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The Synthesis of 12α-Fluorohydrocortisone 21-Acetate and 12α-Chlorohydrocortisone

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The synthesis of 12α-fluorohydrocortisone 21-acetate and 12α-chlorohydrocortisone is reported. The key intermediate for this synthesis was 11β,12β-oxidoprogesterone which was prepared from both 12α-bromo-5β-pregnane-3α-ol-11,20-dione 3-acetate and Δ^{11}-5β-pregnene-3,20-dione. An attempt to prepare 12α-fluorohydrocortisone from 12α-fluoro-11β-hydroxyprogesterone failed.

The enhancement of the biological activity of steroids by the introduction of halogen and particularly fluorine at various positions in the molecule has been the subject of considerable interest in recent years.[1] A systematic study in this Laboratory[2] on the substitution of halogen in the 9α-position of steroids has shown that there is a direct relationship between the electronegativity of the 9α-substituent and the resulting increased biological activity of the steroid. Further, since substituents in the 12α-position bear the same steric relationship to 11-substituents as do those in the 9α-position, the study was extended by us[3-5] and others[6] to the synthesis of 12α-halogenated steroids with the result that the same relationship of biological activity to electronegativity of substituent prevailed. Only in the case of 12α-chlorocortisone[5] (XXVIIIa) where the steroid carried a 17α-hydroxyl group was no appreciable glucocorticoid activity observed. This anomaly has been attributed to the hydrogen bonding possible between the 17α-hydroxy group and the 12α-chlorine atom, both of which are in a 1,3-diaxial conformation.[1,7] In this paper we wish to present an extension of the above studies to the synthesis of 12α-fluorohydrocortisone 21-acetate (XXVIa) and 12α-chlorohydrocortisone (XXVII).

It was decided at the outset to use as intermediates the corresponding progesterone derivatives 12α-fluoro- and 12α-chloro-11β-hydroxyprogesterone[3] and to complete the synthesis by introduction of the 17α- and 21-hydroxyl groups. Several variants of our original synthesis[3] of the 12α-halo-11β-hydroxyprogesterones have been employed. One such route utilizes the readily available 12α-bromo-5β-pregnane-3α-ol-11,20-dione 3-acetate[8] (I). Hydrolysis of the latter with dilute perchloric acid in methanol gave 12α-bromo-5β-pregnane-3α-ol-11,20-dione (IV) which on selective reduction with sodium borohydride in tetrahydrofuran or isopropyl alcohol was converted into 12α-bromo-5β-pregnane-3α,20β-diol-11-one (V). Further reduction of V with lithium borohydride followed by elimination of hydrogen bromide with potassium carbonate gave the epoxide diol IIIa. In a simplified procedure reduction of I with lithium borohydride gave a mixture of the bromohydrin II and the 11β,12β-oxide III, which when treated *in situ* with dilute potassium carbonate yielded predominantly 11β,12β-oxido-5β-pregnane-3α,20β-diol (IIIa) together with a small amount of the 20α-hydroxy isomer IIIb.[9] Mild chromic acid oxidation[10] of IIIa or IIIb furnished 11β,12β-oxido-5β-pregnane-3,20-dione[3] (VI), which on treatment with bromine in acetic acid containing hydrogen bromide gave an excellent yield of 4β,12α-dibromo-5β-pregnane-11β-ol-3,20-dione (VII).

Compound VII could also be synthesized conveniently and in good yield from Δ^{11}-5β-pregnene-3,20-dione[11] (VIII) by reaction with N-bromoacetamide in the presence of perchloric acid[3] to give 12α-bromo-5β-pregnane-11β-ol-3,20-dione[8] (IX), which on bromination gave VII. Dehydrobromination with lithium chloride in dimethylformamide[12] furnished in an unexpected substitution reaction the known 12α-chloro-11β-hydroxyprogesterone[3,13] (Xa). When lithium chloride was replaced by lithium bromide and the reaction time extended from 2 to 4 hours the desired 12α-bromo-11β-hydroxyprogesterone[3] (Xb) was obtained in excellent yield.

(1) For review articles in this field see (a) J. Fried, "Some Recent Advances in Steroid Chemistry," Biological Activities of Steroids in Relation to Cancer, Academic Press, Inc., New York, N. Y., 1960; and (b) J. Fried and A. Borman, *Vitamins and Hormones*, **16**, 303 (1958).

(2) (a) J. Fried and E. F. Sabo, *J. Am. Chem. Soc.*, **75**, 2273 (1953); (b) **76**, 1455 (1954); (c) **79**, 1130 (1957); (d) R. Gaunt, J. H. Leathem, C. Howell and N. Antonchack, *Endocrinol.*, **50**, 521 (1952); (e) A. Borman, F. M. Singer and P. Numerof, *Proc. Soc. Exptl. Biol. Med.*, **86**, 570 (1954); (f) J. Fried, J. E. Herz, E. F. Sabo, A. Borman, F. M. Singer and P. Numerof, *J. Am. Chem. Soc.*, **77**, 1068 (1955); (g) J. Fried, A. Borman, W. B. Kessler, P. Grabowich and E. F. Sabo, *ibid.*, **80**, 2338 (1958).

(3) J. E. Herz, J. Fried and E. F. Sabo, *ibid.*, **78**, 2017 (1956).

(4) J. Fried, W. B. Kessler and A. Borman, *Ann. N. Y. Acad. Sci.*, **71**, 494 (1958).

(5) J. Fried, J. E. Herz, E. F. Sabo and M. H. Morrison, *Chemistry & Industry*, 1232 (1956).

(6) D. Taub, R. D. Hoffsommer and N. L. Wendler, *J. Am. Chem. Soc.*, **78**, 2912 (1956); **79**, 452 (1957).

(7) Support for this hypothesis has been obtained by converting 12α-fluoro-Δ^4-pregnene-11β,16α,17α-triol-3,20-dione, which in contrast to its 9α-fluorinated congener possesses no appreciable activity in the liver glycogen assay, into its highly active 16α,17α-acetonide (*cf.* ref. 1a, p. 14).

(8) J. von Euw, A. Lardon and T. Reichstein, *Helv. Chim. Acta*, **27**, 821 (1944).

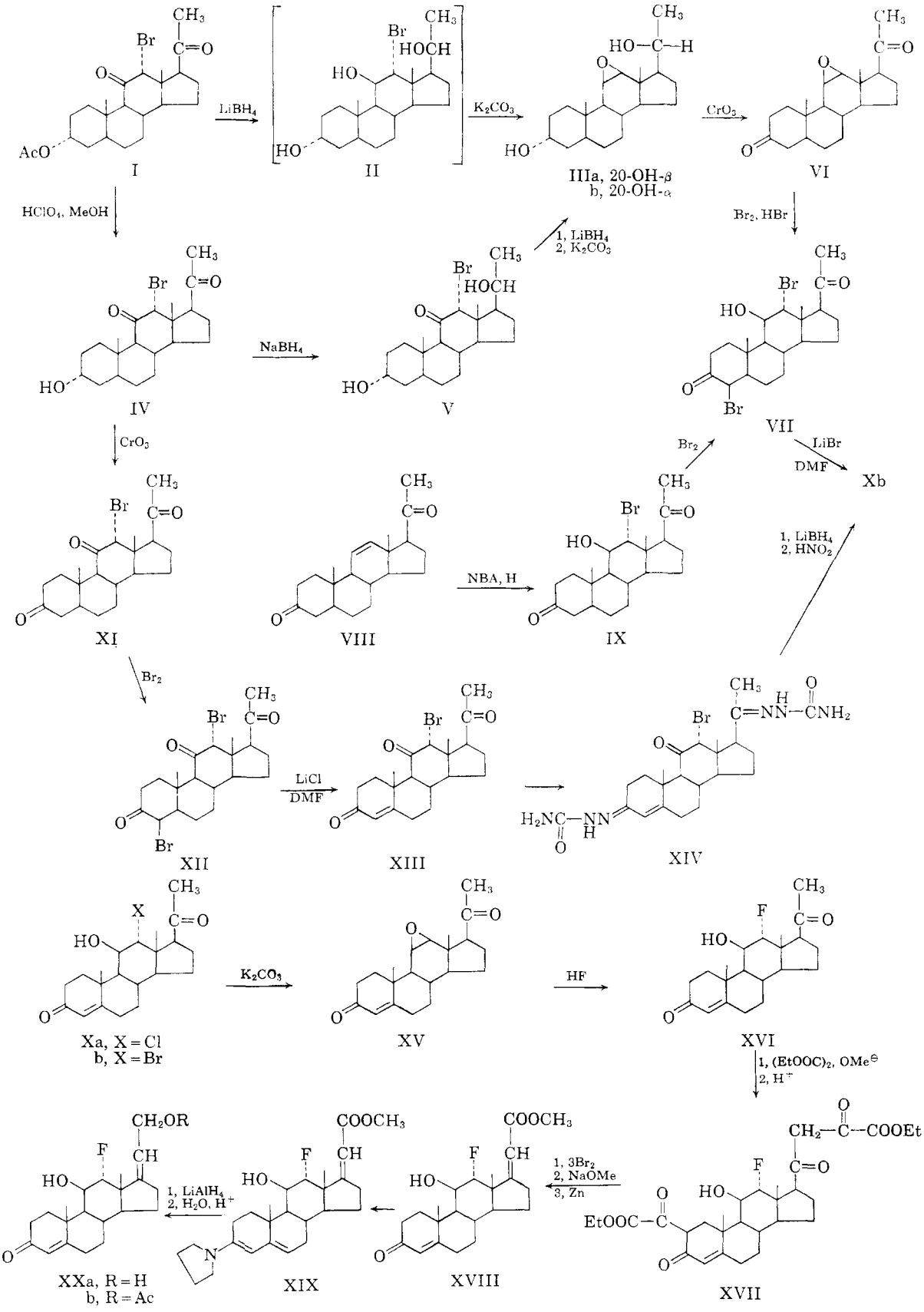
(9) The assignment of the 20β-configuration to the more abundant isomer is based on analogy with the work of others (E. P. Oliveto, C. Gerold and E. B. Hershberg, *J. Am. Chem. Soc.*, **76**, 6111 (1954); **76**, 6113 (1954); E. P. Oliveto and E. B. Hershberg, *ibid.*, **75**, 488 (1953); O. Mancera, H. Ringold, C. Djerassi, G. Rosenkranz and F. Sondheimer, *ibid.*, **75**, 1286 (1953)) who observed that reduction of 20-ketones by lithium borohydride or sodium borohydride led predominantly to the 20β-isomer.

(10) K. Bowden, I. M. Heilbron, E. R. H. Jones and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946).

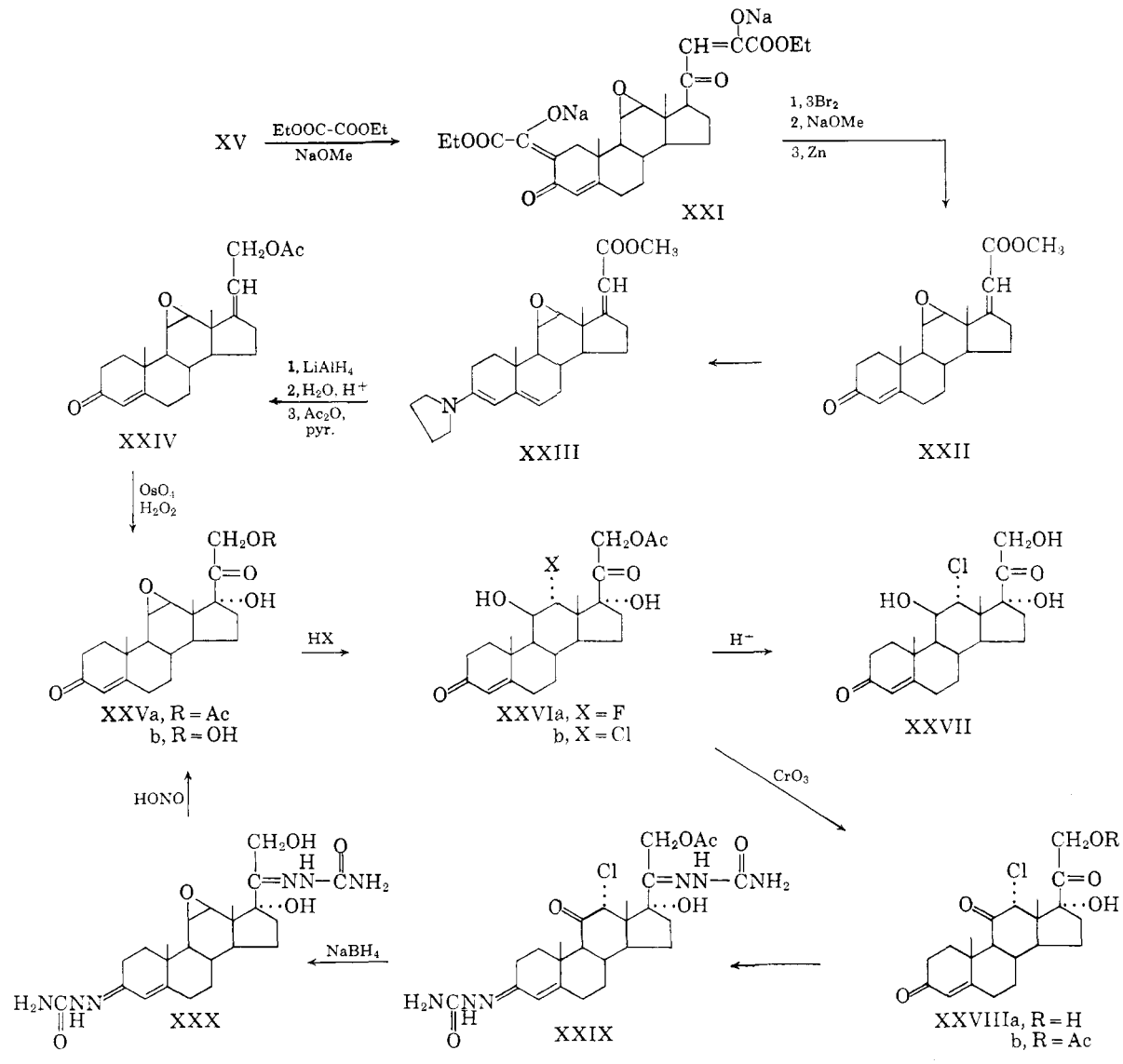
(11) P. Hegner and T. Reichstein, *Helv. Chim. Acta*, **26**, 721 (1943); G. Just and Ch. R. Engel, *J. Org. Chem.*, **23**, 12 (1958).

(12) R. P. Holysz, *J. Am. Chem. Soc.*, **75**, 4432 (1953).

(13) The retention of configuration suggested 11β,12β-oxidoprogesterone as a possible intermediate in this reaction. The likeliness of such a pathway is enhanced by the finding that 11β,12β-oxidoprogesterone on treatment with lithium chloride in dimethylformamide containing two mole equivalents of hydrogen bromide is indeed converted into 12α-chloro-11β-hydroxyprogesterone. The suggestion for this experiment originated with one of the referees and is hereby acknowledged with thanks.



Yet another though less efficient pathway to 12α-bromo-11β-hydroxyprogesterone involves oxidation of 12α-bromo-5β-pregnane-3α-ol-11,20-dione (IV) with chromic acid to give 12α-bromo-5β-preg-



nane-3,11,20-trione[8] (XI). Bromination of XI followed by dehydrohalogenation utilizing lithium chloride dissolved in dimethylformamide furnished 12α-bromo-11-ketoprogesterone (XIII). This compound was converted to the 3,20-bissemicarbazone (XIV), which on reduction with lithium borohydride followed by cleavage of the semicarbazone residues with nitrous acid gave X. Following the procedure described by Herz, *et al.*,[8] 12α-bromo-11β-hydroxyprogesterone and 12α-chloro-11β-hydroxyprogesterone could be converted to 12α-fluoro-11β-hydroxyprogesterone (XVI) *via* the 11β,12β-oxide XV.

There remained then to be accomplished the hydroxylation of the progesterone side chain to the cortical side chain by the versatile sequence of reactions described by the Upjohn group.[14] 12α-Fluoro-11β-hydroxyprogesterone (XVI) with excess diethyl oxalate in the presence of two equivalents of sodium methoxide furnished the 2,21-bisethyloxalyl derivative XVII, which on bromination (3 moles) yielded the 2,21,21-tribromo derivative. Without isolation the latter was treated with sodium methoxide to remove the oxalyl residues and to induce a Favorskii rearrangement[15] resulting in the 2-bromo derivative of XVIII, which (again without isolation) on reduction with zinc dust afforded methyl 12α-fluoro-$\Delta^{4,17(20)}$-pregnadiene-11β-ol-3-one-21-oate (XVIII).[16] Reaction of XVIII with pyrrolidine gave the dieneamine XIX, which on reduction with lithium aluminum hydride[17] followed by hydrolysis of the dieneamine

(14) (a) J. A. Hogg, P. F. Beal, A. H. Nathan, F. H. Lincoln, W. P. Schneider, B. J. Magerlein, A. R. Hanze and R. W. Jackson, *J. Am. Chem. Soc.*, **77**, 4436 (1955); (b) D. E. Ayer and W. P. Schneider, *ibid.*, **82**, 1249 (1960); (c) B. J. Magerlein, R. D. Birkenmeyer and F. Kagen, *ibid.*, **82**, 1252 (1960); (d) G. B. Spero, J. L. Thompson, B. J. Magerlein, A. R. Hanze, H. C. Murray, O. K. Sebek and J. A. Hogg, *ibid.*, **78**, 6213 (1956).

(15) For a recent review of the Favorskii Rearrangement of Haloketones see A. S. Kende, "Organic Reactions," Vol. XI, John Wiley and Sons, New York, N. Y., Inc., 1960, Chapter 4, pp. 261–316.

(16) No attempt was made to establish the configuration of the substituents attached to the $\Delta^{17(20)}$-double bond. However, on the basis of analogy with previous work (*cf.* ref. 14a) it is assumed that the $\Delta^{17(20)}$-enes reported in this paper possess the *cis* configuration.

(17) An attempt to effect this reduction utilizing lithium borohydride failed in that reduction of the dieneamine occurred to give what

and acetylation yielded 12α-fluoro-$\Delta^{4,17(20)}$-pregnadiene-11β,21-diol-3-one 21-acetate (XXb). Attempts to convert XXb to 12α-fluorohydrocortisone 21-acetate by the Miescher–Schmidlin[18] oxidation using catalytic amounts of osmium tetroxide with hydrogen peroxide in a 3-hour reaction furnished only starting material. When the reaction time was extended to 66 hours, attack was observed exclusively on the 4-double bond rather than the 17(20)-double bond as evidenced by the decrease in absorption at 238 mμ and the absence of a positive tetrazolium reaction.[19] Direct glycolation of XXb using a molar equivalent of osmium tetroxide also failed to give the desired product. Since $\Delta^{14,17(20)}$-pregnadiene-11β-21-diol-3-one 21-acetate[14a] reacts smoothly under these conditions to give hydrocortisone 21-acetate, the failure of XXb to react must be attributed to the presence of the 12α-fluorine atom, which due to steric and/or electronic interference prevents the approach of the osmium tetroxide to the 17(20)-double bond.[20]

In order to eliminate the influence of the 12α-substituent upon the hydrogen peroxide–osmium tetroxide oxidation, an alternate approach was considered employing an 11β,12β-oxide in the oxidation reaction to be followed by opening of the epoxide to the desired halohydrins. Henbest and Wrigley[21] have successfully converted a 5,6-fluorohydrin to the corresponding epoxide by the use of potassium *t*-butoxide in butanol. Such an attempt to convert XXb to the 11β,12β-oxide was unsuccessful. It became necessary, therefore, to prepare the required epoxide XXIV from 11β,12β-oxidoprogesterone (XV) by the sequence of reactions[22] applied previously to XVI, care being taken to use a limited amount of lithium aluminum hydride in the reduction of XXIII in order to prevent reductive opening of the epoxide ring.

Compound XXIV on reaction with hydrogen peroxide and osmium tetroxide was now converted smoothly in 50% yield to 11β,12β-oxidocortexolone 21-acetate (XXVa), which on hydrolysis with dilute alkali gave 11β,12β-oxidocortexolone (XXVb). Opening of the oxide ring in 11β,12β-oxidocortexolone 21-acetate with the appropriate hydrogen halide furnished 12α-fluorohydrocortisone 21-acetate (XXVIa) and 12α-chlorohydrocortisone 21-acetate (XXVIb). Hydrolysis of XXVIb with perchloric acid in methanol gave 12α-chlorohydrocortisone XXVII which could also be obtained directly from 11β,12β-oxidocortexolone (XXVb) by reaction with HCl in chloroform. Oxidation of XXVIb with chromic acid gave 12α-chlorocortisone 21-acetate (XXVIIIb) identical in all physical properties with the material prepared by Fried, *et al.*,[5] from hecogenin.

11β,12β-Oxidocortexolone (XXVb) has also been obtained by reduction of the bissemicarbazone of 12α-chlorocortisone 21-acetate[5] (XXIX) with sodium borohydride in aqueous tetrahydrofuran followed by removal of the semicarbazone groups with nitrous acid.

Neither 12α-chloro- nor 12α-fluorohydrocortisone acetate showed appreciable activity in the liver glycogen and sodium retention assays. These findings lend support to the hydrogen bonding hypothesis proposed on the basis of biological data obtained with other 12α-halo-17α-hydroxycorticoids.[1,7]

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Experimental[23]

12α-Bromo-5β-pregnane-3α-ol-11,20-dione (IV).—A suspension of 12α-bromo-5β-pregnane-3α-ol-11,20-dione 3-acetate[8] (I) (10.0 g.) in 0.275 *N* perchloric acid in methanol (200 ml.) was stirred at room temperature for 63 hours. The clear solution was then adjusted to *p*H 6.0 with 5% $NaHCO_3$, diluted with water (200 ml.) and extracted with chloroform (3 × 300 ml.). The combined chloroform extracts were washed with water (500 ml.), and evaporated to dryness *in vacuo*. Crystallization from acetone–hexane gave the pure 3α-ol IV (7.19 g.), melting at 158–160° $[\alpha]^{26}D$ +9.4° ($CHCl_3$); λ_{max}^{Nujol} 2.95, 5.85, 5.90 μ.

Anal. Calcd. for $C_{21}H_{31}O_3Br$ (411.38): C, 61.31; H, 7.59; Br, 19.40. Found: C, 61.72; H, 7.44; Br, 19.49.

11β,12β-Oxido-5β-pregnane-3α,20β-diol (IIIa). (a). From 12α-Bromo-5β-pregnane-3α-ol-11,20-dione 3-Acetate[8] (I).—To a stirred solution of lithium borohydride (256 mg.) in dry tetrahydrofuran (30 ml.), cooled to 0° by an ice–salt bath, was added dropwise a solution of 12α-bromo-5β-pregnane-3α-ol-11,20-dione 3-acetate (486 mg.) in dry tetrahydrofuran (20 ml.). The mixture was stirred at 0° for 5 hours and the excess lithium borohydride was then decomposed by the cautious addition of 10% acetic acid. The solution was diluted with water (20 ml.), extracted with chloroform (3 × 58 ml.) and the combined chloroform extracts washed with water (100 ml.) and evaporated to dryness *in vacuo*. The residue, consisting of a mixture of 20-epimeric 11,12-bromohydrins and 11,12-epoxides, was redissolved in 40 ml. of methanol, and 10% K_2CO_3 (4 ml.) was added dropwise with stirring. After 20 minutes the solution was neutralized with 10% acetic acid. Water (40 ml.) was then added and the methanol removed *in vacuo*. The residue was extracted with chloroform (2 × 50 ml.) and the chloroform extracts were evaporated to dryness. The residue was crystallized from acetone–hexane to give 11β,12β-oxido-5β-pregnane-3α,20β-diol (298 mg.) melting at 195–196°, $[\alpha]^{28}D$ +36.7° (ethanol), λ_{max}^{Nujol} 3.00 μ.

Anal. Calcd. for $C_{21}H_{34}O_3$ (334.48): C, 75.40; H, 10.24. Found: C, 75.30; H, 10.00.

Concentration of the mother liquors gave 11β,12β-oxido-5β-pregnane-3α,20α-diol (IIIb) (8 mg.) melting at 218–220° $[\alpha]^{22}D$ +47.1° (MeOH), λ_{max}^{Nujol} 3.00 μ.

Anal. Calcd. for $C_{21}H_{34}O_3$ (334.48): C, 75.40; H, 10.24. Found: C, 75.33; H, 9.83.

appears to be the 3β-pyrrolidyl-Δ^5-ene without reduction of the carbomethoxy group [λ_{max}^{alc} 221 mμ ($E_{1cm}^{1\%}$ 312)]. A similar reduction of 3-pyrrolidyl-$\Delta^{3,5}$-androstadiene-17β-ol with lithium borohydride to give 3β-pyrrolidyl-Δ^5-androstene-17β-ol (m.p. 235–236°) has been observed by Dr. F. L. Weisenborn of this Laboratory (private communication). Reductions of $\Delta^{3,5}$-enol acetates by lithium borohydride to give Δ^5-3β-alcohols have been reported by E. Schwenk, M. Gut and J. Belisle, *Arch. Biochem. Biophys.*, **31**, 456 (1951); T. F. Gallagher and B. Belleau, *J. Am. Chem. Soc.*, **73**, 4458 (1951); W. G. Dauben and J. F. Eastham, *ibid.*, **73**, 4463 (1951); J. Iriarte, C. Djerassi and H. J. Ringold, *ibid.*, **81**, 436 (1959).

(18) K. Miescher and J. Schmidlin, *Helv. Chim. Acta*, **33**, 1840 (1950).

(19) W. J. Mader and R. R. Buck, *Anal. Chem.*, **24**, 666 (1952).

(20) Difficulty in glycolation of a Δ^{14}-steroid having a 12α-bromine substituent has been reported by S. Bernstein and R. Littel, *J. Org. Chem.*, **24**, 871 (1959).

(21) H. B. Henbest and T. I. Wrigley, *J. Chem. Soc.*, 4765 (1957).

(22) In addition to XXII a small amount of a by-product was obtained which analyzed correctly for $C_{21}H_{30}O_5$, and which contained two methoxyl groups. The ultraviolet spectrum of this compound exhibited λ_{max}^{alc} 232 mμ (ε 23,800), which supports the presence of both the α,β-unsaturated ketone and α,β-unsaturated ester chromophores. On the basis of the above facts the compound is tentatively formulated as a 2- or 6-methoxy derivative of XXII.

(23) All melting points were taken in open capillaries and are uncorrected. Ultraviolet spectra were taken in absolute ethanol.

(b) From 12α-Bromo-5β-pregnane-3α-ol-11,20-dione (IV) *via* Sodium Borohydride Followed by Lithium Borohydride Reduction.—To a solution of sodium borohydride (309 mg.) in tetrahydrofuran (25 ml.) and water (5 ml.) a solution of 12α-bromo-5β-pregnane-3α-ol-11,20-dione (605 mg.) in tetrahydrofuran (10 ml.) was added and the resulting solution was left at room temperature for 5 hours. The excess reducing agent was decomposed with 10% acetic acid and the tetrahydrofuran was removed *in vacuo*. The residue was extracted with chloroform, the chloroform phase was washed with water and evaporated to dryness *in vacuo*. The residue on crystallization from aqueous methanol gave 12α-bromo-5β-pregnane-3α,20β-diol-11-one (V) (300 mg.) melting at 237–237.5°, $[\alpha]^{26}D$ − 33.0° (ethanol); λ_{max}^{Nujol} 3.00, 5.85 μ.

Anal. Calcd. for $C_{21}H_{29}O_3Br$ (413.39): C, 61.01; H, 8.04; Br, 19.33. Found: C, 61.42; H, 8.10; Br, 19.35.

Isopropyl alcohol could be substituted as solvent in place of the tetrahydrofuran and water mixture. Under these altered conditions the reaction was run at room temperature for 21 hours.

Further reduction of 12α-bromo-5β-pregnane-3α,20β-diol-11-one by lithium borohydride in tetrahydrofuran as described above, followed by epoxidation with potassium carbonate, gave 11β,12β-oxido-5β-pregnane-3α,20β-diol.

11β,12β-Oxido-5β-pregnane-3,20-dione (VI).—To a stirred solution of 11β,12β-oxido-5β-pregnane-3α,20β-diol (IIIa) (1.00 g.) in acetone (reagent grade) (100 ml.) cooled in an ice-bath a solution containing chromic anhydride (430 mg.), sulfuric acid (689 mg.) and water (2.3 g.) in 20 ml. acetone was added dropwise. After 20 minutes the excess oxidizing agent was decomposed with ethanol and the precipitated chromic sulfate was filtered and washed with acetone. The filtrate was diluted with water (100 ml.) and the acetone removed, *in vacuo*. The residue was extracted with chloroform (2 × 100 ml.) and the combined chloroform extracts were washed with water (2 × 100 ml.) and evaporated to dryness, *in vacuo*. Crystallization from acetone–hexane gave platelets of 11β,12β-oxido-5β-pregnane-3,20-dione (VI) (583 mg.) melting at 143–144°. The infrared spectrum of this compound is identical with that of an authentic sample.[8]

In like manner 11β,12β-oxido-5β-pregnane-3α,20α-diol could be oxidized to 11β,12β-oxido-5β-pregnane-3,20-dione.

12α-Bromo-5β-pregnane-11β-ol-3,20-dione[8] (IX).—To a solution of 100 g. (0.318 mole) of Δ^{11}-pregnene-3,20-dione[11] in 3 l. of dioxane contained in a 5-l. round-bottom flask, 1.7 l. of 0.167 *N* perchloric acid was added. N-Bromoacetamide (50.4 g., 0.365 mole) was then added with swirling until it dissolved completely. The solution was left in the dark at room temperature for 30 minutes, during which time it turned amber and the 12α-bromo-11β-hydroxy-5β-pregnane-3,20-dione crystallized. The excess N-bromoacetamide was decomposed by the addition of 5% sodium sulfite (color change from amber to straw yellow) and the precipitate filtered, washed with 1 l. dioxane–water (1:1) and dried to give 78.7 g. of IX[3], m.p. 231–233°, $[\alpha]^{23}D$ +76° (dioxane); λ_{max}^{Nujol} 2.96, 5.84, 5.94 μ.

The filtrate and washings were extracted with two 1-l. portions of chloroform. The combined chloroform extracts were neutralized with dilute $NaHCO_3$, washed with water and evaporated to dryness. The residue on leaching with acetone gave an additional 7.5 g. of 12α-bromo-5β-pregnane-11β-ol-3,20-dione. Addition of hexane to the acetone mother liquor followed by concentration gave 10 g. of $\Delta^{9(11)}$-5β-pregnene-12α-ol-3,20-dione,[3] m.p. 174–175°; λ_{max}^{Nujol} 2.92, 5.85–5.89 μ.

4β,12α-Dibromo-5β-pregnane-11β-ol-3,20-dione (VII). (a) From VI.—To a solution of 213 mg. of 11β,12β-oxido-5β-pregnane-3,20-dione (VI) in glacial acetic acid (15 ml.) a solution (1.13 ml.) containing bromine (98.2 mg./ml.) in glacial acetic acid was added dropwise after priming the bromination with a few drops of 11% HBr in acetic acid. Ten minutes after the addition of bromine was completed 10% sodium acetate solution (≈1 ml.) was added until the straw-yellow color disappeared. The acetic acid was then removed *in vacuo*. The residue was taken up in chloroform (25 ml.), washed with water (2 × 25 ml.) and evaporated to dryness *in vacuo*. The residue was crystallized from acetone–hexane to give 4β,12α-dibromo-5β-pregnane-11β-ol-3,20-dione (VII) (218 mg.), m.p. (165°) 212–214°; $[\alpha]^{24}D$ + 80° ($CHCl_3$); λ_{max}^{Nujol} 2.96, 5.78, 5.93 μ.

Anal. Calcd. for $C_{21}H_{30}O_3Br_2$ (490.28): C, 51.45; H, 6.16; Br, 32.60. Found: C, 51.19; H, 6.31; Br, 33.16.

(b) From IX.—To a stirred solution of 86.2 g. (0.21 mole) of 12α-bromo-5β-pregnane-11β-ol-3,20-dione in 4.5 l. of chloroform and 4.5 l. of acetic acid, a solution of bromine (115 mg./ml.) and sodium acetate (37 mg./ml.) in acetic acid was added dropwise over a period of about 1 hour until 34.6 g. (.216 mol) of bromine had been added. (The bromination was primed by the addition of 2 ml. of 33% HBr in acetic acid.) Four liters of water was added, the chloroform phase separated off and washed twice with 4 l. of water. The chloroform was then neutralized with $NaHCO_3$ solution, washed again with water and evaporated to dryness. Crystallization of the residue from acetone–hexane gave 67.3 g. of 4β,12α-dibromo-5β-pregnane-11β-ol-3,20-dione, m.p. 217–219°; λ_{max}^{Nujol} 2.96, 5.78, 5.93 μ.

4β,12α-Dibromo-5β-pregnane-3,11-20-trione (XII).—A solution of 12α-bromo-5β-pregnane-3,11,20-trione[3] (199 mg.) prepared from compound IV by the chromic acid oxidation procedure described above for the preparation of compound VI, in glacial acetic acid was treated dropwise with a solution (0.72 ml.) of bromine (112 mg./ml.) in acetic acid after priming with a drop of 11% HBr in acetic acid. The solution was then poured into cold water (30 ml.) and the precipitate filtered, washed with water, 5% sodium bicarbonate and then water again. Recrystallization from ethanol gave 4β,12α-dibromo-5β-pregnane-3,11,20-trione (200 mg.) melting at 164–165°; λ_{max}^{Nujol} 5.79, 5.86 μ.

Anal. Calcd. for $C_{21}H_{28}O_3Br_2$ (488.27): C, 51.65; H, 5.78; Br, 32.74. Found: C, 51.71; H, 5.61; Br, 34.00.

12α-Bromo-11-ketoprogesterone (XIII).—A solution of 4β,12α-dibromo-5β-pregnane-3,11,20-trione (5.80 g.) and lithium chloride (1.90 g.) in dimethylformamide (75 ml.) was heated on a steam-bath for 3 hours. It was then concentrated *in vacuo* to about 40 ml. and water (15 ml.) was added to the hot solution. On cooling, crystalline needles separated which were filtered, washed with water and dried; weight 2.59 g., m.p. 165–167°, $[\alpha]^{24}D$ +82.4° ($CHCl_3$), $\lambda_{max}^{methanol}$ 237 mμ (ε 15,200); λ_{max}^{Nujol} 5.85, 6.00, 6.18 μ. The properties of the above sample are identical with those of an authentic sample of 12α-bromo-11-ketoprogesterone.[3]

12α-Bromo-11-ketoprogesterone-3,20-bissemicarbazone (XIV).—To a warm solution of 12α-bromo-11-ketoprogesterone (500 mg.) in methanol (20 ml.) and water (5 ml.), semicarbazide hydrochloride (825 mg.) and pyridine (0.6 ml.) were added. After 10 minutes a micro-crystalline precipitate of the bissemicarbazone separated. It was filtered, washed with water and dried; weight 625 mg., m.p. 279° dec.; λ_{max}^{Nujol} 2.93, 3.10–3.25, 3.40, 5.85–6.00, 6.45 μ.

Anal. Calcd. for $C_{23}H_{33}N_6O_3Br$ (521.47): N, 16.11. Found: N, 15.84.

12α-Bromo-11β-hydroxyprogesterone (Xb). (a) From VII.—To a hot solution of 285 g. (3.24 moles) of lithium bromide in 2.7 l. of dimethylformamide (free of dimethylamine), 67.3 g. (0.137 mole) of 4β,12α-dibromo-5β-pregnane-11β-ol-3,20-dione was added and the resulting solution heated under nitrogen on a steam-bath for 4 hours. Three liters of water was then added to the hot solution and, on cooling, crystalline 12α-bromo-11β-hydroxyprogesterone (Xb)[3] separated. It was filtered, washed with water and dried to give 35.0 g., m.p. 216–219°, $[\alpha]^{23}D$ + 128°, $\lambda_{max}^{alc.}$ 239 mμ (ε 16,000); λ_{max}^{Nujol} 2.97, 5.92–5.97, 6.18 μ.

(b) From XIV.—To a solution of 86.5 mg. of lithium borohydride in 25 ml. of dry tetrahydrofuran 164 mg. of the bissemicarbazone XIV was added and the mixture stirred at room temperature for 3 hours. The excess lithium borohydride was decomposed with 10% acetic acid, the mixture diluted with 25 ml. of water and the tetrahydrofuran taken off *in vacuo*. The precipitate which separated was filtered and then redissolved in a mixture of 7 ml. of acetic acid and 3 ml. of water. To the resulting solution was added at 5° a solution of 500 mg. of sodium nitrite in 3 ml. of water. Thirty minutes later a solution of 3 g. of urea in 5 ml. of water was added dropwise and the solution lyophilized. The residue was distributed between 20 ml. each of chloroform and water. The chloroform was separated and evaporated to dryness *in vacuo*. Crystallization from methanol gave 10 mg. of 12α-bromo-11β-hydroxyprogesterone.

12α-Chloro-11β-hydroxyprogesterone (Xa).—A solution of 35 mg. of 4β,12α-dibromo-5β-pregnane-11β-ol-3,20-dione and 45 mg. of lithium chloride in 1.75 ml. of dimethylformamide was heated on the steam-cone for 2 hours. After

cooling, the mixture was diluted with chloroform, the chloroform solution extracted thoroughly with water, dried over sodium sulfate and evaporated to dryness *in vacuo*. The residual 12α-chloro-11β-hydroxyprogesterone (15 mg.) after recrystallization from acetone–hexane melted at 230–231° and had an infrared spectrum identical with that of an authentic sample.[3]

Anal. Calcd. for $C_{21}H_{29}O_3Cl$: C, 69.12; H, 8.01. Found: C, 68.59; H, 7.79.

Evidence that an 11β,12β-oxido compound is a likely intermediate in the above reaction was adduced as follows: A solution of 33 mg. of 11β,12β-oxidoprogesterone (0.1 mmole) and 86 mg. of lithium chloride (2 mmoles) in 1.5 ml. of dimethylformamide containing 16 mg. of hydrogen bromide (0.2 mmoles) was heated on the steam-bath for 2 hours. The mixture was worked up as described above and furnished 33 mg. of 12α-chloro-11β-hydroxyprogesterone, m.p. 231–232°.

11β,12β-Oxidoprogesterone (XV).—To a stirred suspension of 35.0 g. (85.6 mmoles) of 12α-bromo-11β-hydroxyprogesterone in 2.5 l. of methanol, 185 ml. of 10% potassium carbonate was added dropwise over a 20-min. period, during which time the steroid dissolved completely. After 30 minutes at room temperature, the solution was diluted with 1250 ml. of water, neutralized with 10% acetic acid and then concentrated *in vacuo* until 1 l. of methanol had been removed. On further dilution with water (600 ml.), crystals separated. They were filtered, washed with water and dried to give 12.1 g. of 11β,12β-oxidoprogesterone,[3] m.p. 171–173°, $[\alpha]D$ + 203° (chlf.), λ_{max}^{alc} 238 mμ (ε 16,300); λ_{max}^{Nujol} 5.90, 6.01, 6.21 μ.

The filtrate and washings were extracted with two 1-l. portions of chloroform. The combined chloroform extracts were washed with water and evaporated to dryness to give 17.4 g. of residue which on crystallization from acetone–hexane gave an additional 5.3 g. of 11β,12β-oxidoprogesterone.

12α-Chloro-11β-hydroxyprogesterone could likewise be converted into 11β,12β-oxidoprogesterone as follows: a solution of 13 mg. of 12α-chloro-11β-hydroxyprogesterone in 1 ml. of 0.13 *N* methanolic KOH was allowed to remain at room temperature for 3 hours. The mixture was neutralized with acetic acid, diluted with water and extracted with chloroform. The chloroform extract was washed with water, dried over sodium sulfate and evaporated to dryness *in vacuo*. Recrystallization of the residue from acetone–hexane gave 5.5 mg. of 11β,12β-oxidoprogesterone, m.p. 168–169°.

12α-Fluoro-11β-hydroxyprogesterone (XVI).—To a solution of 4.0 g. (12.2 mmoles) of 11β,12β-oxidoprogesterone in a mixture of 25 ml. of chloroform and 6.2 ml. (76 mmoles) of tetrahydrofuran (freshly distilled from lithium aluminum hydride) contained in a 125-ml. polyethylene bottle equipped with a polyethylene magnetic stirrer and cooled to −60° by an acetone–Dry Ice-bath, 5.0 ml. (246 mmoles) of hydrogen fluoride was added dropwise by means of a polyethylene pipet. After 10 minutes, the acetone–Dry Ice-bath was replaced by an ice-bath and the reaction left at 0° for 4 hours. The reaction mixture was then poured into a polyethylene beaker containing 200 ml. of chloroform and 200 ml. of ice-water and solid sodium bicarbonate was added in small portions until the hydrogen fluoride was neutralized. The mixture was then transferred to a separatory funnel, the chloroform separated, washed twice with water and evaporated to dryness. Crystallization of the residue from acetone–hexane gave 2.8 g. of 12α-fluoro-11β-hydroxyprogesterone,[3] m.p. 182–183°, $[\alpha]^{23}D$ +193°, λ_{max}^{alc} 239 mμ (ε 18,000); λ_{max}^{Nujol} 3.00, 5.89, 6.05, 6.20 μ.

2,21-Bisethyloxalyl-12α-fluoro-11β-hydroxyprogesterone (XVII).—To a solution of 503 mg. (1.44 mmoles) of 12α-fluoro-11β-hydroxyprogesterone in 8 ml. of dry *t*-butyl alcohol warmed to about 50°, 1.30 ml. (9.35 mmoles) of diethyloxalate and 2.58 ml. (3.22 mmoles) of 1.25 *N* sodium methoxide in methanol were added. The mixture was stirred under anhydrous conditions at room temperature for 3 hours, whereafter the precipitated sodium dienolate of 2,21-bisethyloxalyl-12α-fluoro-11β-hydroxyprogesterone was filtered, washed with ether and dissolved in 50 ml. of water. The solution was acidified with dilute hydrochloric acid and the precipitate filtered and dried to give 475 mg. (60% yield) of 2,21-bisethyloxalyl-12α-fluoro-11β-hydroxyprogesterone.

Anal. Calcd. for $C_{29}H_{37}O_9F$ (548.60): C, 63.49; H, 6.80. Found: C, 64.18; H, 6.91.

Methyl 12α-Fluoro-$\Delta^{4,17(20)}$-pregnadiene-11β-ol-3-one-21-oate (XVIII).—To a solution of 102 mg. (0.186 mmole) of 2,21-bisethyloxalyl-12α-fluoro-11β-hydroxyprogesterone and 73 mg. (0.744 mmole) of anhydrous potassium acetate in 2 ml. of methanol cooled to 0° in an ice-bath a solution of 67 mg. (0.42 mmole) of bromine in 0.84 ml. of methanol was added to produce 2,21,21-tribromo-2,21-bisethyloxalyl-12α-fluoro-11β-hydroxyprogesterone. To the resulting solution 0.73 ml. (1.23 mmoles) of sodium methoxide in methanol (1.72 *N*) was added and the mixture stirred under nitrogen at room temperature for 5 hours; 25 ml. of water was then added and the mixture extracted with three 15-ml. portions of chloroform. The combined chloroform extracts were washed with water and evaporated to dryness *in vacuo*. The residue was dissolved in a mixture of 4 ml. of benzene, 2 ml. of methanol and 1 ml. of glacial acetic acid and 100 mg. of zinc dust were added. After stirring at room temperature for 3 hours the mixture was filtered and the zinc washed with warm benzene. The combined filtrate and washings were washed with water, 5% sodium bicarbonate and again with water, dried over sodium sulfate and evaporated to dryness. The residue was crystallized from ethyl acetate–hexane to give 14 mg. of methyl 12α-fluoro-$\Delta^{4,17(20)}$-pregnadiene-11β-ol-3-one-21-oate having a m.p. 248–250°, $[\alpha]^{25}D$ +185°, λ_{max}^{alc} 235 mμ (ε 21,500); λ_{max}^{Nujol} 3.00, 5.81, 6.05, 6.17 μ.

Anal. Calcd. for $C_{22}H_{29}O_4F$ (377.45): C, 70.00; H, 7.77. Found: C, 70.12; H, 8.09.

Methyl 3-(N-Pyrrolidyl)-12α-fluoro-$\Delta^{3,5,17(20)}$-pregnatriene-11β-ol-21-oate (XIX).—To a warm solution of 131 mg. (0.347 mmole) of methyl 12α-fluoro-$\Delta^{4,17(20)}$-pregnadiene-11β-ol-3-one-21-oate in 7 ml. of methanol was added under nitrogen 0.4 ml. of pyrrolidine. The mixture was warmed on a steam-bath for 5 minutes; upon cooling the crystalline dieneamine separated. It was filtered, washed with cold methanol and dried; yield 124 mg., m.p. 235–242°; $\lambda_{max}^{5\%\ HCl-MeOH}$ 220 mμ (ε 18,000), 274 mμ (ε 19,050); λ_{max}^{Nujol} 2.91, 5.81, 6.04, 6.15, 6.27 μ.

Anal. Calcd. for $C_{26}H_{36}O_3NF$ (429.56): C, 72.69; H, 8.45; N, 3.26. Found: C, 72.54; H, 8.52; N, 3.57.

12α-Fluoro-$\Delta^{4,17(20)}$-pregnadiene-11β,21-diol-3-one (XXa).—A solution of 66.4 mg. of methyl 3-(N-pyrrolidyl)-12α-fluoro-$\Delta^{3,5,17(20)}$-pregnatriene-11β-ol-21-oate in 5 ml. of dry tetrahydrofuran was added dropwise to a suspension of 100 mg. of lithium aluminum hydride in 3 ml. of dry tetrahydrofuran. The mixture was stirred at room temperature for 1 hour and then the excess lithium aluminum hydride was decomposed with a few drops of ethyl acetate followed by methanol. Ten milliliters of a buffer consisting of 4 g. of sodium acetate in 10 ml. of water, 4 ml. of glacial acetic acid and 50 ml. of methanol was added and the mixture refluxed under nitrogen for 4 hours. The mixture was then evaporated to near dryness and the residue distributed between chloroform and 2 *N* HCl. The chloroform phase separated, washed with dilute sodium bicarbonate, then twice with water and evaporated to dryness. Crystallization of the residue from acetone–hexane gave 34 mg. of 12α-fluoro-$\Delta^{4,17(20)}$-pregnadiene-11β,21-diol-3-one, m.p. 199–200°, $[\alpha]^{23}D$ +154° (chlf.), λ_{max}^{alc} 242 mμ (ε 15,000); λ_{max}^{Nujol} 3.00, 6.04, 6.20 μ.

Anal. Calcd. for $C_{21}H_{29}O_3F$: F, 5.45. Found: F, 5.22.

12α-Fluoro-$\Delta^{4,17(20)}$-pregnadiene-11β,21-diol-3-one 21-acetate (XXb).—A solution of 47.8 mg. (0.137 mmol) of 12α-fluoro-$\Delta^{4,17(20)}$-pregnadiene-11β,21-diol-3-one in 5 ml. of pyridine and 2 ml. of acetic anhydride was protected from moisture and left overnight at room temperature. The reagents were then removed *in vacuo* and the residue distributed between chloroform and 2 *N* hydrochloric acid. The chloroform solution was separated, washed successively with 5% $NaHCO_3$ and twice with water, dried and evaporated to dryness *in vacuo*. The residue on crystallization from acetone–hexane gave 25 mg. of 12α-fluoro-$\Delta^{4,17(20)}$-pregnadiene-11β,21-ol-3-one 21-acetate having m.p. 227–230°, $[\alpha]^{23}D$ +199° (chlf.), λ_{max}^{alc} 240 mμ (ε 15,800); λ_{max}^{Nujol} 2.98, 5.72, 6.06, 6.20 μ.

Anal. Calcd. for $C_{23}H_{31}O_4F$ (390.48): C, 70.74; H, 8.00; F, 4.86. Found: C, 70.82; H, 8.02; F, 4.91.

Disodium Enolate of 2,21-Bisethyloxalyl-11β,12β-oxidoprogesterone (XXI).—To a solution of 2.00 g. (6.09 mmoles) of 11β,12β-oxidoprogesterone in 250 ml. of dry benzene 6.1 ml. (40 mmoles) of diethyl oxalate and 6.3 ml. (12.8 mmoles)

of 2.04 *N* sodium methoxide in methanol were added and the mixture stirred overnight at room temperature. Anhydrous ether (300 ml.) was then added and after stirring for 30 minutes the precipitated sodium dienolate of 2,21-bisethyloxalyl - 11β,12β - oxidoprogesterone was filtered, washed with ether and dried; yield 3.42 g.

Methyl 11β,12β-Oxido-$\Delta^{4,17(20)}$-pregnadiene-3-one-21-oate (XXII).—To a solution of 9.11 g. (15.9 mmoles) of the sodium enolate of 2,21-bisethyloxalyl-11β,12β-oxidoprogesterone in 300 ml. of methanol, 1.8 ml. (31.8 mmoles) of glacial acetic acid and 4.90 g. (62 mmoles) of anhydrous sodium acetate were added. The solution was cooled to 0° in an ice-bath and then titrated to persistent bromine color with a solution containing 7.5 g. (46.8 mmoles) of bromine in 75 ml. of methanol. The solution was then flushed with nitrogen and 51.5 ml. (97.4 mmoles) of 1.89 *N* sodium methoxide in methanol was added and the mixture stirred under nitrogen at room temperature for 2.5 hours. Acetic acid (57 ml.) and zinc dust (3.8 g.) were then added and after stirring at room temperature for 40 minutes the mixture was filtered, the zinc washed with methanol and the combined filtrate and washings evaporated to dryness *in vacuo*. The residue was distributed between 500 ml. each of chloroform and water. The chloroform solution was washed successively with 5% $NaHCO_3$ and twice with water and then evaporated to dryness *in vacuo*. The resulting residue (5.7 g.) was dissolved in 200 ml. of benzene–hexane (1:1, v.:v.) and absorbed on 114 g. of Merck acid-washed alumina. Elution with benzene and benzene plus 10% chloroform followed by evaporation of the solvents gave material which on crystallization from acetone–hexane yielded 1.87 g. of methyl 11β,12β-oxido-$\Delta^{4,17(20)}$-pregnadiene-3-one-21-oate melting at 169–171° and having $[\alpha]^{23}D$ +184° (chlf.), λ_{max}^{alc} 235 mμ (ε 23,500); λ_{max}^{Nujol} 5.84, 6.01, 6.10 and 6.21 μ.

Anal. Calcd. for $C_{22}H_{28}O_4$ (356.46): C, 74.13; H, 7.92. Found: C, 73.91; H, 7.81.

Further elution with chloroform–benzene (1:9) and crystallization of the residue from acetone–hexane gave a second compound[22] having m.p. 180–183°, $[\alpha]^{22}D$ +201° (chlf.), λ_{max}^{alc} 232 mμ (ε 23,800); λ_{max}^{Nujol} 5.84, 5.92, 6.10, 6.20 μ.

Anal. Calcd. for $C_{23}H_{30}O_5$ (386.47): C, 71.48; H, 7.82; OCH_3, 16.06. Found: C, 71.08; H, 7.68; OCH_3, 16.02.

Methyl 3-(N-Pyrrolidyl)-11β,12β-oxido-$\Delta^{3,5,17(20)}$-pregnatriene-21-oate (XXIII).—To a solution of 119 mg. (0.336 mmole) of methyl 11β,12β-oxido-$\Delta^{4,17(20)}$-pregnadiene-3-one-21-oate in 2 ml. of methanol, 0.2 ml. of pyrrolidine was added and the mixture warmed under nitrogen for 5 minutes. On cooling, the crystalline methyl 3-(N-pyrrolidyl)-11β,12β-oxido - $\Delta^{3,5,17(20)}$ - pregnatriene - 21 - oate separated. It was filtered, washed with a little cold methanol and dried. It had melting point 165–167°; λ_{max}^{alc} 226 mμ (ε 16,600), 277 mμ (ε 18,300); λ_{max}^{Nujol} 5.92, 6.07, 6.15, 6.25 and 12.13 μ.

Anal. Calcd. for $C_{26}H_{35}O_2N$ (409.55): C, 76.24; H, 8.61; N, 3.42. Found: C, 75.76; H, 8.67; N, 3.72.

11β,12β-Oxido-$\Delta^{4,17(20)}$-pregnadiene-21-ol-3-one 21-Acetate (XXIV).—To a solution of 1.78 g. (4.35 mmoles) of methyl 3-(N-pyrrolidyl)-11β,12β-oxido-$\Delta^{3,5,17(20)}$-pregnatriene-21-oate in 12 ml. of tetrahydrofuran (freshly distilled from lithium aluminum hydride), 140 mg. (3.57 mmoles) of lithium aluminum hydride was added and the reaction left at room temperature for 1 hour; 25 ml. of an acetic acid (4 ml.)–sodium acetate (4 g.) buffer in methanol (50 ml.)–water (10 ml.) was added and the mixture refluxed under nitrogen for 2 hours. After cooling, the mixture was diluted with 100 ml. each of chloroform and water. The aqueous phase was acidified with 2 *N* HCl, the chloroform layer was then separated, washed successively with 5% $NaHCO_3$ and twice with water and evaporated to dryness *in vacuo*. The residue (1.39 g.) was dissolved in 5 ml. of dry pyridine and 2 ml. of acetic anhydride protected from moisture and left overnight at room temperature. The reagents were then removed *in vacuo*, the residue distributed between chloroform and water, and the chloroform phase washed successively with dilute hydrochloric acid, 5% $NaHCO_3$, twice with water and evaporated to dryness. Crystallization from acetone–hexane gave 800 mg. of 11β,12β-oxido-$\Delta^{4,17(20)}$-pregnadiene-21-ol-3-one 21-acetate, m.p. 190–191°, $[\alpha]^{23}D$ +148° (chlf.), λ_{max}^{alc} 238 mμ (ε 14,700); λ_{max}^{Nujol} 5.76, 5.99 and 6.19 μ.

Anal. Calcd. for $C_{23}H_{30}O_4$ (370.47): C, 74.56; H, 8.16. Found: C, 74.41; H, 8.37.

11β,12β-Oxido-Δ^4-pregnene-17α,21-diol-3,20-dione 21-Acetate (XXVa).—To a solution of 298 mg. (0.804 mmole) of 11β,12β-oxido-$\Delta^{4,17(20)}$-pregnadiene-21-ol-3-one 21-acetate in 15 ml. of dry *t*-butyl alcohol, there were added 0.2 ml. of pyridine and 0.7 ml. of a solution of osmium tetroxide in dry *t*-butyl alcohol (6 mg./ml.). While stirring, 2.3 ml. of a 0.875 *N* solution of hydrogen peroxide in dry *t*-butyl alcohol was added dropwise over a 10-minute period. The reaction was left at room temperature for 4 hours, during which time it first darkened and then lightened and became cloudy. Nitrogen was bubbled through the reaction mixture for 15 minutes and a solution of 300 mg. of sodium sulfite in 15 ml. of water, which previously had also been nitrogenated for 15 minutes, was added. After 5 minutes the mixture was neutralized with 10% acetic acid and diluted with 100 ml. of water. It was then extracted with 100-ml. and 50-ml. portions of chloroform and the combined chloroform extracts were washed twice with water, dried over sodium sulfate and evaporated to dryness. The residue was dissolved in 5 ml. of pyridine and 2 ml. of acetic anhydride and left at room temperature overnight. The reagents were then removed *in vacuo* and the residue distributed between chloroform and water. The chloroform solution was washed successively with 2 *N* HCl, 5% $NaHCO_3$ and twice with water and then evaporated to dryness. The residue on crystallization from acetone–hexane gave 150 mg. of 11β,12β-oxido-Δ^4-pregnene-17α,21-diol-3,20-dione 21-acetate, m.p. 245–247°, λ_{max}^{alc} 238 mμ (ε 16,000); λ_{max}^{Nujol} 2.95, 5.71, 5.79, 6.04 and 6.11 μ.

Anal. Calcd. for $C_{23}H_{30}O_6$ (402.47): C, 68.63; H, 7.51. Found: C, 68.85; H, 7.61.

11β,12β-Oxido-Δ^4-pregnene-17α,21-diol-3,20-dione (XXVb).—To a solution of 100 mg. of 11β,12β-oxido-Δ^4-pregnene-17α,21-diol-3,20-dione 21-acetate in 10 ml. of methanol which had been heated to boiling and then cooled to room temperature under a stream of nitrogen, 0.5 ml. of a 10% K_2CO_3 (O_2-free) was added and the mixture stirred under nitrogen for 1 hour. It was then neutralized with 10% acetic acid, diluted with 15 ml. of water and the methanol removed, *in vacuo*. The mixture was then extracted with ethyl acetate, and the resulting extract was washed with water, dried over sodium sulfate and evaporated to dryness, *in vacuo*. Crystallization of the residue from acetone–hexane gave 65 mg. of 11β,12β-oxido-Δ^4-pregnene-17α,21-diol-3,20-dione (XXVb), m.p. 232–234°, $[\alpha]^{22}D$ +155° (dioxane), λ_{max}^{alc} 239 mμ (ε 16,200); λ_{max}^{Nujol} 2.82, 5.91, 6.02 and 6.22 μ.

Anal. Calcd. for $C_{21}H_{28}O_5$ (360.44): C, 69.97; H, 7.83. Found: C, 69.78; H, 7.70.

11β,12β-Oxido-Δ^4-pregnene-17α,21-diol-3,20-dione (XXVb) from 12α-Chlorocortisone Acetate (XXVIIIb).—To 2.8 ml. of a semicarbazide solution prepared by dissolving 415 mg. of semicarbazide hydrochloride and 0.3 ml. of pyridine in 2.5 ml. of water and 10 ml. of methanol was added 35 mg. of 12α-chlorocortisone acetate and the mixture refluxed for 16 hours on the steam-cone. The methanol was removed *in vacuo* and the resulting crystalline precipitate of the 3,20-bissemicarbazone of 12α-chlorocortisone acetate (XXIX) was removed by centrifugation and washed thoroughly with water. On drying, 60 mg. of material was obtained which did not melt up to 300°.

Without further purification the bissemicarbazone XXIX (60 mg.) was dissolved in 3 ml. of redistilled tetrahydrofuran and 2.25 ml. of water and treated with 33 mg. of sodium borohydride. The resulting solution was stirred at room temperature for 8 hours. The mixture was then neutralized with 10% acetic acid, the tetrahydrofuran removed *in vacuo*, and the resulting crystals removed by centrifugation and washed with water. The dried material no longer gave a Beilstein reaction. It represents the 3,20-bissemicarbazone of 11β,12β-oxido-Δ^4-pregnene-17α,21-diol-3,20-dione (XXX).

Without further purification the above material was dissolved in 2 ml. of 2.5 *N* hydrochloric acid, and to this solution there was added at 5° over a period of 15 minutes 0.25 ml. of a 10% sodium nitrite solution in water. The reaction was allowed to proceed at 5° for an additional 30 minutes, after which time 0.25 ml. of a 60% solution of urea in water was added. The reaction mixture was removed from the ice-bath and neutralized by the addition of a concentrated sodium bicarbonate solution. Ethyl acetate was then

added and after separation of the layers the ethyl acetate extract was washed thoroughly with water, dried over sodium sulfate and evaporated to dryness *in vacuo*. The total residue amounted to 33 mg., from which on recrystallization from acetone, 13.4 mg. of material melting at 227–229° was obtained. An additional recrystallization furnished analytically pure material, m.p. 230–231°, $[\alpha]^{23}D$ + 154° (absolute ethanol).

Anal. Calcd. for $C_{21}H_{28}O_5$: C, 69.97; H, 7.83. Found: C, 70.18; H, 8.12.

The infrared spectrum of this material was identical with that obtained by the alternate procedure. Acetylation of 6 mg. of this material in 0.5 ml. of pyridine and 0.25 ml. of acetic anhydride at room temperature overnight gave after recrystallization from acetone–hexane 6 mg. of 11β,12β-oxido-Δ⁴-pregnene-17α,21-diol-3,20-dione 21-acetate, m.p. 235–237°, $[\alpha]D$ +157° ($CHCl_3$), $\lambda_{max}^{alc.}$ 238 mμ (ε 16,700). Its infrared spectrum was found to be identical with that of a sample prepared by the alternate procedure.

12α-Fluoro-Δ⁴-pregnene-11β,17α,21-triol-3,20-dione 21-Acetate (12α-Fluorohydrocortisone 21-Acetate) (XXVIa).—Fifty milligrams of 11β,12β-oxido-Δ⁴-pregnene-17α,21-diol-3,20-dione 21-acetate was dissolved in a mixture of 5 ml. of chloroform and 2.5 ml. of dry tetrahydrofuran contained in a polyethylene bottle and the solution cooled to −80° by means of an acetone–Dry Ice-bath. To this solution there was added slowly with stirring 2.0 ml. of hydrogen fluoride by means of a polyethylene pipet. The reaction mixture was maintained at −80° for 10 minutes, following which the acetone–Dry Ice-bath was replaced by an ice–salt-bath, thereby maintaining a reaction temperature of −10° for 6 hours. The reaction mixture was then pipetted into a stirred mixture of 50 ml. of chloroform and 50 ml. of ice-water in a polyethylene beaker and carefully neutralized with sodium bicarbonate. The chloroform solution was separated, washed with water, dried over sodium sulfate and evaporated to dryness. Crystallization of the residue from acetone–hexane gave 17 mg. of 12α-fluorohydrocortisone 21-acetate melting at 228–229° and having $[\alpha]^{22}D$ +106° (chlf.); λ_{max}^{Nujol} 3.00, 5.75, 5.85 and 6.07μ.

Anal. Calcd. for $C_{23}H_{31}O_6F$ (422.48): C, 65.39; H, 7.39. Found: C, 65.22; H, 7.27.

12α-Chloro-Δ⁴-pregnene-11β,17α,21-triol-3,20-dione 21-Acetate (12α-Chlorohydrocortisone 21-Acetate) (XXVIb).—To a solution of 200 mg. of 11β,12β-oxido-Δ⁴-pregnene-17α,-21-diol-3,20-dione 21-acetate in 50 ml. of chloroform, cooled in an ice-bath, 3.55 ml. of a 1.08 *M* solution of hydrogen chloride in chloroform was added dropwise. After 1 hour at 0° the solution was neutralized with 5% sodium bicarbonate solution, washed with water and evaporated to dryness, *in vacuo*. Crystallization of the residue from acetone–hexane gave 82 mg. of 12α-chloro-Δ⁴-pregnene-11β,17α,21-triol-3,20-dione 21-acetate, m.p. 255–256°, $[\alpha]^{23}D$ +120° (95% EtOH); λ_{max}^{Nujol} 2.71, 2.95, 5.76, 6.02, 6.21 μ.

Anal. Calcd. for $C_{23}H_{31}O_6Cl$ (438.93): C, 62.93; H, 7.12. Found: C, 62.71; H, 7.16.

12α-Chloro-Δ⁴-pregnene-11β,17α,21-triol-3,20-dione (12α-Chlorohydrocortisone) (XXVII). (a) **From XXVIb.**—A suspension of 50 mg. of 12α-chloro-Δ⁴-pregnene-11β,17α,21-triol-3,20-dione in 5 ml. of methanol containing 0.12 ml. of 70% perchloric acid was stirred at room temperature for 17 hours, during which time the compound dissolved. The solution was neutralized with 5% $NaHCO_3$, diluted with 40 ml. of water and extracted with chloroform. The chloroform extract was washed with water and evaporated to dryness *in vacuo*. Crystallization of the residue from acetone–hexane gave 30 mg. of XXVII, m.p. 210–212°, $[\alpha]^{23}D$ +86° (dioxane), $\lambda_{max}^{alc.}$ 239 mμ (ε 16,000); λ_{max}^{Nujol} 3.94, 5.90, 6.01, 6.22 μ.

Anal. Calcd. for $C_{21}H_{29}O_5Cl$ (396.90): C, 63.55; H, 7.36; Cl, 8.94. Found: C, 63.79; H, 7.93; Cl, 8.90.

(b) **From XXVb.**—To a solution of 70 mg. of XXVb in 10 ml. of dioxane 2.8 ml. of 2.5 *N* hydrochloric acid was added and the solution left at room temperature for 1 hour; ten 10 ml. each of chloroform and water were then added and the mixture neutralized with 5% $NaHCO_3$. The chloroform layer was separated, washed with water and evaporated to dryness *in vacuo*. Crystallization of the residue from acetone gave 30 mg. of XXVII.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF WAYNE STATE UNIVERSITY, DETROIT 2, MICH.]

Conformational Analysis. XX. The Conformation of the Acetyl Side Chain of Pregnane-20-one[1,2]

BY NORMAN L. ALLINGER AND MARGARET A. DAROOGE[3]

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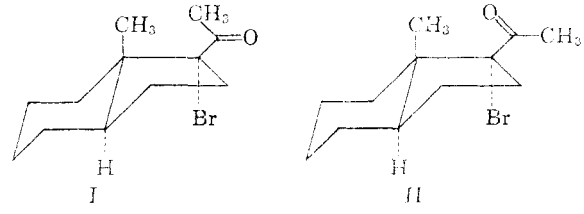
Dipole moment measurements have been used to show that the preferred conformation of the side chain in the pregnane-20-one system is one in which the oxygen attached to C-20 is nearly eclipsed by C-16 and is slightly above the plane defined by carbons 16, 17 and 20.

In general there exist small barriers to rotation about single bonds. With the steroid system there exists a fairly high degree of rigidity and little opportunity for rotational isomers. In the special case of pregnane-20-one, however, the conformation of the side chain is not clear *a priori*. Since various chemical and biological properties of the compound are dependent on the "polarity" of such a system, and the "polarity" is in turn dependent on the side chain conformation, this conformation is of some interest.

Djerassi[4] has suggested from application of the α-haloketone rule[5] to 17α-bromo-5α-pregnane-3β-acetoxy-20-one that the latter has the side chain in the general conformation I rather than the general alternative II.



I II

The present work has been undertaken to try to answer the question of the orientation of the side chain in pregnane-20-one itself. Since it is known that the presence of a halogen atom in an α-halo

(1) Paper XIX, J. Allinger, N. L. Allinger, L. E. Geller and C. Djerassi, *J. Org. Chem.*, **26**, 3521 (1961).

(2) This research was supported in part by the Office of Ordnance Research, U. S. Army.

(3) Predoctoral U. S. Public Health Service Fellow, General Division of Medical Sciences, 1960–1962.

(4) C. Djerassi, "Optical Rotatory Dispersion," McGraw-Hill Book Co., Inc., New York, N. Y., 1960, p. 128.

(5) Reference 4, p 120