3.94. A sample of the product was dried at 110° *in vacuo* for 12 hr.

Anal. Calcd. for $C_{56}H_{85}N_{15}O_{17}$: C, 54.22; H, 6.91; N, 16.94. Found: C, 54.05; H, 7.16; N, 17.36.

For the paper chromatography of the synthetic bradykinin, five different solvent systems were employed: *t*-butyl alcohol:acetic acid:water (2:1:1); benzene: *n*-butyl alcohol: pyridine:water (1:5:3:3); *n*-butyl alcohol saturated with 3% ammonium hydroxide; *n*-butyl alcohol: 2.5% phenol; 2% piperidine-water saturated; isopropyl alcohol: concd. ammonium hydroxide:water (70:5:25). The corresponding R_f values obtained were 0.64; 0.1; 0.175; 0.108; 0.44. The spots were developed with ninhydrin, Bromphenol Blue, and Sakaguchi reagents and in all cases only single spots were observed. Paper electrophoresis of the final product was carried out in acetate buffer, pH = 5.6, using a constant current of 30 milliamp. for 3 hr. The product migrated as a single component toward the cathode a distance of 6.7 cm. from the origin.

High voltage electrophoresis[16] of bradykinin gave a well defined single spot with Sakaguchi reagent. The peptide migrated 11 to 12 cm. toward the cathode during 60 min. at a voltage of 43 v. per cm. using a pyridine acetate buffer, pH 3.5, with Varsol as a paper coolant.

(16) The authors wish to express their sincere appreciation to Dr. Ervin G. Erdös of the Mellon Institute for kind permission to publish this work.

The synthetic nonapeptide was assayed on the guinea-pig ileum for its bradykinin activity and was found to possess the full potency of natural trypsin bradykinin.[17]

A previous sample of synthetic nonapeptide which appeared less pure by paper chromatography and paper electrophoresis possessed bradykinin activity,[18,19] but was found to be about 75% as active as the pure synthetic material described above.

Acknowledgment. We wish to thank Mr. C. E. Childs and his staff for the microanalyses which are reported and Dr. J. M. Vandenbelt, Mrs. Carola Spurlock, and Mrs. Vivien Lee for the optical rotations.

ANN ARBOR, MICH.

(17) We are indebted to Dr. H. O. J. Collier and Miss P. G. Shorley, Parke, Davis and Co., Hounslow, England, for the biological comparison of the nonapeptide with natural bradykinin.

(18) P. G. Shorley and H. O. J. Collier, *Nature*, **188**, 999 (1960).

(19) G. P. Lewis, *Nature*, **188**, 999 (1960).

[CONTRIBUTION FROM THE ORGANIC CHEMICAL RESEARCH SECTION, LEDERLE LABORATORIES, A DIVISION OF AMERICAN CYANAMID CO.]

Preparation of 6-Methoxycorticoids

MILTON HELLER AND SEYMOUR BERNSTEIN

Received February 22, 1961

The synthesis of 6α- and 6β-methoxycortisone, -hydrocortisone, -prednisolone, and 6α-methoxy-9α-fluoroprednisolone is described.

The report[1] that a methoxy function has been found on metabolites of known active steroid hormones, prompts one to synthesize this type of compound in the corticoid field. Corticoids with a methoxyl group at positions C-9[2] and C-16[3] of the steroid molecule have been described. It is the purpose of this report to detail the synthesis of C-6 methoxylated corticoids.[4]

Treatment of a suspension of 21-acetoxy-5ξ,6ξ-epoxy-3-ethylenedioxy-17α-hydroxy-pregnene-11,-20-dione (I)[5] (mixture of α- and β-epoxides) in methanol with 70% perchloric acid for twenty-two hours yielded 6β-methoxycortisone acetate (IIa) after reacetylation. This structure was supported by an analysis for a methoxyl function and by the ultraviolet absorption spectrum, which showed a peak at 230 mμ. It is most probable that part of I which existed as the 5α,6α-epoxide was opened under the acidic conditions in methanol to an intermediate 5α-hydroxy-6β-methoxy-3-one, which was further dehydrated to the 6β-methoxy-Δ⁴-3-one (IIa). The 21-acetate IIa was then easily saponified to 6β-methoxycortisone (IIb). The hypsochromic effect (8 mμ) and the lowering of the molecular extinction coefficient by about 3000 in the ultraviolet spectra of IIa or IIb when compared to the spectra of cortisone acetate or cortisone strongly suggests the 6β-methoxyl configuration in IIa and IIb. It is, of course, well known that a 6β-hydroxy or acetoxy group exerts a hypsochromic effect of 3–5 mμ[5,6] on the ultraviolet spectrum of a Δ⁴-3-one. Further proof of this configuration is discussed later. The small shift in the conjugated carbonyl absorption of

(1) S. Kraychy and T. F. Gallagher, *J. Am. Chem. Soc.*, **79**, 754 (1957); J. Fishman and T. F. Gallagher, *Arch. Biochem. and Biophys.*, **77**, 511 (1958); L. Axelrod, P. Narasimba Rao, and J. W. Goldzieher, *Arch. Biochem. and Biophys.*, **87**, 152 (1960).

(2)(a) J. Fried and E. F. Sabo, *J. Am. Chem. Soc.*, **79**, 1130 (1957); (b) S. Bernstein, R. H. Lenhard, W. S. Allen, M. Heller, R. Littell, S. M. Stolar, L. I. Feldman, and R. H. Blank, *J. Am. Chem. Soc.*, **81**, 1689 (1959).

(3) W. T. Moreland, R. G. Berg, D. P. Cameron, C. E. Maxwell III, J. S. Buckley, and G. D. Laubach, *Chemistry & Industry*, 1084 (1960); S. Bernstein, M. Heller, and S. M. Stolar, *Chemistry & Industry*, 516 (1961).

(4) The only C-6 ethers reported to date in the literature are revealed by A. Bowers, E. Denot, R. Urquiza, and L. M. Sanchez-Hidalgo, *Tetrahedron*, **8**, 116 (1960).

(5) F. Sondheimer, O. Mancera, and G. Rosenkranz, *J. Am. Chem. Soc.*, **76**, 5020 (1954).

the infrared spectrum toward higher wave numbers[6a,7] for a C-6 substituted Δ^4-3-one was also observed.

In some runs a small amount of 21-acetoxy-17α-hydroxyallopregnane-3,6,11,20-tetrone (III) was also obtained as a by-product. This last compound was also prepared by hydrogen chloride treatment of the 6β-methoxy-Δ^4-3-one IIa.[8]

In a further attempt to determine the configuration of the grouping at C-6 in the above discussed methanol-perchloric acid cleavage of an epoxide, the same type of reaction was run on I using benzyl alcohol-perchloric acid.[11] In this case 21-acetoxy-6β-benzyloxy-5α,17α-dihydroxypregnane-3,11,20-trione (IV) was isolated plus a fair amount of the tetrone III. It is possible the acid concentration in benzyl alcohol is not as great as in methanol so that considerable amounts of the 5α-hydroxy-6β-alkoxy intermediate can be isolated. Further treatment of the trione IV with perchloric acid in methanol followed by reacetylation yielded more tetrone III plus some amorphous material which had ultraviolet and infrared spectra indicative of the desired 21-acetoxy-6β-benzyloxy-17α-hydroxy-4-pregnene-3,11,20-trione (IIc). The latter compound proved difficult to crystallize and consequently work on this approach was abandoned.

It should be mentioned that an attempt was made to epimerize the 6β-methoxycortisone (IIb) using the procedure described by Cooley and associates[12] which involved treatment of a 6β-methyl-Δ^4-3-one with 0.05N sodium hydroxide. In the case of the 6β-methoxy compound IIb only starting material was obtained.

In a similar fashion to the experiments already described, 3,20-bisethylenedioxy-5α,6α-epoxypregnane-11β,17α,21-triol(V)[13] was treated in methanol with 70% perchloric acid to give only 11β,17α,21-trihydroxyallopregnane-3,6,20-trione (VII) which compared quite well with an authentic sample.[14] However, reaction of V in methanol for only thirty-five minutes with 10% perchloric acid afforded in satisfactory yield 20-ethylenedioxy-5α,11β,17α,21-tetrahydroxy-6β-methoxypregnan-3-one (VI). The fortunate fact that VI still contained a C-20 ethylene ketal moiety enabled the dehydration of the 5α-hydroxy group under basic conditions to be worked out with some care.

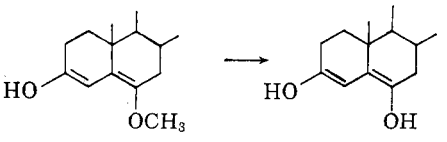
Treatment of the tetrol VI with 0.05N sodium hydroxide in methanol for eighteen hours yielded 20-ethylenedioxy-11β,17α,21-trihydroxy-6β-methoxy-4-pregnen-3-one (VIIIa) which again showed a large hypsochromic shift (10 mμ) in the ultraviolet spectrum. On the other hand, treatment of VI with 0.15N sodium hydroxide (or refluxing with 2.5% sodium hydroxide) in methanol afforded 20-ethylenedioxy-11β,17α,21-trihydroxy-6α-methoxy-4-pregnen-3-one (IXa). The latter compound IXa showed no hypsochromic effect in the ultraviolet spectrum. This difference in the ultraviolet absorption spectra and also the obvious need for more drastic basic conditions to epimerize the axial 6β-methoxy compound VIIIa to the equatorial 6α-methoxy compound IXa quite definitely established the stereochemistry of these C-6 epimers. It should be noticed that the basic conditions required for this epimerization are somewhat more strenuous than those needed for epimerization of the C-6 methyl compounds.[12,15] This explains the failure to epimerize 6β-methoxycortisone (IIb) under mild conditions as mentioned above.

Acetic acid hydrolysis of the 20-ketal-6β-methoxy-Δ^4-3-one (VIIIa) and the 20-ketal-6α-methoxy-Δ^4-3-one (IXa) gave 6β-methoxyhydrocortisone (Xa) and 6α-methoxyhydrocortisone (XIa), respectively. The features of the ultraviolet spectra,

(6)(a) P. T. Herzig and M. Ehrenstein, *J. Org. Chem.*, **16**, 1050 (1951); (b) C. P. Balant and M. Ehrenstein, *J. Org. Chem.*, **17**, 1587 (1952); (c) L. Dorfman, *Chem. Revs.*, **53**, 72 (1953), Table 12; (d) D. H. Peterson, S. H. Eppstein, P. D. Meister, B. J. Magerlein, J. C. Murray, H. M. Leigh, A. Weintraub, and L. M. Reineke, *J. Am. Chem. Soc.*, **75**, 412 (1953); (e) J. Romo, G. Rosenkranz, C. Djerassi, and F. Sondheimer, *J. Org. Chem.*, **19**, 1509 (1954); (f) C. Amendolla, G. Rosenkranz, and F. Sondheimer, *J. Chem. Soc.*, 1226 (1954).

(7) R. N. Jones and F. Herling, *J. Org. Chem.*, **19**, 1252 (1954).

(8) It is possible that the tetrone III in the original experiment was obtained directly from the 5ξ,6ξ-epoxide I as shown by Mr. Ehrenstein [ref. 6a and *J. Org. Chem.*, **13**, 214 (1948)]. However, in view of the lability of IIa to acid, it is possible to consider the tetrone arising from the already formed 6-methoxy compound. Thus, easy acid cleavage of the allylic ether grouping[9] would form an intermediate 6-hydroxy-Δ^4-3-one,[10] the precursor to a tautomeric rearrangement to the tetrone III. An alternative proposal to be considered would be enolization of the Δ^4-3-one under the acidic conditions to form an enol ether diene such as *A* followed by cleavage of the enol ether grouping to give the enol form *B* of the 3,6-dione system.



A B

(9) W. C. Wildman, *Chemistry & Industry*, 1090 (1956); R. Skrabal, *Z. physik. Chem.* (Leipzig), **A185**, 81 (1939).

(10) One of the epimers, 6β-hydroxycortisone acetate, has been previously prepared; see ref. (5).

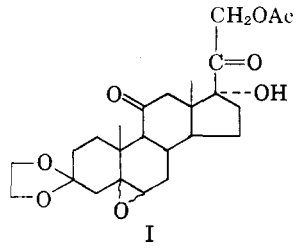
(11) It was hoped that compound IIc might be obtained in good purity so that preferential hydrogenation could be used to prepare 6β- (or 6α)-hydroxyhydrocortisone which could be compared to an authentic sample.[5]

(12) G. Cooley, B. Ellis, D. N. Kirk, and V. Petrow, *J. Chem. Soc.*, 4112 (1957).

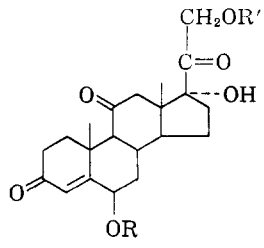
(13) R. Littell and S. Bernstein, *J. Am. Chem. Soc.*, **78**, 984 (1956).

(14) We thank R. Littell of these Laboratories for this sample.

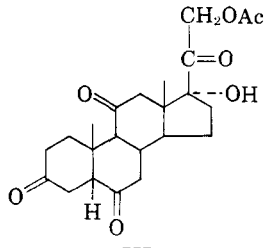
(15) G. B. Spero, J. L. Thompson, B. J. Magerlein, A. R. Hanze, H. C. Murray, O. K. Sebek, and J. A. Hogg, *J. Am. Chem. Soc.*, **78**, 6213 (1956); G. B. Spero, J. L. Thompson, F. H. Lincoln, W. P. Schneider, and J. A. Hogg, *J. Am. Chem. Soc.*, **79**, 1515 (1957).



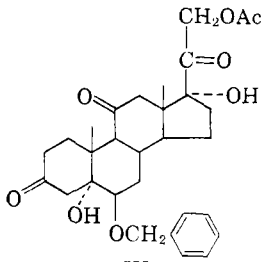
I



IIa. R = CH_3; R′ = Ac
IIb. R = CH_3; R′ = H
IIc. R = CH_2 ; R′ = Ac



III



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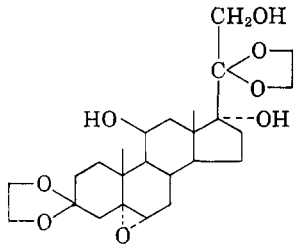
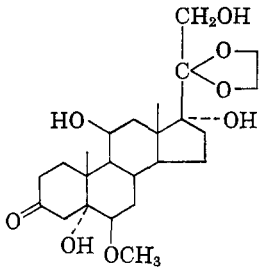
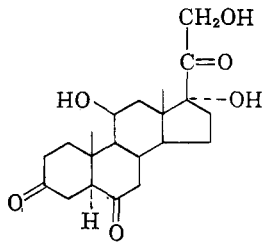


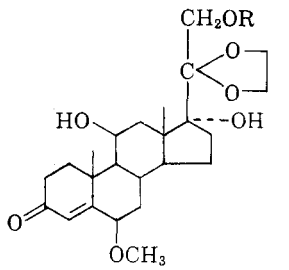
V



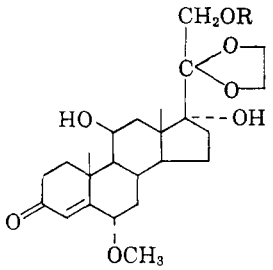
VI



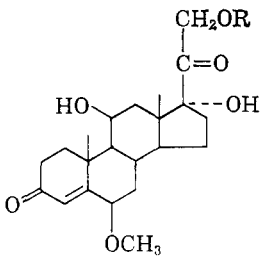
VII

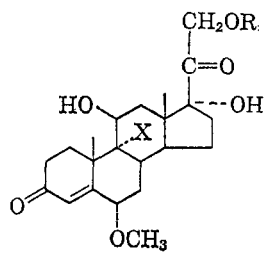


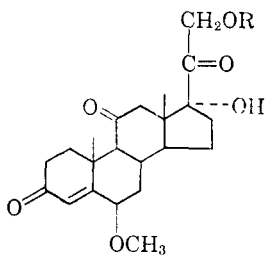
VIIIa. R = H
VIIIb. R = Ac



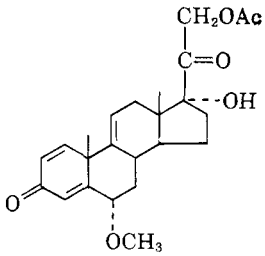
IXa. R = H
IXb. R = Ac







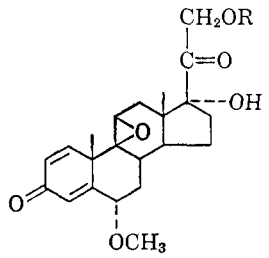
XIIa. R = H
XIIb. R = Ac



XIII

Xa. R = H
Xb. R = Ac
Xc. Δ^1; R = Ac
Xd. Δ^1; R = H

XIa. R = X = H
XIb. R = Ac; X = H
XIc. Δ^1; R = Ac; X = H
Xid. Δ^1; R = X = H
XIe. Δ^1; R = Ac; X = Br
XIf. Δ^1; R = Ac; X = F
XIg. Δ^1; R = H; X = F



XIVa. R = Ac
XIVb. R = H

mentioned previously are retained in these compounds. In the earliest acid hydrolyses of VIIIa-crude starting material was used. Careful chromatography of the product indicated that the more polar 6α-methoxyhydrocortisone (XIa) was present with the 6β-methoxy steroid Xa, which again indicates the equatorial nature of the C-6 position of XIa as compared to Xa.

6β-Methoxyhydrocortisone acetate (Xb) and 6α-methoxyhydrocortisone acetate (XIb) were obtained in the usual manner from Xa and XIa, respectively. The 20-ethylene ketal compound IXa gave after acetylation 21-acetoxy-20-ethylenedioxy-11β,17α-dihydroxy-6α-methoxy-4-pregnene-3 one (IXb). A small amount of 21-acetoxy-20-ethylenedioxy-11β,17α-dihydroxy-6β-methoxy-4-pregnene-3,20-dione (VIIIb) was also isolated from the acetylation of a crude mixture of 6β-methoxyhydrocortisone (Xa) and its 20-ketal VIIIa. The observation should be made at this time that the 6-methoxyhydrocortisones (Xa and XIa) and the 21-acetates (Xb and XIb) were very difficult to handle if one compound was contaminated to any degree with its epimer. The mixture of epimers invariably in each case gave solvated crystals which could not be crystallized apart, but had to be separated by chromatographic means. Once pure, the compounds were handled quite easily.

Oxidation of the 6β-methoxy-11β-ol 21-acetate Xb gave the already described 6β-methoxycortisone acetate (IIa), thereby confirming its stereochemistry at C-6. Similarly, oxidation of the 6α-methoxy-11β-ol 21-acetate XIb furnished 6α-methoxycortisone acetate (XIIb) which yielded 6α-methoxycortisone (XIIa) upon basic ester exchange conditions. Again the ultraviolet spectra were consistent with the previous dicussion.

Treatment of 6α-methoxyhydrocortisone acetate (XIb) with selenium dioxide in *t*-butyl alcohol[16] gave 6α-methoxyprednisolone acetate (XIc) which was converted to the free alcohol XId by reaction with potassium carbonate. In a similar fashion 6β-methoxyhydrocortisone acetate (Xb) afforded 6β-methoxyprednisolone acetate (Xc) which was saponified in turn to 6β-methoxyprednisolone (Xd).

It is interesting to notice that the position of the ultraviolet absorption maxima of the $\Delta^{1,4}$-6α-methoxy compounds (XIc and XId) and that of the $\Delta^{1,4}$-6β-methoxy compounds (Xc and Xd) were all at approximately 242 mμ. This is markedly different from the 6β-methoxy-Δ^4-compounds which had a hypsochromic shift of 8–10 mμ from the absorption peak of the 6α-methoxy-Δ^4-compounds.

Treatment of 6α-methoxyprednisolone (XId) with acid for four and one-half hours at room temperature resulted in no reaction at all. This was in contrast to the case of cleaving and tautomerizing the 6-methoxy-Δ^4-3-ones described above. It has been noticed[17] previously that a 7α-hydroxyl function which is normally very easily stripped out in acid when it is β to a Δ^4-3-keto system becomes quite stable when the A ring system becomes a $\Delta^{1,4}$-3-one moiety. Both of these results along with the previously mentioned ultraviolet spectral data indicate the C-6 position allylic to the Δ^4-double bond has quite altered properties when the Δ^4-double bond becomes further conjugated to the Δ^1-double bond.

In order to gain a more significant evaluation of the biological activities of the 6-methoxy compounds, it was thought desirable to prepare a 9α-fluoro derivative of this type of compound, since it is well known that the addition of the 9α-fluoro atom to the corticoid molecule significantly increases activity.[18]

Treatment of 6α-methoxyprednisolone acetate (XIc) with thionyl chloride in pyridine for ten minutes at −5° afforded 21-acetoxy-17α-hydroxy-6α-methoxy-1,4,9(11)-pregnatriene-3,20-dione (XIII). This compound was then treated in the usual manner[2] to elaborate the C ring halohydrin structure. Addition of the elements of hypobromous acid to XIII gave the bromohydrin XIe which was cyclized with potassium acetate in absolute alcohol to yield 21 - acetoxy - 9β,11β - epoxy - 17α - hydroxy - 6α-methoxy-1,4-pregnadiene-3,20-dione (XIVa). Treatment of the 9,11-epoxide XIVa with hydrogen fluoride gave the fluorohydrin XIf which was deacetylated to form 9α-fluoro-11β,17α,21-trihydroxy-6α-methoxy-1,4-pregnadiene-3,20-dione (6α-methoxy-9α-fluoroprednisolone) (XIg). In a preliminary experiment designed to prepare the fluorohydrin XIg, crude mother liquors from a preparation of the fluorohydrin acetate XIf were deacetylated to give a glass. Partition chromatography of this glass gave 9β,11β-epoxy-17α,21-dihydroxy-6α-methoxy-1,4-pregnadiene-3,20-dione (XIVb) plus some fluorohydrin triol XIg.

A most interesting observation may be noticed with respect to the optical rotations. In all the previously described 6-substituted Δ^4-3-ones[19] the 6α-epimer is more dextrorotatory than the 6β-epimer. In the 6-methoxy-11β-hydroxy cases, just the opposite fact pertains; the 6β-methoxy epimer is more positive in rotation than the 6α-methoxy epimer. This unexpected fact also is confirmed in the $\Delta^{1,4}$-3-one series of compounds. The situation, however, is more usual in the 6-methoxy-11-one series. The 6α-methoxy 11-one 21-acetate XIIb is more positive than its 6β-methoxy epimer IIa. The free alcohols IIb and XIIa have surprisingly almost identical optical rotations.

Another interesting observation is that all the 6β-alkoxy-Δ^4-3-one 21-acetates (IIa, IIc, and Xb) described have a doublet for the peak of the C-3 carbonyl grouping in the infrared spectra done in potassium bromide. Solution infrared spectra of IIa and IIc show only one absorption peak for the C-3 carbonyl function. Both halohydrin acetates (XIe and XIf) gave a doublet for the C—O acetate stretch band in the infrared spectra (potassium bromide). A solution spectrum gave only one peak for this band for the bromohydrin XIe.

Bioassay.[20] In a forty-eight-hour thymus involution assay (intact immature female rats) 6α-methoxy-9α-fluoroprednisolone (XIg) displayed a definite activity but less than one-fourth that of hydrocortisone. This compound was found not to produce sodium retention.

EXPERIMENTAL

Melting points. All melting points are uncorrected.

Absorption spectra. The ultraviolet spectra were determined in methanol; the infrared spectra (unless otherwise noted) were determined in a potassium bromide disk.

Petroleum ether. The fraction used, unless indicated otherwise, had a b.p. of 60–70°.

21-Acetoxy-17α-hydroxy-6β-methoxy-4-pregnene-3,11,20-trione (IIa). A. To a stirred suspension of 1 g. of 21-acetoxy-5

(16) C. Meystre, H. Frey, W. Voser, and A. Wettstein, *Helv. Chim. Acta*, **39**, 734 (1956); S. Szpilfogel, T. Posthumus, M. De Winter, and D. Van Dorp, *Rec. Trav. Chim.*, **75**, 475 (1956).

(17) A. L. Nussbaum, G. Brabazon, T. L. Poppen, and E. P. Oliveto, *J. Am. Chem. Soc.*, **80**, 2722 (1958).

(18) See ref. [2 (a)] and other references cited therein.

(19) A. Bowers, M. B. Sánchez, and H. J. Ringold, *J. Am. Chem. Soc.*, **81**, 3702 (1959) and references cited therein.

(20) The bioassays were carried out by the Pharmacological Research Department of the Experimental Therapeutics Research Section of these Laboratories.

5ξ,6ξ-epoxy-3-ethylenedioxy-17α-hydroxypregnane-11,20-dione (I) (mixture of α- and β-epoxides) in 50 ml. of methanol was added 0.4 ml. of 72% perchloric acid. After the suspension was stirred for 22 hr. at room temperature a clear solution resulted. Solid sodium bicarbonate was added, the mixture filtered and the solvent evaporated *in vacuo*. The resultant semisolid (1.73 g.) was acetylated with 5 ml. of pyridine and 2 ml. of acetic anhydride at room temperature for 16 hr., when the mixture was poured into water. Extraction with ethyl acetate and evaporation gave 0.90 g. of a glass which was chromatographed on silica gel. The ether-acetone (4:1) eluant yielded 0.13 g. of solid IIa from acetone-petroleum ether, m.p. 181–183°. The analytical sample from acetone-water had a m.p. of 186.5–188°; λ_{max} 230 mμ (ε 13,600); ν_{max} 3450, 1750, 1730, 1711, 1682, 1667, 1621, 1270, and 1231 cm.$^{-1}$; $\nu_{max}^{CHCl_3}$ 3450, 1750, 1730, 1710, 1681, and 1621 cm.$^{-1}$; $[\alpha]_D^{25}$ + 147° (chloroform).

Anal. Calcd. for $C_{24}H_{32}O_7$ (432.5): C, 66.65; H, 7.46; OCH_3, 7.40. Found: C, 66.61; H, 7.56; OCH_3, 6.79.

B. In a run identical to that above, 0.18 g. of IIa, m.p. 186–187°, was recovered from the ether-acetone (9:1) eluants from a silica gel column. The ether-acetone (4:1) eluants yielded 32 mg. of 21-acetoxy-17α-hydroxyallopregnane-3,6,11,20-tetrone (III), m.p. 234–235°, with an infrared absorption spectrum identical to that of the material described below.

C. A solution of 0.355 g. of crude 21-acetoxy-11β,17α-dihydroxy-6β-methoxy-4-pregnene-3,20-dione(IXb) in 6 ml. of pyridine was added to a suspension formed by adding 300 mg. of chromium trioxide to 3 ml. of pyridine. After standing at room temperature for 18 hr., the mixture was poured into water and filtered. The residue was boiled in ethyl acetate and filtered. The original filtrate was extracted with ethyl acetate and the combined ethyl acetate solutions were dried and the solvent removed under reduced pressure. Crystallization from dilute acetone gave 65 mg. of IIa, m.p. 180–182°. The infrared spectrum was identical to that of the analytical specimen prepared above.

17α,21-Dihydroxy-6β-methoxy-4-pregnene-3,11,20-trione (IIb). To a solution of 155 mg. of 6β-methoxycortisone acetate (IIa) in methanol placed under a nitrogen atmosphere and held at 0° was added 30 mg. of potassium hydroxide. After standing for 0.5 hr. at room temperature, the reaction mixture was neutralized with acetic acid and the solvent was evaporated. Crystallization from dilute methanol yielded 65 mg. of IIb, m.p. 233–235°. The analytical sample from methanol-water had a m.p. of 244.5–245°; λ_{max} 230 mμ (ε 14,500); ν_{max} 3500, 1710, 1670, and 1626 cm.$^{-1}$; $[\alpha]_D^{25}$ + 148° (methanol).

Anal. Calcd. for $C_{22}H_{30}O_6$ (390.46): C, 67.67; H, 7.74; OCH_3, 7.94. Found: C, 67.69; H, 7.87; OCH_3, 8.49.

21-Acetoxy-17α-hydroxyallopregnane-3,6,11,20-tetrone (III). To a solution of the acetate IIa (310 mg.) in 5 ml. of chloroform was added 35 ml. of chloroform previously saturated with hydrogen chloride. The solution was allowed to stand at room temperature for 4 hr. The chloroform solution was then washed with sodium bicarbonate solution, treated with activated carbon, filtered, and the solvent evaporated to give 180 mg. of III, m.p. 240.5–242.5°. Two crystallizations from acetone-petroleum ether gave pure tetrone III, m.p. 242–243°; ν_{max} 3430, 1755 (inflection), 1715, 1274, and 1238 cm.$^{-1}$; $[\alpha]_D^{24}$ + 68° (chloroform).

Anal. Calcd. for $C_{23}H_{30}O_7$ (418.47): C, 66.01; H, 7.23. Found: C, 66.01; H, 7.45.

Essentially the same experiment as above was performed at −10° to −15° to give the same product.

21-Acetoxy-6β-benzyloxy-5α,17α-dihydroxypregnane-3,11,-20-trione (IV). A. A slurry of 1.6 g. of the 5ξ, 6ξ-epoxy-21-acetate I (mixture of α- and β-epoxides) in 50 ml. of benzyl alcohol and 0.5 ml. of 72% perchloric acid was stirred for 17 hr. The resultant clear solution was neutralized with sodium bicarbonate, filtered, and the solvent removed by evaporation. Acetic anhydride (2 ml.) and pyridine (5 ml.) were added to the residue and the resultant solution was allowed to stand at room temperature overnight. The solution was then poured into water and the mixture was extracted with ethyl acetate. The extract was dried, treated with activated carbon, and the solvents were removed by evaporation to give a glass. Crystallization from acetone–petroleum ether gave 0.47 g. of IV, m.p. 243–245°. Several more crystallizations gave a m.p. of 251.5–253°; λ_{max} 248 mμ (ε 168), 252 mμ (ε 205), 258 mμ (ε 247), 264 mμ (ε 212), 268 mμ (ε 161 shoulder), and 290 mμ (ε 134); ν_{max} 3490, 1735, 1717, 1702, 1270, and 1233 cm.$^{-1}$; $[\alpha]_D^{24}$ + 8.6° (methanol).

Anal. Calcd. for $C_{30}H_{38}O_8$ (526.6): C, 68.42; H, 7.27. Found: C, 68.15; H, 7.49.

B. In an experiment run similar to the above on 5.27 g. of I, when the product was chromatographed on silica gel the ether elutions gave 0.605 g. of IV, m.p. 240–243°. The ether-acetone (4:1) eluates gave 0.14 g. of the tetrone III, m.p. 241–243°.

11β,17α,21-Trihydroxyallopregnane-3,6,20-trione (VII). A mixture of 1 g. of 3,20-bisethylenedioxy-5α,6α-epoxypregnane-11β,17α,21-triol (V) in 50 ml. of methanol and 0.5 ml. of 72% perchloric acid was stirred for 4 hr. at room temperature; solution occurred after 15 min. The solution was then neutralized with potassium bicarbonate and the solvents were removed *in vacuo*. Water was added and the resultant crude solid was collected. One recrystallization from acetone–petroleum ether gave 0.14 g. of VII, m.p. 246.5–249°. Repeated crystallizations from acetone gave a constant m.p. of 259–260°; ν_{max} 3490, 1709, and 1682 cm.$^{-1}$

Anal. Calcd. for $C_{21}H_{30}O_6$ (378.45): C, 66.64; H, 7.99. Found: C, 66.24; H, 8.28.

This compound was identical with an authentic sample[21] as shown by admixture melting point determination and the infrared spectral analysis.

20-Ethylenedioxy-5α,11β,17α,21-tetrahydroxy-6β-methoxy-pregnan-3-one (VI). To a stirred suspension of 10 g. of the 5α,6α-epoxide V in 500 ml. of methanol was added 10 ml. of 10% perchloric acid and the stirring continued for 35 min. at room temperature whereupon most of the solid went into solution. The resultant mixture was filtered to give 1.27 g. of starting material V. The filtrate was neutralized with a saturated sodium bicarbonate and almost all the solvent was then removed at room temperature. Filtration yielded 5.245 g. of VI, m.p. 257.5–260°. Further concentration of the mother liquor gave a second crop (1.625 g.) of the tetrol VI, m.p. 259–262°. Several crystallizations of this material from acetone afforded a constant m.p. of 258.5–260°; ν_{max} 3500, 1702, and 1092 cm.$^{-1}$; $[\alpha]_D^{25}$ − 11.5° (methanol).

Anal. Calcd. for $C_{24}H_{38}O_8$ (454.54): C, 63.41; H, 8.43. Found: C, 63.17; H, 8.71.

20-Ethylenedioxy-11β,17α,21-trihydroxy-6β-methoxy-4-pregnen-3-one (VIIIa). To a solution of 0.28 g. of the tetrol VI in 26 ml. of methanol was added 26 ml. of 0.1*N* sodium hydroxide and the mixture was allowed to stand at room temperature for 18 hr. The solution was then neutralized with acetic acid and the solvent evaporated at room temperature. The residue was washed with water, dissolved in acetone, and dried. Crystallization from acetone–petroleum ether gave 0.105 g. of VIIIa. Further crystallization from the same solvent pair gave m.p. 225.5–226.5°; λ_{max} 232 mμ (ε 12,700); ν_{max} 3500, 1669, 1625 (inflection), 1080, and 1039 cm.$^{-1}$; $[\alpha]_D$ + 51° (methanol).

Anal. Calcd. for $C_{24}H_{36}O_7$ (436.53): C, 66.03; H, 8.31. Found: C, 65.96; H, 8.62.

21-Acetoxy-20-ethylenedioxy-11β,17α-dihydroxy-6β-methoxy-4-pregnen-3-one (VIIIb). A mixture (4.07 g.) of 6β-methoxyhydrocortisone (Xa) and its 20-ethylene ketal VIIIa was acetylated in 15 ml. of pyridine and 5 ml. of acetic anhydride in the usual fashion. The resultant solid was crystallized from acetone to give 0.20 g. of VIIIb, m.p. 260–262°. Recrystallization from acetone afforded a product melting at

(21) This sample[14] had an m.p. of 262–264°; $[\alpha]_D^{25}$ + 11.5° (pyridine). *Anal.*: Found: C, 66.31, H, 8.14.

271.5–272.5°, λ_{max} 233 mμ (ε 13,900); ν_{max} 3460, 1738, 1665, 1229, and 1075 cm.$^{-1}$, $[\alpha]_D$ + 38° (pyridine).

Anal. Calcd. for $C_{26}H_{38}O_8$ (478.56): C, 65.21; H, 8.00. Found: C, 64.81; H, 7.94.

The mother liquors of the above crystallization were concentrated, and petroleum ether added to give 1.4 g. of 6β-methoxyhydrocortisone acetate (Xb), m.p. 181.5–186°.

20-Ethylenedioxy-11β,17α,21-trihydroxy-6α-methoxy-4-pregnen-3-one (IXa). A solution of 1 g. of the tetrol VI in 100 ml. of methanol was treated with 100 ml. of 0.3*N* sodium hydroxide for 18 hr. and then worked up exactly as was done to isolate VIIIa. This gave after crystallization from acetone 0.69 g. of IXa, m.p. 205–225°. Two crystallizations from acetone yielded the pure 6α-methoxy compound IXa, m.p. 238–239.5°; λ_{max} 242 mμ (ε 15,600); ν_{max} 3380, 1680, 1622, 1111, and 1055 cm.$^{-1}$; $[\alpha]_D^{25}$ + 35° (methanol).

Anal. Calcd. for $C_{24}H_{36}O_7$ (436.53): C, 66.03; H, 8.31. Found: C, 66.09; H, 8.47.

The above reaction has also been done in approximately the same yield by refluxing the steroid in a 2.5% sodium hydroxide methanol solution for 40 min.

21-Acetoxy-20-ethylenedioxy-11β,17α-dihydroxy-6α-methoxy-4-pregnen-3-one (IXb). Acetylation of 0.87 g. of crude IXa in 5 ml. of pyridine and 1 ml. of acetic anhydride gave after one crystallization from acetone 0.24 g. of IXb, m.p. 260–263.5°. Recrystallization from acetone gave a m.p. 265.5–266°, λ_{max} 242 mμ (ε 17,200); ν_{max} 3420, 1740, 1642, 1615, 1236, and 1099 cm.$^{-1}$; $[\alpha]_D^{25}$ + 98° (chloroform).

Anal. Calcd. for $C_{26}H_{38}O_8$ (478.56): C, 65.25; H, 8.00. Found: C, 65.26; H, 8.04.

11β,17α,21-Trihydroxy-6β-methoxy-4-pregnene-3,20-dione (Xa). A crude sample (4.4 g., mixture of epimers at C-6) of 20-ethylenedioxy-11β,17α,21-trihydroxy-6-methoxy-4-pregnen-3-one was heated in a mixture of 45 ml. of acetic acid and 30 ml. of water on a steam bath for 40 min. after solution occurred. It was then poured into water, and resultant solution was extracted with ethyl acetate, and the extract was washed with dilute sodium bicarbonate followed by saline solution. The dried extract was evaporated and the residue partitioned on a Celite[22] column using the solvent system cyclohexane:dioxane:water (5:5:1). The fractions collected from the latter half of the third hold back volume and first half of the fourth hold back volume were combined and evaporated to give after crystallization from acetone-petroleum ether 1.7 g. of Xa, m.p. 221–227.5°. Further crystallization from the same solvent pair gave a m.p. of 238–240°, λ_{max} 232 mμ (ε 13,100); ν_{max} 3480, 1718, 1670, and 1630 (shoulder) cm.$^{-1}$; $[\alpha]_D$ + 104° (methanol).

Anal. Calcd. for $C_{22}H_{32}O_6$ (397.48): C, 67.32; H, 8.22; OCH_3, 7.82. Found: C, 67.16; H, 8.31; OCH_3, 7.44.

Evaporation of the fifth hold back volume of the above described column gave after crystallization from ethyl acetate 0.345 g. of 6α-methoxy-hydrocortisone (XIa), m.p. 215–217°, which upon further crystallization gave a m.p. of 233–235°. This compound is characterized below.

21-Acetoxy-11β,17α-dihydroxy-6β-methoxy-4-pregnene-3,20-dione (Xb). A crude sample (0.75 g.) of 6β-methoxyhydrocortisone (Xa) was acetylated in the usual manner in 5 ml. of pyridine with 2 ml. of acetic anhydride. The resultant glass was submitted to partition chromatography on Celite[22] with the system heptane:ethyl acetate:methanol:water (3:2:3:2). The fraction consisting of the third hold back volume and the first part of the fourth hold back volume was evaporated and crystallized from acetone-petroleum ether to give 0.325 g. of Xb, m.p. 188–189°. Recrystallization from the same solvent pair afforded a m.p. of 190–191°; λ_{max} 232 mμ (ε 13,200); ν_{max} 3470, 1750 (shoulder), 1725, 1680, 1670, 1628, 1272, and 1235 cm.$^{-1}$; $[\alpha]_D^{25}$ + 115° (methanol).

Anal. Calcd. for $C_{24}H_{34}O_7$ (434.51): C, 66.34; H, 7.89; OCH_3, 7.13. Found: C, 66.18; H, 7.92; OCH_3, 7.13.

(22) Celite is Johns-Manville's registered trademark for diatomaceous silica products.

11β,17α,21-Trihydroxy-6α-methoxy-4-pregnene-3,20-dione (XIa). A quantity (1.12 g.) of the triol IXa was dissolved in 15 ml. of acetic acid by heating on the steam bath, 5 ml. of water was added and the heating continued for 1.5 hr. The reaction mixture was then worked up exactly as in the preparation of Xa except that purification by chromatography was not required. Concentration of the final ethyl acetate extract gave 0.51 g. of XIa, m.p. 228–231°. The pure sample from ethyl acetate had a m.p. 234–238°; λ_{max} 242 mμ (ε 13,900); ν_{max} 3470, 1711, 1660, and 1622 cm.$^{-1}$; $[\alpha]_D^{25}$ + 93.5° (methanol).

Anal. Calcd. for $C_{22}H_{32}O_6$ (397.48): C, 67.32; H, 8.22; OCH_3 7.82. Found: C, 67.30; H, 8.50; OCH_3, 7.81.

21-Acetoxy-11β-17α-dihydroxy-6α-methoxy-4-pregnene-3,20-dione (XIb). Acetylation of 0.73 g. of crude 6α-methoxyhydrocortisone (XIa) with 3 ml. of pyridine and 1 ml. of acetic anhydride in the usual fashion afforded 0.5 g. of crude residue, m.p. 176–178.5°. Crystallization from acetone–petroleum ether gave a m.p. of 183–184°[23]; λ_{max} 241 mμ (ε 13,700); ν_{max} 3490, 1750, 1730, 1665, 1625, and 1232 cm.$^{-1}$; $[\alpha]_D^{25}$ + 104° (methanol).

Anal. Calcd. for $C_{24}H_{34}O_7$ (434.51): C, 66.34; H, 7.89; OCH_3, 7.13. Found: C, 66.10; H, 7.74; OCH_3, 7.33.

21-Acetoxy-17α-hydroxy-6α-methoxy-4-pregnene-3,11,20-trione (XIIb). A solution of 1.26 g. of 6α-methoxyhydrocortisone acetate (XIb) in 12 ml. of pyridine was added to a suspension of 1.2 g. of chromium trioxide in 12 ml. of pyridine, and the resultant mixture was allowed to stand at room temperature for 17 hr. The mixture was worked up exactly as described in the preparation of IIa by the procedure labeled C. The resultant colored residue (0.64 g., m.p. 225–227°) was dissolved in methylene chloride, slurried with Magnesol and filtered. The filtrate was evaporated to give after crystallization from acetone-petroleum ether 0.38 g. of 6α-methoxycortisone acetate (XIIb), m.p. 229–231°; λ_{max} 238 mμ (ε 14,100); ν_{max} 3360, 1743, 1725, 1709, 1665, 1622, 1271, and 1232 cm.$^{-1}$; $[\alpha]_D^{25}$ +166° (chloroform).

Anal. Calcd. for $C_{24}H_{32}O_7$ (432.50); C, 66.65; H, 7.46; OCH_3, 7.40. Found: C, 66.25; H, 7.57; OCH_3, 7.14.

Slurrying the Magnesol residue with ether, then with ether-acetone (14:1) gave an additional 0.18 g. of XIIb, m.p. 225–227°.

17α,21-Dihydroxy-6α-methoxy-4-pregnene-3,11,20-trione (XIIa). To a solution of 165 mg. of the 21-acetate XIIb in 20 ml. of methanol placed under a nitrogen atmosphere was added 2.5 ml. of a solution of 150 mg. of potassium hydroxide in 15 ml. of methanol. The solution was allowed to stand at room temperature under nitrogen for 0.5 hr., then neutralized with acetic acid. Evaporation of the solvents gave a residue which was crystallized from acetone-petroleum ether to afford 70 mg. of XIIa, m.p. 201–202°; λ_{max} 238 mμ (ε 13,400); ν_{max} 3490, 1710, 1660, 1625, and 1095 cm.$^{-1}$; $[\alpha]_D^{26}$ +150° (methanol).

Anal. Calcd. for $C_{22}H_{30}O_6$ (390.46): C, 67.67; H, 7.74; OCH_3, 7.94. Found: C, 67.46; H, 7.86; OCH_3, 8.44.

21-Acetoxy-11β,17α-dihydroxy-6α-methoxy-1,4-pregnadiene-3,20-dione (XIc). A mixture of 1.27 g. of 6α-methoxyhydrocortisone acetate (XIb) and 1.38 g. of selenium dioxide in 127 ml. of *t*-butyl alcohol and 1.5 ml. of water was refluxed under nitrogen for 26 hr. when paper strip chromatography indicated the reaction had gone nearly to completion. The resultant mixture was filtered and evaporated. The residue was dissolved in chloroform, filtered once again, and the solution was washed with sodium bicarbonate solution and with saline, dried, and evaporated. The residue was dissolved in 50 ml. of ethanol and stirred for 2 hr. with 1 tea-

(23) In many later preparations of XIb, an m.p. of 207–207.5° was achieved, which was probably due to polymorphism, since the infrared spectra of the two samples were identical in solution, but somewhat different in a potassium bromide disk.

spoonful of deactivated Raney nickel,[24] filtered and the methanol removed to give 0.97 g. of crude solid. This was submitted to partition chromatography on Celite[22] using the system heptane (3 parts), ethyl acetate (2 parts), methanol (2 parts), and water (2 parts). Evaporation of holdback volumes seven and eight gave 65 mg. of starting material. Evaporation of holdback volumes nine and ten gave 0.3 g. of the $\Delta^{1,4}$-pregnadiene XIc, m.p. 219.5–222°. Crystallization of this sample from acetone-petroleum ether raised the m.p. to 221.5–224°,[25] λ_{max} 242 mμ (ε 14,800); ν_{max} 3410, 1750, 1730, 1661, 1619, 1608, and 1235 cm.$^{-1}$, $[\alpha]_D^{25}$ +59° (Methyl Cellosolve).

Anal. Calcd. for $C_{24}H_{32}O_7$ (432.50): C, 66.65; H, 7.46; OMe, 7.17. Found: C, 66.33; H, 7.79; OCH_3, 7.88.

11β,17α,21-Trihydroxy-6α-methoxy-1,4-pregnadiene-3,20-dione (XId). A solution of 0.61 g. of XIc in 60 ml. of methanol and 1.015 ml. of 10% potassium carbonate solution was allowed to stand under nitrogen for 20 min. After neutralization with acetic acid, the solution was concentrated at room temperature and water was added. The crude solid (0.375 g.) so obtained was collected and crystallized from acetone-petroleum ether to give pure XId, m.p. 249–250.5°; λ_{max} 242.5 mμ (ε 13,800); ν_{max} 3475, 1720, 1669, 1625, and 1612 (shoulder) cm.$^{-1}$, $[\alpha]_D^{25}$ + 65° (methanol).

Anal. Calcd. for $C_{22}H_{30}O_6$ (390.46): C, 67.67; H, 7.74; OCH_3 8.00. Found: C, 67.43; H, 7.87; OCH_3, 8.18.

21-Acetoxy-11β,17α-dihydroxy-6β-methoxy-1,4-pregnadiene-3,20-dione (Xc). A mixture of 1.605 g. of 6β-methoxyhydrocortisone acetate (Xb) and 1.74 g. of selenium dioxide in 160 ml. of *t*-butyl alcohol and 1.9 ml. of water was refluxed under nitrogen for 28 hr. An additional 1.75 g. of selenium dioxide was then added and the refluxing was continued under nitrogen for an additional 25 hr. when paper chromatographic analysis indicated the reaction had gone substantially to completion. The mixture was worked up as in the preparation of XIc. The fifth holdback volume yielded 0.12 g. of starting material while the sixth holdback volume gave 0.3 g. of Xc, m.p. 200–210°. An additional 45 mg., m.p. 204.5–208° was accumulated from the mother liquor. Crystallization of the combined solid from acetone-petroleum ether gave 205 mg. of 6β-methoxyprednisolone acetate (Xc), m.p. 214–215°; λ_{max} 242.5 mμ (ε 16,000); ν_{max} 3300, 1742, 1718, 1652, 1608, 1592 (infl.), and 1227 cm.$^{-1}$, $[\alpha]_D^{25}$ + 81° (Methyl Cellosolve).

Anal. Calcd. for $C_{24}H_{32}O_7$ (432.50): C, 66.65; H, 7.46; OCH_3 7.17. Found: C, 66.56, 66.20; H, 7.74, 7.52; OCH_3, 7.36.

11β,17α,21-Trihydroxy-6β-methoxy-1,4-pregnadiene-3,20-dione (Xd). A crude sample (200 mg.) of 6β-methoxyprednisolone acetate (Xc) was dissolved in 20 ml. of methanol and 0.33 ml. of 10% potassium carbonate under nitrogen at room temperature. After standing for 20 min., the solution was neutralized with acetic acid and evaporated. Crystallization of the residue from acetone-petroleum ether furnished 50 mg. of Xd, m.p. 221–225°. The analytical specimen had a m.p. of 223–225°, λ_{max} 242 mμ (ε 16,300); ν_{max} 3360, 1708, 1652, and 1609 cm.$^{-1}$, $[\alpha]_D^{25}$ + 79° (methanol).

Anal. Calcd. for $C_{22}H_{30}O_6$ (390.46): C, 67.67; H, 7.74; OCH_3, 8.00. Found: C, 67.49; H, 8.03; OCH_3, 7.71.

21-Acetoxy-17α-hydroxy-6α-methoxy-1,4,9(11)-pregnatriene-3,20-dione (XIII). To a solution of 0.375 g. of 6α-methoxyprednisolone acetate (XIc) in 5 ml. of pyridine at −5° was added 0.5 ml. of thionyl chloride. After standing at this temperature for 10 min., the solution was poured into ice water, extracted with ethyl acetate, and dried. Removal of the solvent gave 0.145 g. of crude triene XIII, m.p. 206–208°. Crystallization from methanol afforded the analytically pure sample, m.p. 226–228.5°; λ_{max} 239 mμ (ε 15,300); ν_{max} 3400 (shoulder), 3300, 1760, 1740, 1670, 1732 (shoulder), 1715, and 1232 cm.$^{-1}$; $[\alpha]_D^{25}$ + 30° (methanol).

Anal. Calcd. for $C_{24}H_{30}O_6$ (414.48): C, 69.54; H, 7.30; OCH_3 7.87. Found: C, 69.63; H, 7.56; OCH_3, 7.96.

21-Acetoxy-9α-bromo-11β,17α-dihydroxy-6α-methoxy-1,4-pregnadiene-3,20-dione (XIe). To a solution of the pregnatriene XIII (0.2 g.) in 8 ml. of dioxane and 1.6 ml. of water kept at 20° was added 0.8 ml. of 10% perchloric acid and 0.133 g. of *N*-bromoacetamide. After the solution remained at this temperature for 15 min., an excess of saturated sodium sulfite was added, followed by water. The mixture was extracted with chloroform, and the extract was washed with saline and dried. Evaporation at 45–50° gave a solid which was recrystallized from acetone-petroleum ether (b.p. 60–70°) to give 0.095 g., m.p. 207° dec.; λ_{max} 242 mμ (ε 14,300); ν_{max} 3430, 3320, 1768, 1755, 1730, 1665, 1627, 1612, and 1231 cm.$^{-1}$; $\nu_{max}^{pyridine}$ 3220, 1758, 1732, 1672, 1642, and 1622 (shoulder) cm.$^{-1}$; $[\alpha]_D^{25}$ + 135° (methanol).

Anal. Calcd. for $C_{24}H_{31}O_7Br$ (511.40): C, 56.36; H, 6.11; Br, 15.63; OCH_3, 6.08. Found: C, 56.65; H, 6.16; Br, 15.23; OCH_3, 6.80.

21-Acetoxy-9β,11β-epoxy-17α-hydroxy-6α-methoxy-1,4-pregnadiene-3,20-dione (XIVa). The total crude solid of the bromohydrin XIe obtained from a preparation starting with 0.5 g. of the pregnatriene XIII was dissolved in 100 ml. of absolute ethanol, and 750 mg. of dry potassium acetate was added. The resultant solution was refluxed for 18 hr., and the solvent was removed under reduced pressure. Water and ethyl acetate were added and the organic layer was separated. After being dried, the ethyl acetate extract was evaporated to give an oil which was crystallized from acetone-petroleum ether to yield 0.342 g. of XIVa, m.p. 222–228°. Recrystallization from the same solvent pair gave the analytical sample, m.p. 234–235°; λ_{max} 248 mμ (ε 15,900); ν_{max} 3400, 3300, 1751, 1730, 1667, 1631 (inf.), 1620, and 1228 cm.$^{-1}$; $[\alpha]_D^{25}$ + 58° (methanol).

Anal. Calcd. for $C_{24}H_{30}O_7$ (430.48): C, 66.96; H, 7.02; OCH_3, 7.21. Found: C, 66.91; H, 7.34; OCH_3, 7.44.

9β-11β-Epoxy-17α,21-dihydroxy-6α-methoxy-1,4-pregnadiene-3,20-dione (XIVb). Crude mother liquors (0.28 g.) from a preparation of the fluorohydrin XIa were dissolved in 27.5 ml. of methanol and 0.467 ml. of 10% potassium carbonate was added under nitrogen. After standing for 20 min. under nitrogen at room temperature, the solution was neutralized with acetic acid and the solvent was evaporated to give a glass. This glass was partitioned on a Celite[22] column with the solvent system heptane, ethyl acetate, methanol water (60:40:12:8). Evaporation of the fourth holdback volume gave a solid (0.095 g.) which was crystallized from from acetone-petroleum ether, m.p. 204–205.5°; λ_{max} 248.5 mμ (ε 15,300); ν_{max} 3400, 1709, 1666, 1625, and 1610 (shoulder) cm.$^{-1}$; $[\alpha]_D^{25}$ +42° (methanol).

Anal. Calcd. for $C_{22}H_{28}O_6$ (388.44): C, 68.02; H, 7.27; OCH_3, 7.94. Calcd. for $C_{22}H_{28}O_6 \cdot 1/4\ H_2O$ (392.95): C, 67.24 H, 7.31; OCH_3, 7.92. Found: C, 67.46; H, 7.58; OCH_3, 8.12.

The methanol wash from the above described column was resubmitted to a partition column on Celite[22] with the system heptane, ethyl acetate, methanol, water (50:50:12:8). Evaporation of the third holdback volumn gave 0.015 g. of solid, m.p. 258–259°. The infrared spectrum of this sample was identical to that of authentic XIg.

21-Acetoxy-9α-fluoro-11β,17α-dihydroxy-6α-methoxy-1,4-pregnadiene-3,20-dione (XIf). The 9β,11β-epoxide XIVa (0.48 g.) was dissolved in 30 ml. of methylene chloride and 2.5 ml. of tetrahydrofuran. The solution was cooled to −60° and 2 ml. of hydrogen fluoride was added. The resultant solution was allowed to stand at −5° for 3.5 hr., then poured slowly into a flask containing a saturated sodium bicarbonate solution and 100 ml. of methylene chloride. The methylene chloride layer was further washed with sodium bicarbonate solution, dried, and evaporated. Crystallization from acetone–petroleum ether gave a solid, m.p. 218.5–227°. Recrystallization from the same solvent pair afforded pure XIf, m.p. 250–250.5°; λ_{max} 238 mμ (ε 15,450);

(24) We are indebted for this procedure to Dr. Sidney Fox, formerly of the Chemical Production Section, Lederle Laboratories. The catalyst was prepared essentially according to P. L. Julian, C. C. Cochrane, A. Magnani, and W. J. Karpel, *J. Am. Chem. Soc.*, **78**, 3153 (1956).

(25) Later samples have given melting points as high as 227–228°.

ν_{max} 3420, 1769, 1756, 1730, 1670, 1629, 1612, and 1230 cm.$^{-1}$; $[\alpha]_D^{25}$ + 87° (methanol).

Anal. Calcd. for $C_{24}H_{31}O_7F$ (450.49): C, 63.98; H, 6.94; F; 4.22; OCH_3, 6.90. Found: C, 64.12; H, 7.26; F, 4.31, OCH_3, 7.58.

9α-Fluoro-11β,17α,21-trihydroxy-6α-methoxy-1,4-pregnadiene-3,20-dione (XIg). A solution of 0.26 g. of the fluorohydrin acetate XIf in 25 ml. of methanol under nitrogen was treated with 0.45 ml. of 10% potassium carbonate. After standing at room temperature under nitrogen for 20 min., the solution was neutralized with acetic acid and the solvent was evaporated. Crystallization from acetone-petroleum ether gave 0.12 g. of XIa, m.p. 263–264°; λ_{max} 238 mμ (ε 14,100); ν_{max} 3430, 1712, 1668, 1630, and 1613 cm.$^{-1}$; $[\alpha]_D^{25}$ + 72.5° (methanol).

Anal. Calcd. for $C_{22}H_{29}O_6F$ (408.45): C, 64.69; H, 7.16 F, 4.65; OCH_3, 7.61. Found: C, 64.79; H, 7.41; F, 4.90; OCH_3 8.70.

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PEARL RIVER, N. Y.

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An Optical Rotatory Dispersion Study of Side Chain Epimers in the Pregnane Series

WILLIAM A. STRUCK AND RONALD L. HOUTMAN

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A number of side chain epimers of pregnan-20-ones have been studied by means of optical rotatory dispersion in order to determine the consistency of the large negative effect encountered with the 17α side chain. This effect has been found to be the same throughout the entire series, and may be used with confidence to determine the configuration of the side chain in pregnan-20-ones complicated by substitution at C-16 in either α or β configuration, and by the presence of additional ketone functions at 3 and 11, even when the 3-ketone is conjugated with a 4 double bond.

The unique contributions of optical rotatory dispersion to the stereochemistry of steroids have been well established by Djerassi and co-workers. One of the more dramatic examples of this use is the differentiation of 5α and 5β isomers of steroids with ketones at C-3 or C-7, a distinction not readily made by other physical methods.[1] Similar striking behavior is noted for 17α- and 17β-acetyl side chains in the pregnane series, as exemplified by 3α-hydroxy-5β-pregnan-20-one acetate and 3α-hydroxy-5β,17α-pregnan-20-one acetate.[2] The 20-ketone in the normal (β) acetyl side chain gives a large positive Cotton effect curve, while the iso (α) side chain gives a Cotton effect which is almost the mirror image.

In the course of a study of 16-substituted pregnenedi- and triones, it became necessary to distinguish between α- and β-acetyl side chains in a group of compounds somewhat more complicated than those cited above. The complicating factors were the existence of a C-4 double bond in conjugation with the 3-ketone, and the presence of certain substituent groups in both the α and β configuration at C-16.

The presence of the conjugated ketone at C-3 would be expected to increase the rotation in a positive direction and introduce the fine structure characteristic of α,β-unsaturated ketones.[3] Substituent groups at C-16 would be expected to contribute effects that would vary depending on the group and its configuration, especially as C-16 would become asymmetric under these conditions.

The perturbing effect of substituents in the vicinity of optically active chromophores, such as the 20-ketone, has been well established. Several examples of α-halo ketones are available which show various vicinal effects.[4] Similarly alkyl substituents, especially in the vicinity of α,β-unsaturated ketones, may exert a profound vicinal action.[5] In general, the axial substituent has the larger effect. Substituents at C-16, therefore, might exert a sufficient vicinal action on the optically active chromophore at C-20 to complicate the behavior of the iso side chain.

In view of these facts it was considered necessary to examine as many pairs of side chain epimers as possible in order to ascertain whether the effect of the acetyl side chain in the α configuration, first noted by Djerassi,[2] was substantially consistent for 3-keto-Δ^4-pregnenes variously substituted at C-16.

The compounds of interest all had the Δ^4,3-ketone as well as the 20-ketone. Some had, in addition, a ketone at C-11, and most were substituted at C-16 with CH_3, CH_2OH, CH_2F, CO_2CH_3, or

(1) C. Djerassi, *Optical Rotatory Dispersion*, McGraw Hill, New York, 1960, p. 50.

(2) C. Djerassi, *Optical Rotatory Dispersion*, McGraw Hill, New York, 1960, p. 52.

(3) C. Djerassi, R. Riniker, and B. Riniker, *J. Am. Chem. Soc.*, **78**, 6377 (1956).

(4) C. Djerassi, J. Osiecki, R. Riniker, and B. Riniker, *J. Am. Chem. Soc.*, **80**, 1216 (1958).

(5) C. Djerassi, O. Halpern, V. Halpern, and B. Riniker, *J. Am. Chem. Soc.*, **80**, 4001 (1958).