dichloride gave, on crystallization of the product from ethyl acetate, 18,21-anhydro-17α-hydroxyaldosterone (VIIIa) as prisms (295 mg.), identical with material obtained earlier[2] from cortisol 3,20-bisethylene ketal. The stream of nitrogen is important since it removes the formaldehyde as it is formed. In its absence only intractable products result.

Reaction of the *anti*-Oximino-ketone XV.—The *anti*-oximino-ketone XV (3.0 g.) in pyridine (30 ml.) and phosphorus oxychloride (3.0 ml.) was kept at room temperature overnight and then poured onto a mixture of sodium bicarbonate and ice and extracted into methylene dichloride. After chromatography in methylene dichloride over alumina (100 g.) the product was crystallized from ethyl acetate–methylene dichloride to give the nitrile-lactone XVI as prisms (430 mg.), m.p. 275–278°, $[\alpha]_D$ −103° (*c* 0.80), γ_{max}^{KBr} 2240 and 1735 (no hydroxyl band); $\gamma_{max}^{CHCl_3}$ 2250 and 1730 cm.$^{-1}$.

Anal. Calcd. for $C_{23}H_{29}O_6N$: C, 66.49; H, 7.04; N, 3.37. Found: C, 66.58; H, 6.87; N, 3.36.

The nitrile-lactone XVI (250 mg.) in methanol (25 ml.) and 5% aqueous sodium hydroxide (12.5 ml.) was refluxed for 15 min. The acidic product crystallized from acetone–hexane to give the hydroxy-acid nitrile XVII (145 mg.), m.p. 229–236°, $[\alpha]_D$ −90° (*c* 0.90), γ_{max}^{KBr} 3500, 330–2600, 2220 and 1715; $\gamma_{max}^{CHCl_3}$ 3600, 3100, 2240 and 1715 cm.$^{-1}$.

Anal. Calcd. for $C_{23}H_{31}O_7N$: C, 63.72; H, 7.21; O, 25.84; N, 3.23. Found: C, 63.55; H, 7.10; O, 25.70; N, 3.62.

This hydroxy-acid nitrile (350 mg.), treated in methanol (10 ml.) with an excess of ethereal diazomethane, gave the desired methyl ester XVIIa. Crystallized from methylene dichloride–ethyl acetate this formed prisms, m.p. 199-203°, $[\alpha]D$ −78° (*c* 0.80); γ_{max} 3650, 2250 and 1740; γ_{max}^{KBr} 3700, 2240 and 1740 cm.$^{-1}$.

Anal. Calcd. for $C_{24}H_{33}O_7N$: C, 64.41; H, 7.43; O, 25.03; N, 3.13.

This methyl ester XVII (250 mg.) in acetone (10 ml.) was treated with an excess of 8 *N* aqueous chromic acid at room temperature for 5 min. Crystallization from ethyl acetate furnished ketone methyl ester nitrile as prisms, m.p. 181–183°, $[\alpha]D$ −62° (*c* 0.80); γ_{max}^{KBr} 2250, 1740 and 1705 cm.$^{-1}$.

Anal. Calcd. for $C_{24}H_{31}O_7N$: C, 64.70; H, 7.01; O, 25.14; N, 3.14. Found: C, 64.72; H, 7.14; O, 25.09; N, 3.15.

17α-Hydroxyaldosterone (XId).—18,21-Anhydro-17α-hydroxyaldosterone (VIIIa) (880 mg.) in glacial acetic acid (92 ml.), acetic anhydride (8.75 ml.) and ethyl acetate (1.05 ml.) was stirred at 13° during dropwise addition (5 min.) of 70% perchloric acid (0.78 ml.) and the stirring continued for 55 min. at 14–16°. The solution was poured rapidly onto ice and water (1400 ml.) containing 10 *N* ammonium hydroxide (95 ml.). After standing for 20 min. the suspension was filtered and the solid (240 mg.) was discarded. The filtrate was extracted into methylene dichloride. Removal of the solvent and crystallization from acetone–hexane gave 17α-hydroxyaldosterone 17,18,21-triacetate (XIe) (866 mg.) as prisms, m.p. 110–135°. The analytical specimen had m.p. 114–124°; $[\alpha]D$ +114° (*c* 1.00), +111° (*c* 0.80); λ_{max} 239 mμ (ε 17,200); γ_{max}^{KBr} 1755, 1675 and 1620 cm.$^{-1}$.

Anal. Calcd. for $C_{27}H_{34}O_9$: C, 64.53; H, 6.82; O, 28.65; (3)Ac, 25.7. Found: C, 64.84; H, 6.86; O, 28.56; Ac, 25.63, 25.45.

The triacetate XIe (602 mg.) in methanol (75 ml.) was stirred at 0° under nitrogen during rapid addition of 0.1 *N* aqueous sodium hydroxide (13.2 ml.) and the stirring continued for 1 hr. at this temperature. Water (75 ml.) containing glacial acetic acid (0.1 ml.) was added and then saturated aqueous sodium chloride solution (240 ml.). Thorough extraction (5 × 250 ml.) with methylene dichloride and subsequent crystallization from methanol gave 17α-hydroxy-aldosterone (XI) (289 mg.) as needles, m.p. 211–220°. The analytical specimen had m.p. 215–220°, $[\alpha]D$ +104° (*c* 0.50 in dioxane), λ_{max} 240 mμ (ε 16,300); γ_{max}^{KBr} 3450, 1655 and 1615 cm.$^{-1}$.

Anal. Calcd. for $C_{21}H_{28}O_6$: C, 67.00; H, 7.50. Found: C, 67.26; H, 7.53.

17α-Hydroxyaldosterone 17,18,21-triacetate (XIe) (160 mg.) in *tert*-butyl alcohol (6.5 ml.) containing pyridine (0.025 ml.) and selenium dioxide (65 mg.) was refluxed for 65 hr. Dilution with water, extraction into methylene dichloride and washing with water, ammonium sulfide solution, 0.2 *N* aqueous hydrochloric acid and finally saturated aqueous sodium chloride gave, after crystallization from ethyl acetate–hexane, 1-dehydro-17α-hydroxyaldosterone 17,18,21-triacetate (XIa), identical (m.p., mixture m.p. and infrared spectrum) with material obtained (see above) from prednisolone acetate.

1-Dehydro-9α-fluoro-17α-hydroxy-16α-methylaldosterone (XIg).—17,20;20,21-Bismethylenedioxydexamethasone (Ve) (prepared according to directions kindly provided by Dr. E. P. Oliveto, Dr. C. H. Robinson and their colleagues of the Schering Corp.[15]) (17.5 g.) was converted to the nitrite and the total product in toluene (650 ml.) containing a trace of pyridine was photolyzed at 25° for 2.6 hr. under nitrogen in the usual way.[2,4] The precipitate formed (11.3 g.) was filtered off and crystallized from acetone–hexane to furnish the 18-oximino derivative[15] (8.21 g.) as prisms, m.p. 288–297°. This oxime (2.0 g.) in glacial acetic acid (150 ml.) and water (50 ml.) was cooled to −2° and treated with sodium nitrite (3.75 g.) in water (25 ml.) for 15 min. at ambient temperature. Chromatography of the product over Florisil (50 g.) in methylene dichloride containing increasing proportions of methanol gave the monomethylenedioxy derivative VIId (1.02 g.). Recrystallized from ethyl acetate, this[15] had m.p. 243–260°.

Anal. Calcd. for $C_{23}H_{27}O_6F$: C, 66.01; H, 6.50. Found: C, 66.01; H, 6.81.

The monomethylenedioxy derivative VIId (1.55 g.) in glacial acetic acid (60 ml.) and acetic anhydride (16 ml.) was treated with stirring at 20° under nitrogen with aqueous 47% hydriodic acid (4 ml.) and the stirring continued at ambient temperature for 15 min. Dilution with 2% aqueous sodium thiosulfate, and extraction into methylene dichloride afforded, after working up in the usual way, a semi-solid gum. This was taken up in methanol (120 ml.), water (12 ml.) and 10% aqueous potassium carbonate (12 ml.) and kept under nitrogen at room temperature for 40 min. Removal of the methanol *in vacuo*, extraction with methylene dichloride and chromatography over alumina in this solvent containing increasing proportions of methanol, gave, after crystallization from acetone–hexane, 18,21-anhydro-1-dehydro-9α-fluoro-17α-hydroxy-16α-methylaldosterone (VIIIb) as prisms (680 mg.), m.p. 261–276°. The analytical specimen had m.p. 267–280°, $[\alpha]D$ +112° (*c* 0.80 in dioxane), λ_{max} 238 mμ (ε 17,400); γ_{max}^{KBr} 3500, 1730, 1660 and 1625 cm.$^{-1}$.

Anal. Calcd. for $C_{22}H_{25}O_5F$: C, 68.02; H, 6.49; F, 4.89. Found: C, 67.89; H, 6.71; F, 4.67.

This anhydro compound VIIIb (2.3 g.) in glacial acetic acid (240 ml.) and acetic anhydride (150 ml.) was treated with stirring at room temperature with 70% aqueous perchloric acid (3.0 ml.) and the stirring continued for 2.8 hr. The solution was poured into ice-water containing concd. aqueous ammonia (390 ml.). Extraction into methylene dichloride and crystallization from acetone–hexane afforded the 17,18,21-triacetate XIh as needles (2.3 g.), m.p. 254–267°. The analytical specimen had m.p. 258–269°, $[\alpha]D$ +64° (*c* 1.20), λ_{max} 237 mμ (ε 16,700); ν_{max}^{KBr} 1750, 1710, 1660, 1625 and 1610 cm.$^{-1}$.

Anal. Calcd. for $C_{28}H_{33}O_9F$: C, 63.15; H, 6.26; F, 3.57. Found: C, 63.31; H, 6.35; F, 3.24.

This triacetate XIh (500 mg.) in methanol (105 ml.) was stirred at 0° under nitrogen with 0.1 *N* aqueous sodium hydroxide (13.8 ml.) and the stirring continued for 45 min. Crystallization of the product from acetone–hexane–methanol gave 1-dehydro-9α-fluoro-16α-methyl-17α-hydroxyaldosterone (XIg) as minute plates (170 mg.), m.p. 255–265°. The analytical specimen had m.p. 256–265°, $[\alpha]D$ +36° (*c* 0.80 in dioxane), λ_{max} 239 mμ (ε 17,200); γ_{max}^{KBr} 3500, 1660, 1620 and 1610 cm.$^{-1}$.

Anal. Calcd. for $C_{22}H_{27}O_6F$: C, 65.01; H, 6.70; F, 4.67. Found: C, 65.24; H, 6.76; F, 4.39.

The above-mentioned compound (120 mg.) in pyridine (5 ml.) was treated with chromium trioxide (500 mg.) suspended in pyridine (10 ml.) and left at room temperature for 20 hr. Crystallization of the product from acetone–hexane gave the 18 → 11-lactone XIIb as needles, m.p. 225–236° (36 mg.). The analytical specimen had m.p. 232–237°, $[\alpha]D$ +118° (*c* 1.00), λ_{max} 236 mμ (ε 15,700); γ_{max}^{KBr} 1780, 1740, 1665, 1630 and 1610 cm.$^{-1}$.

Anal. Calcd. for $C_{20}H_{21}O_4F$: C, 69.75; H, 6.15. Found: C, 69.48; H, 6.06.

Treatment of the Monomethylenedioxy Derivative VIId with Hydrogen Bromide.—The monomethylenedioxy derivative VIId (2.4 g.) in glacial acetic acid (74 ml.) was treated with gaseous hydrogen bromide (28 g.) in the same solvent (94 g.) for 1.75 hr. at room temperature. The product was chromatographed over Florisil in methylene dichloride to give 16ξ-bromo-1-dehydro-9α-fluoro-16ξ-methylaldosterone 18,21-diacetate (XVIII) as prisms (264 mg.) from ethyl acetate–hexane; m.p. 196–199°. The analytical specimen had m.p. 202–206°, $[\alpha]D$ 0° (*c* 0.70), λ_{max} 237 mμ (ε 17,100); γ_{max}^{KBr} 1755, 1725, 1665, 1630 and 1610; $\gamma_{max}^{CHCl_3}$ 1755, 1735, 1670, 1635 and 1610 cm.$^{-1}$.

Anal. Calcd. for $C_{26}H_{30}O_7BrF$: C, 56.42; H, 5.46. Found: C, 56.28; H, 5.35.

This compound (82 mg.) in pyridine (2.5 ml.) was refluxed for 40 min. Chromatography of the product over alumina (2.0 g.) in methylene dichloride containing 1% methanol gave, after crystallization from acetone–hexane, a compound (28 mg.), m.p. 218–220°, λ_{max} 241 mμ (ε 23,600); γ_{max}^{KBr} 1755, 1675, 1635 and 1610 cm.$^{-1}$, which should be 1,16-bis-dehydro-9α-fluoro-16-methylaldosterone 18,21-diacetate. Lack of material presented a more thorough characterization of this substance.

Treatment of Cortisol with Hydrogen Bromide.—Cortisol (5.0 g.) in glacial acetic acid (60 ml.) was added to the same solvent (94 g.) containing gaseous hydrogen bromide (28 g.) at room temperature and left for 70 min. Chromatography of the product in methylene dichloride with increasing proportions of methanol over alumina (225 g.) gave 21-acetoxy-16ξ-bromopregna-4,9(11)-diene-3,20-dione (XXb) as needles (610 mg.) from acetone–hexane; m.p. 146–148°. Concentration of the mother liquors afforded additional material (270 mg.), m.p. 136–144°. The analytical specimen had m.p. 145–149°, $[\alpha]D$ +88° (*c* 1.35), λ_{max} 239 mμ (ε 17,500); γ_{max}^{KBr} 1755, 1735, 1670 and 1620 cm.$^{-1}$.

Anal. Calcd. for $C_{23}H_{29}O_4Br$: C, 61.47; H, 6.50; Br, 17.78. Found: C, 61.57; H, 6.31; Br, 17.69.

This compound (104 mg.) in pyridine (2.5 ml.) was heated under nitrogen for 1 hr. on the steam-bath followed by 40 min. under reflux. Crystallization of the product from acetone–hexane gave 21-acetoxypregna-4,9(11),16-triene-3,20-dione (XXIb) as needles (65 mg.), m.p. 128–130°, $[\alpha]D$ +189° (*c* 1.10), λ_{max} 239 mμ (ε 24,800); γ_{max}^{KBr} 1750, 1680, 1655, 1620 and 1595 cm.$^{-1}$. The data are in good agreement with those recorded in the literature.[16]

Anal. Calcd. for $C_{23}H_{28}O_4$: C, 74.97; H, 7.66. Found: C, 74.96; H, 7.68.

Treatment of Cortisone with Hydrogen Bromide.—Cortisone (5.0 g.) was treated with hydrogen bromide exactly as above to

furnish, after crystallization from acetone–hexane, 21-acetoxy-16-bromopregn-4-ene-3,11,20-trione (XXa) as needles (660 mg.), m.p. 166–168°. Concentration of the mother liquors gave additional material (420 mg.), m.p. 148–166°. The analytical specimen had m.p. 159–162°, $[\alpha]_D$ +180° (*c* 1.20), λ_{max} 238 mμ (ε 16,800); γ_{max}^{KBr} 1755, 1740, 1705, 1670 and 1620 cm.$^{-1}$.

Anal. Calcd. for $C_{23}H_{29}O_5Br$: C, 59.35; H, 6.28; Br, 17.17. Found: C, 59.26; H, 6.13; Br, 17.09.

This compound (100 mg.) in pyridine (2.5 ml.) was refluxed for 50 min. under nitrogen. Crystallization of the product from acetone–hexane gave 21-acetoxypregna-4,16-diene-3,11,20-trione (XXIa) as prisms (77 mg.), m.p. 189–191°, $[\alpha]_D$ +215° (*c* 1.10), λ_{max} 237 mμ (ε 24,800); these data are in good agreement with the literature.[16]

21-Acetoxypregna-4,16-diene-3,11,20-trione (XXIb) (2.09 g.) in glacial acetic acid (65 ml.) containing gaseous hydrogen bromide (12.5 g.) was left at room temperature for 1 hr. Crystallization of the product from acetone–hexane gave 21-acetoxy-16ξ-bromopregn-4-ene-3,11,20-trione (XXa) (2.1 g.) identical with the compound described above.

In a further experiment 21-acetoxy-16ξ-bromopregn-4-ene-3,11,20-trione (XXa) (140 mg.) in ethanol (5 ml.) was refluxed with Raney nickel (500 mg.) for 5 hr. Chromatography of the product over alumina (3.0 g.) in methylene dichloride gave 11-dehydrocorticosterone acetate (45 mg.), identical with an authentic specimen.

17,20;20,21-Bismethylenedioxy-11-epicortisol and Derivatives.—11-Epicortisol (200 g.) in chloroform (7 l.) and 12 *N* hydrochloric acid (1.7 l.) for one hr. Crystallization of the product from chloroform–ethyl acetate gave 17,20;20,21-bismethylenedioxy-11-epicortisol (90.7 g.), m.p. 225–242°. The analytical specimen crystallized from ethyl acerate–hexane as prisms, m.p. 241–246°, $[\alpha]_D$ −13° (*c* 1.10), λ_{max} 241 mμ (ε 17,000), γ_{max}^{KBr} 3550, 1650 and 1605 cm.$^{-1}$.

Anal. Calcd. for $C_{23}H_{32}O_6$: C, 68.29; H, 7.98; O, 23.73. Found: C, 67.99; H, 7.96; O, 23.80.

This compound (38.5 g.) in pyridine (250 ml.) was treated with *p*-toluenesulfonyl chloride (33 g.) for 64 hr. at room temperature. The product was taken up in glacial acetic acid (900 ml.) containing sodium acetate (36 g.) and refluxed for 2.75 hr. The reaction mixture was poured onto slurried ice (2500 ml.) containing 10 *N* ammonium hydroxide (1040 ml.) and the product filtered. Crystallization from acetone–hexane gave 17,20;20,21-bismethylenedioxy-9(11)-dehydrocortexolone (18.1 g.), m.p. 210–217°. The analytical specimen had m.p. 216–220°, $[\alpha]_D$ −26° (*c* 1.30), λ_{max} 239 mμ (ε 16,300), γ_{max}^{KBr} 1670 and 1620 cm.$^{-1}$.

Anal. Calcd. for $C_{23}H_{30}O_5$: C, 71.48; H, 7.82; O, 20.70. Found: C, 71.48; H, 7.82; O, 20.73.

This compound (18.0 g.) in freshly purified dioxane (260 ml.) containing 0.5 *N* aqueous perchloric acid (12.0 ml.) was treated with stirring with N-bromoacetamide (5.0 g.). The stirring was continued and after (two) 15-min. intervals further portions (5.0 g.) of N-bromoacetamide (total 15.0 g.) were added. After a further hour of stirring 10% aqueous sodium sulfite (220 ml.) was added and the 9,11-bromohydrin Vg was filtered off (17.0 g.), m.p. 175° dec. Recrystallization from ethyl acetate–methylene dichloride–hexane gave an analytical specimen, as prisms, m.p. 178° dec., $[\alpha]_D$ +25° (*c* 0.50 in tetrahydrofuran), λ_{max} 243 mμ (14,800); γ_{max}^{KBr} 3700, 1670 and 1630 cm.$^{-1}$.

Anal. Calcd. for $C_{23}H_{31}O_6Br$: C, 57.14; H, 6.46. Found: C, 57.20; H, 6.19.

Photolysis of 17,20;20,21-Bismethylenedioxy-9α-bromocortisol (Vg) Nitrite.—The bromohydrin (8.0 g.) in pyridine (180 ml.) was treated with an excess of nitrosyl chloride at room temperature in the usual way. Addition of ice and water gave a precipitate which was taken up in toluene (650 ml.) containing pyridine (0.1 ml.) and photolyzed for 1 hr. at 0° under nitrogen in the usual way.[2-4] Dilution with methylene dichloride (2 l.) and chromatography over Florisil (300 g.), eluting with methylene dichloride containing increasing proportions of methanol, gave the following compounds: (i) 17,20;20,21-bis-methylenedioxy-9α-bromocortisone (5%): recrystallized from acetone this formed prisms, m.p. 178–188° dec., $[\alpha]_D$ +111° (*c* 1.10), λ_{max} 238 mμ (ε 14,800); γ_{max}^{KBr} 1705, 1670 and 1625 cm.$^{-1}$.

Anal. Calcd. for $C_{23}H_{29}O_6Br$: C, 57.38; H, 6.07; O, 19.94; Br, 16.60. Found: C, 57.52; H, 6.28; O, 19.98; Br, 16.52.

(ii) 17,20;20,21-Bismethylene dioxy-9α-bromocortisol (Vg) (see above) (5%). (iii) 17,20;20,21-Bismethylene-dioxy-9α-bromo-18-oximinocortisol (VIb) (1.23 g.; 14.5%): eluted with methylene dichloride containing 2% methanol and crystallized from acetone–hexane, this formed prisms, m.p. 170° dec., $[\alpha]_D$ +20° (*c* 0.74 in dioxane), λ_{max} 243 mμ (ε 15,500); γ_{max}^{KBr} 3300, 3175, 1670 and 1630 cm.$^{-1}$.

Anal. Calcd. for $C_{23}H_{30}O_7BrN$; C, 53.91; H, 5.90; Br, 15.60; N, 2.73. Found: C, 53.91, 54.24; H, 5.96, 6.10; Br, 15.25; N, 2.91.

This oxime (950 mg.) in glacial acetic acid (70 ml.) and water (15 ml.) was treated at 0° with sodium nitrite (1.75 g.) in water (20 ml.) for 25 min. After dilution with water (400 ml.) containing concd. aqueous ammonia (70 ml.) and extraction in the usual way into methylene dichloride, the product was chromatographed over Florisil (30 g.) in methylene dichloride containing increasing proportions of methanol. Eluted first was the monomethylenedioxy derivative VIIe (585 mg.). Crystallized from acetone–hexane this had m.p. 180° dec., $[\alpha]_D$ −20° (*c* 0.84 in dioxane), λ_{max} 242 mμ (ε 16,300); γ_{max}^{KBr} 3550, 1700, 1665 and 1620 cm.$^{-1}$.

Anal. Calcd. for $C_{22}H_{27}O_6Br$: C, 56.54; H, 5.82. Found: C, 56.43; H, 5.76.

Eluted second was the oximino-lactone XXIIa (37 mg.). Crystallized from acetone–hexane this had m.p. 340° dec., $[\alpha]_D$ −38° (*c* 0.40 in dioxane), λ_{max} 240 mμ (ε 15,900); γ_{max}^{KBr} 3550, 1695, 1670 and 1620 cm.$^{-1}$.

Anal. Calcd. for $C_{23}H_{28}O_7BrN$: C, 54.12; H, 5.53; O, 21.94; Br, 15.66; N, 2.74. Found: C, 54.09, 54.05; H, 5.62, 5.62; O, 21.80, 21.75; Br, 15.94, 15.78; N, 3.06.

The monomethylenedioxy derivative VIIe (1.0 g.) in glacial acetic acid (60 ml.) was stirred vigorously with a moist (ethanol) zinc–copper couple (9.4 g.), prepared as described recently,[20] for 35 min. Crystallization of the product from acetone–hexane gave the debromination compound XXIV as needles (348 mg.), m.p. 165–173°. The analytical specimen had m.p. 165–171° dec., $[\alpha]_D$ +145° (*c* 0.50), λ_{max} 240 mμ (ε 17,400); γ_{max}^{KBr} 3500, 1660 and 1620 cm.$^{-1}$.

Anal. Calcd. for $C_{22}H_{28}O_6$: C, 68.02; H, 7.26. Found: C, 67.91; H, 7.53.

The oximino-lactone XXIIa (205 mg.) was stirred with zinc dust (1.0 g.) in glacial acetic acid (16 ml.) on the steam-bath for 10 min. Additional zinc dust (1.0 g.) was added and the stirring continued at room temperature for 18 hr. Crystallization of the product from methylene dichloride–acetone–hexane gave the 18-hydroxamic acid XXIII (66 mg.), m.p. 252–261°. Recrystallization from acetone gave the analytical specimen as plates, m.p. 255–258° dec., $[\alpha]_D$ +66° (*c* 0.40), λ_{max} 238 mμ (ε 15,900); γ_{max}^{KBr} 3550, 3200, 3100, 1680 and 1640 cm.$^{-1}$.

Anal. Calcd. for $C_{23}H_{29}O_7N$: C, 64.02; H, 6.77; O, 25.96; N, 3.25. Found: C, 63.69; H, 6.79; O, 25.73; N, 3.51.

The compound gave the deep red-violet color with ferric chloride typical of hydroxamic acids.

Acknowledgments.—We thank Dr. M. M. Pechet for his interest and encouragement and Miss L. Gendron and Mrs. C. Pantuck for their able assistance throughout the course of this work.

(20) D. H. R. Barton and P. T. Gilham, *J. Chem. Soc.* 4596 (1960).