Addition of Alkyl Vinyl Ethers to Δ^{16}-20-Keto Steroids. II[1]

J. E. PIKE, G. SLOMP, AND F. A. MACKELLAR

Research Laboratories, The Upjohn Company, Kalamazoo, Michigan

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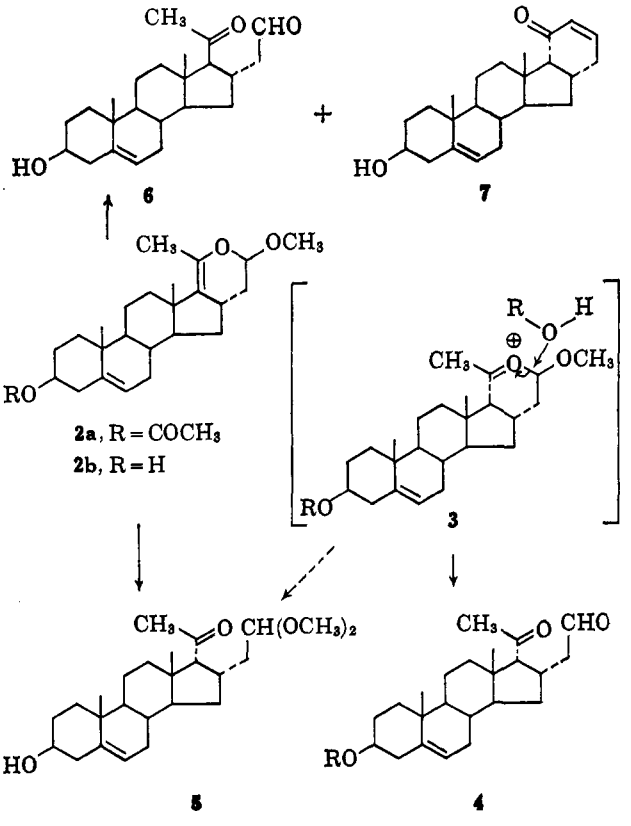
Acidic hydrolysis of the pentacyclic dihydropyrans obtained by reaction of a variety of Δ^{16}-20-keto steroids with methyl vinyl ether has afforded 16α-substituted 20-ketopregnanes, the configuration at C-17 depending on the reaction conditions. Hydroxylation of the 17(20)-double bond in these dihydropyrans with osmium tetroxide has given novel 17α-hydroxy-16α-acetaldehyde γ-lactols which on further oxidation led to the corresponding γ-lactones. Employing this method, 9α-fluoro-11β,17α-dihydroxy-6α-methyl-3,20-dioxopregna-1,4-dien-16α-acetaldehyde γ-lactol (**17a**) and the corresponding lactone (**17b**) were prepared. Preliminary biological data are recorded.

In the previous paper[2] the addition of methyl vinyl ether to 16-dehydropregnenolone acetate (**1a**) and the selective addition of the ether to some Δ^4- and $\Delta^{1,4}$-3-keto steroids was described.[3] Largely through analysis of the n.m.r. spectrum,[4] the stereochemistry of the major adduct appeared consistent with the 16α-ethyl-16bβ-methoxy-16b,20-epoxy-17(20)-pregnene (**2**), a structure which possessed a 16α-substituent, a potential 20-ketone, and an easily functionalized C-17 position.

Before undertaking the elaboration of these adducts to give cortical and progestational hormones it was necessary first to establish conclusively the configuration at C-16. Acidic hydrolysis of the adduct **2b**, prepared by alkaline saponification of the corresponding acetate, was first investigated with 25% aqueous sulfuric acid in tetrahydrofuran at room temperature. After chromatography of the total product on Florisil, two crystalline products were obtained. The main product was the expected ketoaldehyde **6**. The stereochemistry of the ketoaldehyde was clearly established by the optical rotatory dispersion curve (positive Cotton effect)[5] and the n.m.r. spectrum.[6] Thermal decarbonylation of the ketoaldehyde at 200–220° in the presence of 5% palladium on charcoal[8] gave 16α-methylpregnenolone, identical with an authentic sample.[9] Since it seems safe to assume that no inversion of configuration at C-16 has occurred in this reaction, the acetaldehyde fragment in **6** (and hence the 16-substituent in **2**) must have the α-orientation.

The second minor product from the acidic hydrolysis was an unsaturated ketone (λ_{max}^{EtOH}, 232 mμ, ϵ 8450), assigned structure **7** on the basis of the infrared, ultraviolet, and n.m.r. spectra.[10]



When the adduct **2a** was treated with *p*-toluenesulfonic acid monohydrate in anhydrous methanol, only one product was obtained in good yield. This proved to be the 17βH isomer of the dimethyl acetal **5**. The optical rotatory dispersion curve in this instance gave the expected negative Cotton effect[5] and the n.m.r. spectrum (Fig. 1) confirmed the *cis* 16β-H, 17β-H

(1) This work was first presented at the 2nd International Symposium on the Chemistry of Natural Products, Prague, Czechoslovakia, August 27 to September 3, 1962.

(2) J. E. Pike, M. A. Rebenstorf, G. Slomp, and F. A. MacKellar, *J. Org. Chem.*, **28**, 2499 (1963).

(3) During the course of this work a communication appeared describing the addition of alkyl vinyl ethers to 16-dehydropregnenolone acetate and the conversion of the adduct to the corresponding Δ^4-3-ketone [S. Julia and H. Linares, *Compt. rend.*, **252**, 2560 (1961)].

(4) N.m.r. spectra were obtained and analyzed by G. Slomp and F. A. MacKellar with a Varian DP-60 or A-60 spectrometer operating at 60 Mc. DP-60 spectra were observed on *ca.* 0.15 *M* solutions (generally, unless otherwise indicated in deuteriochloroform) and these spectra were calibrated against internal tetramethylsilane using the audiofrequency sideband technique. Frequencies are reported in cycles per second downfield from tetramethylsilane. The A-60 spectra were run on 0.25 *M* solutions. Any inquiries on the n.m.r. data presented in this paper should be directed to G. Slomp.

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

(6) Absorption of 18-hydrogen (40.5 c.p.s.) was consistent with calculations: 39 c.p.s. (basic frequency[7]), 0 c.p.s. (for 17β-acetyl), 2 c.p.s. (for 16α-carbon substituent). The contribution of a 17α-acetyl group would have been about 17 c.p.s. downfield.

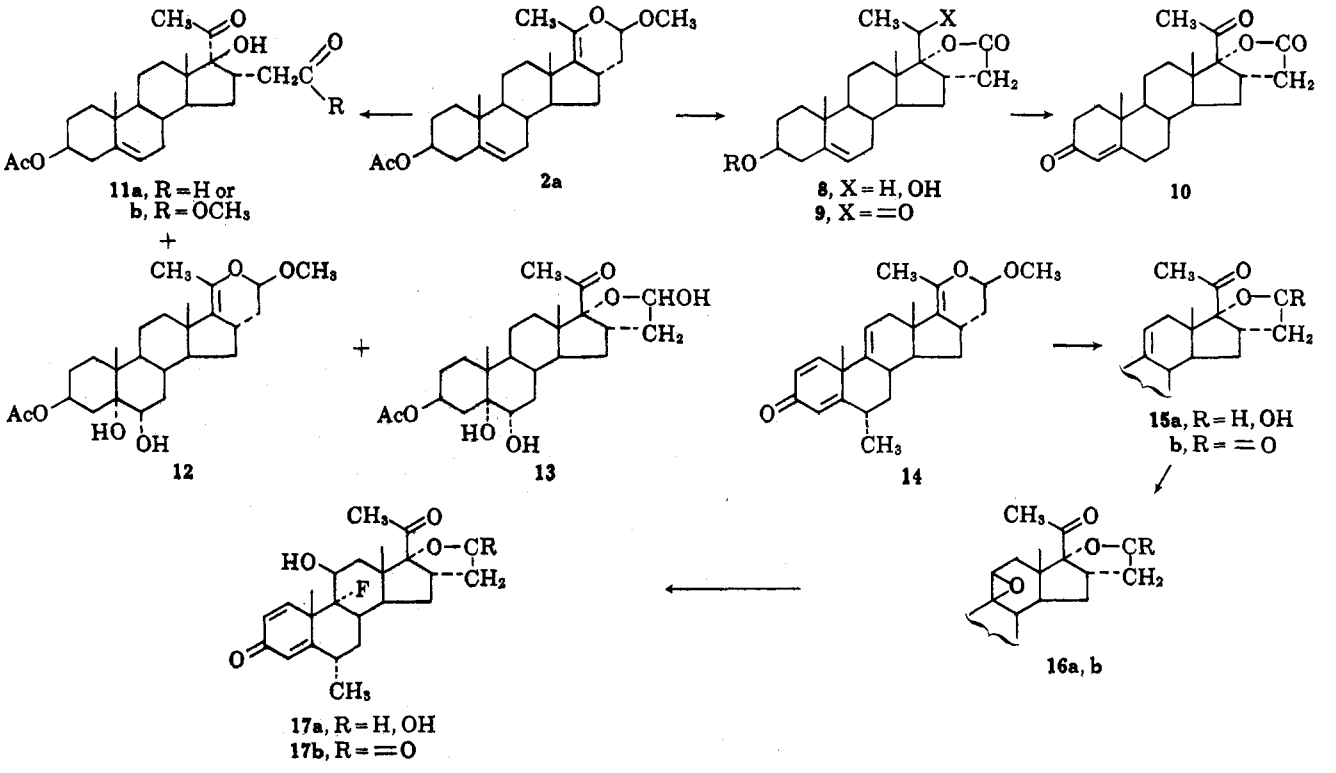
Similarly, absorption of 18-hydrogen (60 c.p.s.) in **4** was consistent with the 16α,17α-configuration; absorption of 18-hydrogen (48.5 c.p.s.) in **8** using +8 c.p.s. for 20-H and +3 c.p.s. for 17α-OR was consistent with the 17β side chain. Again in **9** absorption of 18-H (43.5 c.p.s.) was in agreement with the 17β side chain. Similarly for **10** absorption of the 18-H (46 c.p.s.) indicates the 17β-configuration of the acetyl group. Absorption of 18-H (61 c.p.s.) in **11a** and **11b** using +17 c.p.s. for 17α-acetyl, +5 c.p.s. for 17β-OH, and +2 c.p.s. for 16α-carbon substituent was consistent with the assigned structures.

(7) See ref. 2, particularly footnote 12.

(8) M. S. Newman and H. V. Zahm, *J. Am. Chem. Soc.*, **65**, 1097 (1943).

(9) R. E. Marker and H. M. Crooks, Jr., *ibid.*, **64**, 1280 (1942).

(10) Absorption of the 18-hydrogens at 58 c.p.s. indicated the presence of a neighboring 17α-acyl group,[6] 39 c.p.s. (basic frequency), 17 c.p.s. (17α-acetyl) 2 c.p.s. (16α-carbon substituent).



relationship.[10,11a] Solvolysis under somewhat milder conditions with 90% aqueous acetic acid afforded a high yield (85–90%) of the free 16α,17α-ketoaldehyde **4**. Structural assignments were again made on the basis of the optical rotatory dispersion and n.m.r. spectra.[6,11] A probable explanation for these results appears to lie in the initial proton addition at C-17 which occurs from the β side to give the *cis*-fused cyclic intermediate **3**, which then breaks down as indicated with water or methanol to give the 16α,17α isomer **4**. Under stronger acidic conditions this unstable product partly epimerizes at C-17 to give the more stable 17β-acetyl structure **6**, and partly cyclizes to the unsaturated ketone **7**.

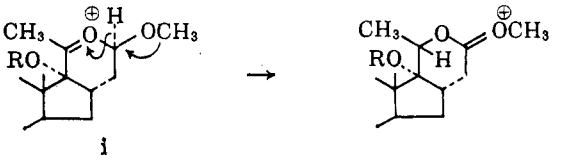
In order to convert these dihydropyrans in which the 16α-configuration has been established, to derivatives of the 17α-hydroxy-20-keto system characteristic of most cortical and many progestational steroids, methods of introducing the hydroxyl group at C-17 were investigated. In the present studies, reaction with osmium tetroxide was chosen as a means of effecting this transformation.

The first experiments on the hydroxylation of the 17(20)-double bond were effected on the adduct **2a**. The reaction was allowed to proceed for three days at room temperature with excess osmium tetroxide in tetrahydrofuran. After isolation with hydrogen sulfide[12] the total product was chromatographed on Florisil. Several products were isolated corresponding to attack at both the 17(20)- and 5(6)-double bonds. The two main products which resulted from selective attack at the 17(20)-double bond were the 20-hydroxylactone **8** and the corresponding 20-ketolactone **9**. The formation of the 20-hydroxylactone **8** (corresponding to an internal oxidation–reduction) is thought to arise by an internal hydride transfer from C-16b to C-20.[13] Although further reaction of **8** under hydroxylation conditions was not studied, it seems likely that oxidation either of a hydroxylactone (such as **8**), a 20-ketolactol (such as **15a**) (*vide infra*), or of an intermediate osmate ester under the reaction conditions could lead to the formation of a 20-ketolactone (such as **9**), which was in fact readily obtained by oxidation of **8** with chromium trioxide–pyridine.[14] Acid-catalyzed hydrolysis of **9** to the 3-alcohol and Oppenauer oxidation gave the corresponding Δ^4-3-ketone **10**. The 20-ketolactones in this series all exhibit optical rotatory dispersion curves with a positive Cotton effect,[5] and the n.m.r. spectra (chemical shift associated with the C-18, methyl absorption)[6] are all consistent with the β-orientation of the 17-acetyl group. The 17-hydroxyl is, therefore, α-oriented and, since a stable *trans*-fused five-ring lactone would seem most unlikely,[15] additional

(11) (a) The 17β-H appears as a doublet (178.5, 171 c.p.s.). The coupling constant of 7.5 c.p.s. by the Karplus relationship[11b] converts to angles of 16° 51′ or 154° 49′. From Dreiding models the 16βH,17βH angle was about 17° and the 16α-H, 17β-H angle was 103°. Hence the configuration of **5** was judged to be the 16β-H,17β-H isomer. In **4** the 17β-H appears at 194.5, 187 c.p.s. and similar reasoning applies; (b) M. Karplus, *J. Chem. Phys.*, **30**, 11 (1959); H. Conroy in "Advances in Organic Chemistry; Methods and Results," Vol. 11, Interscience Publishers, Inc., New York, N. Y., 1960, p. 311.

(12) D. H. R. Barton and D. Elad, *J. Chem. Soc.*, 2090 (1956).

(13) The mechanism for this internal hydride transfer is not clear. One possibility is that the transfer involves an intermediate such as i. A similar



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internal hydride transfer is involved in the acid-catalyzed epimerization of the methyl group at C-25 in the steroidal sapogenins; R. B. Woodward, F. Sondheimer, and Y. Mazur, *J. Am. Chem. Soc.*, **80**, 6693 (1958). An alternative explanation would involve a hydride transfer from C-16[b] in a 20-keto-γ-lactol to give the 20-hydroxy-lactone **8**.

(14) G. I. Poos, G. E. Arth, R. E. Beyler, and L. H. Sarett, *ibid.*, **75**, 422 (1957).

(15) For a discussion of ring fused γ-lactones, see Y. Mazur, N. Danielli, and F. Sondheimer, *ibid.*, **82**, 5889 (1960).

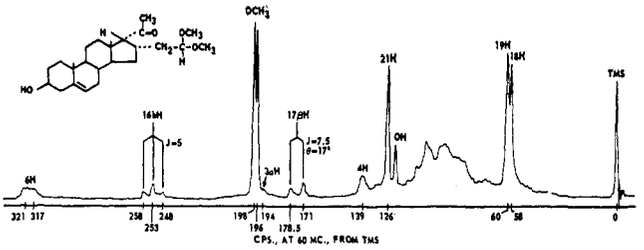

Fig. 1.—Proton magnetic resonance spectrum of dimethylacetal 5.

evidence is obtained for the 16α-substituent both in these products and in the original adducts. A minor by-product in the hydroxylation step is the 17-iso-compound **11b**. This material showed an optical rotatory dispersion curve with a negative Cotton effect,[5] and the structure was consistent[6] with the n.m.r. spectrum (see Experimental). Somewhat different results were obtained when the osmium tetroxide hydroxylation was run in pyridine employing sodium bisulfite to decompose the intermediate complex.[16] The only product isolated which did not involve attack on the 5,6-double bond was the 17-isoaldehyde **11a**. Again, the optical rotatory dispersion spectrum showed a negative Cotton effect and the n.m.r. spectrum was similar to that of the methyl ester **11b** except for the absence of a signal corresponding to the methoxyl of the ester (218 c.p.s.) and the presence of a peak due to the aldehyde C-H (577 c.p.s.). The two other products isolated from the osmium tetroxide–sodium bisulfite–pyridine reaction were the diol **12** and the lactol diol **13**. Other examples have been recorded wherein hydroxylation of a 17(20)-double bond has occurred from the β side.[17]

The hydroxylation sequence was next applied to the 6α-methyl-$\Delta^{1,4,9(11)}$-3-ketone **14** in which greater stability of the A-ring towards osmium tetroxide was anticipated. When the reaction period in tetrahydrofuran was reduced to eighteen hours, the 20-ketolactol **15a** (see Fig. 4) was obtained. Oxidation of this lactol with chromium trioxide–pyridine[14] gave the 20-ketolactone **15b**. Both the lactol **15a** and the lactone **15b** were converted to the corresponding 9α-fluoro-11β-hydroxy compounds by the standard Fried procedure.[18] Addition of hypobromous acid to the 9(11)-double bond gave the 9α-bromo-11β-hydroxy compounds which, on treatment with potassium acetate in acetone, gave the 9,11β-oxides. Treatment of the oxides with hydrogen fluoride–tetrahydrofuran[19] gave the fluorohydrins **17a** and **17b**. To establish further the inter-relationship of the two series, the 9,11β-oxidolactol **16a** (R = H, OH) was oxidized with chromium trioxide–pyridine[14] to the lactone **16** (R = =O) which was identical with the material obtained in the other series.

In preliminary biological evaluations, the 9α-fluorolactone **17b** had an anti-inflammatory activity 72 times that of hydrocortisone (subcutaneous) in the rat granuloma pouch assay,[20] while the 9α-fluorolactol **17a** was 33 times hydrocortisone in this test. The lactone was also 63 times hydrocortisone (subcutaneous) in the rat glycogen deposition assay,[21] was inactive as a salt retainer, and had no effect on water excretion.

(16) J. S. Baran, *J. Org. Chem.*, **25**, 257 (1960).

(17) See L. Feiser and M. Feiser, "Steroids," Reinhold Publishing Corp., New York, N. Y., 1959, p. 632.

(18) J. Fried and E. F. Sabo, *J. Org. Chem.*, **79**, 1130 (1957), and earlier papers.

(19) (a) J. Fried, K. Florey, E. F. Sabo, J. E. Herz, A. R. Restivo, A. Borman, and F. Singer, *J. Am. Chem. Soc.*, **77**, 4181 (1955); (b) R. F. Hirschmann, R. Miller, J. Wood, and R. E. Jones, *ibid.*, **78**, 4956 (1956).

(20) A. Robert and J. E. Nezamis, *Acta Endocrinol.*, **25**, 105 (1957).

Experimental[22]

16α-Ethyl-16b-methoxy-16b,20-oxidopregna-5,17(20)-dien-3β-ol (2b).—A solution of 16α-ethyl-16b-methoxy-16b,20-oxidopregna-5,17(20)-dien-3β-ol acetate (**2a**), (8.1 g.) in tetrahydrofuran (250 ml.) and methanol (250 ml.) was allowed to stir under nitrogen for 18 hr. at room temperature with 40 ml. of 25% aqueous potassium hydroxide solution and 100 ml. of water. At the end of this time acetic acid was added until the pH of the solution was neutral. The solvent was removed *in vacuo* until crystallization commenced. Further water was then added and after refrigeration the crystalline material was collected by filtration, washed with water, and dried *in vacuo* to give 6.41 g. of the 3-hydroxy compound. Crystallization from acetone–Skellysolve B[23] gave **2b**, 5.4 g., m.p. 192–204°. On further crystallization from acetone–Skellysolve B the melting point dropped to 187–190°.

Anal. Calcd. for $C_{24}H_{36}O_3$: C, 77.37; H, 9.74. Found: C, 77.20; H, 9.53.

The infrared spectrum is in agreement with the assigned structure; ν_{max}^{Nujol} 3520, 1695, 1245, 1195, 1160, 1085, 1065, 1015 cm.$^{-1}$.

3β-Hydroxy-20-oxopregn-5-ene-16α-acetaldehyde (6) and 16α-Ethyl-3β-hydroxy-16b,21-cyclopregna-5,16b(21)-dien-20-one (7). A solution of compound **2b** (1.1 g.) in tetrahydrofuran (50 ml.) was allowed to stand 18 hr. at room temperature with 2.5 ml. of 25% aqueous sulfuric acid. Isolation was effected by extraction with methylene chloride. These extracts were washed with sodium bicarbonate solution and water and dried (sodium sulfate). Removal of the solvent gave an oil which in the infrared showed bands at 1710, 1690, and 1650 cm.$^{-1}$. Chromatography of this material in methylene chloride (10 ml.) on Florisil[24] (100 g.) using gradient elution with increasing proportions of acetone in Skellysolve B gave two main peaks. The first crystalline material was crystallized from methanol to give 90 mg., m.p. 226–235°. Further crystallization from methanol gave m.p. 238–242°. Infrared was in agreement with structure **7**; ν_{max}^{Nujol} 3570, 3400, 3260, 3040, 3020, 1655, 1645, 1613, 1097, 1077, 1067, 1057, 1038, 1020, 1000 cm.$^{-1}$; λ_{max}^{EtOH} 232 mμ (ε 8450).

Anal. Calcd. for $C_{23}H_{32}O_2$: C, 81.13; H, 9.47. Found: C, 80.63; H, 9.71.

The n.m.r. spectrum showed a singlet at 58 c.p.s. corresponding to the methyl, and complex AB patterns centered at 366 c.p.s. and 412 c.p.s. corresponding to the conjugated olefinic hydrogens, J_{AB} = 10; 59.5 c.p.s. (C-19-methyl); 317, 321 c.p.s. (6-H).

The second crystalline material was crystallized from acetone–Skellysolve B to give 0.25 g., m.p. 192–198°. Further crystallization from acetone–Skellysolve B gave **6**, m.p. 197–201°; ν_{max}^{Nujol} 3540, 2720, 1720, 1685, 1240, 1185, 1065 cm.$^{-1}$; o.r.d. (*c* 0.1, dioxane), $[M]_{460}$ 260°, $[M]_{315}$ 7180°, $[M]_{300}$ 1910°.

Anal. Calcd. for $C_{23}H_{34}O_3$: C, 77.05; H, 9.56. Found: C, 77.03; H, 9.80.

The n.m.r. spectrum showed a singlet at 40.5 c.p.s. corresponding to the C-18 methyl group, and a triplet (J = 2) centered at 678 c.p.s. corresponding to the aldehyde hydrogen; 61 c.p.s. (C-19-methyl); 318, 322 c.p.s. (6-H); 124 c.p.s. (21-H).

3β-Hydroxy-20-oxo-17α-pregn-5-ene-16α-acetaldehyde, Dimethyl Acetal (5).—A solution of 1 g. of **2a** in methanol (100 ml.) was stirred at room temperature with *p*-toluenesulfonic acid monohydrate (200 mg.) for 18 hr. At the end of this time sodium bicarbonate solution was added and the organic material was isolated by extraction with methylene chloride. These extracts were washed with water and dried (sodium sulfate), and the sol-

(21) R. O. Stafford, L. E. Barnes, B. J. Bowman, and M. M. Meinzinger, *Proc. Soc. Exp. Biol. Med.*, **89**, 371 (1955).

(22) Melting points are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Model 221 spectrophotometer from Nujol mulls. Ultraviolet spectra were taken on 95% ethanol solutions using a Cary Model 14 spectrophotometer. O.r.d. curves were observed on solutions of the samples (10 mg. per 10 ml. of dioxane) with a spectropolarimeter assembled from a Rudolph Model 80 photoelectric polarimeter equipped with an oscillating polarizer and a Perkin-Elmer universal monochromator.

(23) A saturated hydrocarbon fraction, b.p. 64–70°.

(24) Florisil is a synthetic magnesia–silica gel manufactured by the Floridin Co., Warren, Pa.

vent was removed. The residue was dissolved in methylene chloride (10 ml.) and chromatographed on Florisil (60 g.). Elution with increasing per cents of acetone in Skellysolve B gave crystalline material from the 5 to 10% acetone in Skellysolve B eluates. Crystallization from acetone–Skellysolve B gave 0.4 g. of **5**, m.p. 140–144°. Further crystallization (same solvent) gave m.p. 146–148; ν_{max}^{Nujol} 3520, 3460, 1700, 1165, 1125, 1045 cm.$^{-1}$.

Anal. Calcd. for $C_{25}H_{40}O_4$: C, 74.21; H, 9.97. Found: C, 74.23; H, 10.19.

O.r.d. (*c* 0.1, dioxane); $[M]_{460}$ −1160°, $[M]_{315}$ −6500°, $[M]_{280}$ 320°.

The n.m.r. spectrum showed a singlet at 58 c.p.s. (C-18-methyl); a doublet (J = 7.5) centered at 175 c.p.s. (17β-H); a triplet (J = 5) centered at 253 c.p.s. (acetal H split by the adjacent methylene hydrogens); 60 c.p.s. (C-19-methyl); 317, 321 c.p.s. (6-H); 125.5 c.p.s. (21-H); 198, 199.5 c.p.s. (OMe). (See Fig. 1.)

The infrared spectrum is in accord with the structure **5**.

16α-Methylpregnenolone.—3β-Hydroxy-20-oxopregn-5-ene-16α-acetaldehyde (**6**), 1.3 g., was heated at 200–220° with 0.1 g. of 5% palladium-on-charcoal catalyst, with magnetic stirring, *in vacuo* for 20 min. The mixture was cooled, diluted with methylene chloride, and the insoluble material removed by filtration; the catalyst was washed thoroughly with hot methylene chloride. Evaporation of the solvent gave an orange-colored oil which was dissolved in methylene chloride and chromatographed on Florisil (100 g.). Elution with increasing per cents of acetone in Skellysolve B (gradient elution) gave crystalline material (0.203 g.). Crystallization of the combined crystalline fractions from acetone gave material, m.p. 185–191°, with an infrared spectrum identical with that of an authentic sample of 16α-methylpregnenolone.[9]

3β-Hydroxy-20-oxo-17α-pregn-5-ene-16α-acetaldehyde (4).—The adduct **2b** (2.0 g.) was allowed to stand at room temperature for 18 hr. in 50 ml. 90% aqueous acetic acid (45 ml. glacial acetic acid–5 ml. water). Isolation was effected after 18 hr. by adding methylene chloride. The organic layer was washed twice with water, then with sodium bicarbonate solution, and once again with water before being dried (sodium sulfate). Evaporation of the solvent *in vacuo* gave an oil which was dissolved in methylene chloride and chromatographed on Florisil (250 g.). Elution with increasing per cents of acetone in Skellysolve B gave a main peak eluted with 15% acetone–Skellysolve B. The combined fractions weighed 1.69 g.; four crystallizations from acetone–Skellysolve B gave **4**, m.p. 150–155°.

O.r.d. (*c* 0.1, dioxane); $[M]_{250}$ −848°, $[M]_{320}$ −5940°, $[M]_{310}$ 4100°.

The infrared spectrum supports the assigned structure. The n.m.r. spectrum showed a singlet at 60 c.p.s. (C-18 and C-19 methyl groups); a singlet at 125 c.p.s. (21-H); a doublet at 187, 194.5 c.p.s. (17β-H); and a singlet at 520 c.p.s. (aldehyde C-H).

Anal. Calcd. for $C_{23}H_{34}O_3$: C, 77.05; H, 9.56. Found: C, 76.91; H, 9.86.

Reaction of Osmium Tetroxide with 2a. Hydrogen Sulfide Work-Up.[12]—A solution of 10.1 g. of the Diels–Alder adduct **2a** with 10.1 g. of osmium tetroxide in tetrahydrofuran (200 ml.) was allowed to stand 3 days at room temperature. At the end of this time hydrogen sulfide was bubbled through the solution for 15 min., and the solid material was collected by filtration. The solid was re-extracted with hot dioxane and the filtrate combined with the main solution. Evaporation gave the crude product (8.93 g.). This was combined with the total crude (3.1 g.) from a similar run (4.3 g. of adduct, 50 ml. of tetrahydrofuran, 4.3 g. of osmium tetroxide, 25 ml. of diethyl ether; 2 days at room temperature). The total material (12.03 g.) was dissolved in 30 ml. of methylene chloride and chromatographed on 1 kg. of Florisil. Elution with increasing percentages of acetone in Skellysolve B gave the following fractions.

A. Eluted with 5 to 7% acetone–Skellysolve B, 0.502 g.—This was crystallized from acetone–Skellysolve B to give material with m.p. 178–184° (sintering, 130°). Further crystallization (acetone–Skellysolve B) gave **11b**, m.p. 184–186°; ν_{max}^{Nujol} 3440, 1745, 1710, 1255, 1215, 1035 cm.$^{-1}$.

O.r.d. (*c* 0.1, dioxane); $[M]_{460}$ −458°, $[M]_{325}$ −2570°, $[M]_{300}$ −698°.

The n.m.r. spectrum showed a singlet at 61 c.p.s. (C-18-methyl); a singlet at 218 c.p.s. (methoxyl of the ester); a singlet at 133 c.p.s. (C-21-methyl); and a singlet at 121 c.p.s. (3-acetate);

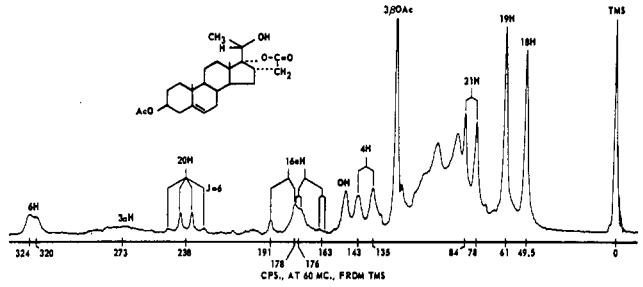

Fig. 2.—Proton magnetic resonance spectrum of 20-hydroxy lactone **8**.

multiplet at 176 c.p.s. (16β-H); multiplet at 158 c.p.s. (16a-H s); 61 c.p.s. (C-19-methyl).

Anal. Calcd. for $C_{26}H_{38}O_6$: C, 69.93; H, 8.58. Found: C, 70.21; H, 8.76.

B. Eluted with 7% acetone–Skellysolve B, 1.281 g.—Crystallization from acetone–Skellysolve B gave 0.6 g., m.p. 176–188° (sintering, 110°). This is assigned structure **9** (R = Ac) is identical to an authentic sample (characterized later) prepared from the corresponding 20-hydroxy lactone.

C. Eluted with 15% acetone–Skellysolve B, 1.282 g.—This is the 20-hydroxy lactone **8** (R = Ac) and it was purified by crystallization from ether, m.p. 230–234°, and then by two recrystallizations from acetone–Skellysolve B to give m.p. 235–240°; ν_{max}^{Nujol} 3480, 1770, 1730, 1240, 1215, 1180, 1100, 1040, 1015 cm.$^{-1}$.

The n.m.r. spectrum (see Fig. 2) showed a singlet at 49.5 c.p.s. (C-18-methyl); a doublet (J = 6.5) centered at 81 c.p.s. (21-methyl, split by the 20-H); a quartet at 247, 241, 235 and 229 c.p.s. (20-H split by the 21-methyl); a complex pattern centered at 177 c.p.s. (lactone CH_2 split by the 16β-H).

Anal. Calcd. for $C_{25}H_{36}O_5$: C, 72.08; H, 8.71. Found: C, 71.97; H, 8.57.

3β,17α-Dihydroxy-20-oxopregn-5-ene-16α-acetic Acid, γ-Lactone, Acetate (9, R = Ac).—A solution of 0.5 g. of the 20-hydroxy lactone **8** (R = Ac) in 10 ml. of pyridine was oxidized for 18 hr. at room temperature with the chromium trioxide–pyridine complex[14] (prepared from 0.5 g. of chromium trioxide and 10 ml. of pyridine). Isolation was effected by adding toluene–ether and removing the insoluble material by filtration. The organic layer was washed with water and dried (sodium sulfate), and the solvent was removed. The residue was crystallized twice from methanol, from acetone–Skellysolve B, and again from methanol to give **9** (R = Ac), m.p. 186–188°; ν_{max}^{Nujol} 1785, 1730, 1720, 1675, 1250, 1155, 1035 cm.$^{-1}$.

The n.m.r. spectrum showed a singlet at 43.5 c.p.s. (C-18-methyl); a singlet at 135 c.p.s. (C-21-H); a doublet at 324, 320 c.p.s. (6-hydrogen); multiplet at 167 c.p.s. (lactone CH_2).

Anal. Calcd. for $C_{25}H_{34}O_5$: C, 72.43; H, 8.27. Found: C, 72.06; H, 8.39.

3β,17α-Dihydroxy-20-oxo-pregn-5-ene-16α-acetic Acid, γ-Lactone (9, R = H).—The lactone **9** (R = Ac) (1.34 g.) was dissolved in methanol (100 ml.) and stirred for 18 hr. at room temperature with *p*-toluenesulfonic acid monohydrate (0.35 g.). Isolation was effected by adding methylene chloride, and the organic layer was washed with sodium bicarbonate solution and water. After drying (sodium sulfate) and removal of the solvent, a crystalline solid was obtained. Crystallization from acetone–Skellysolve B gave 0.6 g., m.p. 210–214°. Two further crystallizations from acetone–Skellysolve B gave m.p. 212–214°; ν_{max}^{Nujol} 3400, 1775, 1715, 1250, 1210, 1155, 1065, 1040, 1025 cm.$^{-1}$.

O.r.d. (*c* 0.1, dioxane); $[M]_{460}$ −336°, $[M]_{327.5}$ 5580°, $[M]_{315}$ 4960°.

Anal. Calcd. for $C_{23}H_{32}O_4$: C, 74.16; H, 8.66. Found: C, 74.26; H, 8.54.

17α-Hydroxy-3,20-dioxopregn-4-ene-16α-acetic Acid, γ-Lactone (10). The 3-hydroxy compound **9** (R = H) (0.6 g.) was oxidized under Oppenauer conditions employing toluene (200 ml.), aluminum isopropoxide (1.4 g.), and cyclohexanone (12 ml.). The reflux period was 18 hr. and a water separator was incorporated into the system. Isolation was effected, after cooling, by washing with saturated Rochelle salt solution and brine and finally by drying (sodium sulfate). Removal of the solvent gave an oil (containing much cyclohexanone). This was dissolved in 30 ml. of methylene chloride and chromatographed on Florisil (150 g.). Crystalline material was obtained from the 10–15% acetone–

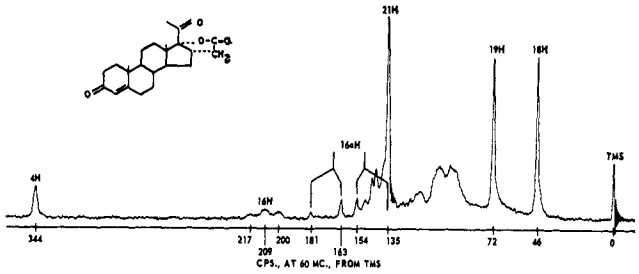

Fig. 3.—Proton magnetic resonance spectrum of 20-hydroxy lactone **10**.

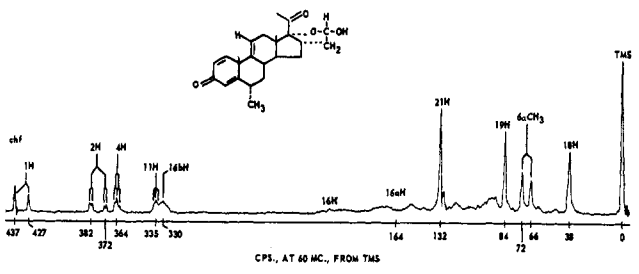

Fig. 4.—Proton magnetic resonance spectrum of 20-keto lactol **15a**.

Skellysolve B eluates. These were combined (0.306 g.) and crystallized from acetone–Skellysolve B to give **10**, 0.235 g., m.p. 242–245°. Further crystallization (acetone–Skellysolve B) gave m.p. 246–248°; ν_{max}^{Nujol} 1778, 1707, 1677, 1615, 1225, 1205, 1185, 1040, 1145, 1130, 1080, 1060, 1025 cm.$^{-1}$; λ_{max}^{EtOH} 240 mμ (ε 17,200).

O.r.d. (*c* 0.1, dioxane); $[M]_{460}$ 486°, $[M]_{320}$ 7780°, $[M]_{310}$ 5170°. (See Fig. 3 for n.m.r. spectrum.)

Anal. Calcd. for $C_{23}H_{30}O_4$: C, 74.56; H, 8.16. Found: C, 74.53; H, 8.22.

Reaction of Osmium Tetroxide with 2a in the Presence of Pyridine.—A solution of 11.8 g. of the Diels–Alder adduct **2a** in 250 ml. of pyridine was stirred at room temperature with 12.0 g. of osmium tetroxide for 72 hr. Isolation was then effected by stirring this mixture with a solution of 22.4 g. of sodium bisulfite dissolved in 360 ml. of water and 180 ml. of pyridine. The organic material was isolated using methylene chloride, and the organic extracts were washed successively with water, ice-cold dilute hydrochloric acid, sodium bicarbonate solution, and water, and then the extracts were dried (sodium sulfate). Removal of the solvent gave material which was dissolved in 100 ml. of methylene chloride and chromatographed on 300 g. of Florisil. Elution with increasing per cents of acetone in Skellysolve B (gradient elution) gave three main peaks.

A. Skellysolve B to 7% acetone–Skellysolve B.—Crystallization (acetone–Skellysolve B) gave 0.42 g., m.p. 186–190°. Two further crystallizations from acetone–Skellysolve B gave m.p. 187–190°; ν_{max}^{Nujol} 3460, 2740, aldehyde C–H; 1725, 1695, 1245, 1035 cm.$^{-1}$. This is assigned the structure **11a**, 3β,17β-dihydroxy-20-oxo-17α-pregn-5-ene-16α-acetaldehyde, 3-acetate.

O.r.d. (*c* 0.1, dioxane); $[M]_{460}$ −442°, $[M]_{325}$ −2813°, $[M]_{310}$ −1975°.

The n.m.r. spectrum showed a singlet at 61 c.p.s. (C-18-methyl); a singlet at 577 c.p.s. (aldehyde C–H); a singlet at 130 c.p.s. (C-21-H); and a singlet at 121.5 c.p.s. (acetate methyl); multiplet at 176 c.p.s. (lactone CH_2 and 16β-H).

Anal. Calcd. for $C_{25}H_{36}O_5$: C, 72.08; H, 8.71. Found: C, 71.84; H, 8.68.

B. Eluted with 10% actone–Skellysolve B.—Crystallization from acetone–Skellysolve B gave 0.795 g., m.p. 182–187°. Further crystallization from acetone–Skellysolve B gave the diol **12**, m.p. 192–193°; ν_{max}^{Nujol} 3550, 3510, 1730, 1690, 1240, 1175, 1135, 1030 cm.$^{-1}$.

The n.m.r. spectrum showed a singlet at 52 c.p.s. (C-18-methyl); a doublet at 108, 109 c.p.s. (C-21-H); and a singlet at 208 c.p.s. (methoxyl); multiplet centered at 294 c.p.s., (acetal H).

Anal. Calcd. for $C_{26}H_{40}O_6$: C, 69.61; H, 8.99. Found: C, 69.53; H, 8.78.

C. Eluted with 20–40% acetone–Skellysolve B.—Crystallization from acetone–Skellysolve B gave 0.44 g., m.p. 211–215°. Further crystallization (acetone–Skellysolve B) gave **13**, m.p. 212–215°; ν_{max}^{Nujol} 3480, 3370, 3350, 1727, 1690, 1265, 1083, 1065, 1057, 1027, 1010 cm.$^{-1}$.

O.r.d. indicates a normal 17β-acetyl structure (*c* 0.1, dioxane); $[M]_{460}$ 215°, $[M]_{322.5}$ 3243°, $[M]_{300}$ 49°.

The n.m.r. spectrum showed a singlet at 37.5 c.p.s. (C-18-methyl); 132 c.p.s. (21-H); multiplet at 338 c.p.s. (hemiacetal H).

Anal. Calcd. for $C_{25}H_{38}O_7$: C, 66.64; H, 8.50. Found: C, 66.46; H, 8.14.

Reaction of Osmium Tetroxide with 14.—A solution of 2.7 g. of the adduct **14**, in tetrahydrofuran (35 ml.) was stirred at room temperature with osmium tetroxide (2.7 g.) for 20 hr. Hydrogen sulfide was bubbled into the solution, and the insoluble material was removed by filtration. After removing the solvent *in vacuo* the residue was dissolved in methylene chloride (35 ml.) and chromatographed on 500 g. of Florisil. Elution with increasing per cents of acetone in Skellysolve B gave (with 20–25% acetone–Skellysolve B) 0.366 g. Crystallization from acetone–Skellysolve B gave **15a**, 0.292 g., m.p. 210–216°. Two further crystallizations from the same solvent raised the melting point to 239–242°; ν_{max}^{Nujol} 3320, 3060, 1705, 1610, 1232, 1215, 1192, 1150, 1095, 1070, 1020 cm.$^{-1}$; λ_{max}^{EtOH} 239 mμ (ε 15,500).

O.r.d. indicates a 17β-acetyl configuration; (*c* 0.1, dioxane); $[M]_{460}$ −209°, $[M]_{325}$ 3410°, $[M]_{315}$ 2320°.

The n.m.r. spectrum showed a singlet at 38 c.p.s. (C-18-methyl); a complex triplet at 330 c.p.s. (acetal H); and a complex pattern centered at 164 c.p.s. (CH_2 of the lactol ring); 131 c.p.s. (21-H) (see Fig. 4).

Anal. Calcd. for $C_{24}H_{30}O_4$: C, 75.36; H, 7.91. Found: C, 74.85; H, 7.53.

17α-Hydroxy-6α-methyl-3,20-dioxopregna-1,4,9(11)-triene-16α-acetic Acid, γ-Lactone (15b).—A solution of the lactol **15a**, 90 mg. in 2.5 ml. pyridine was oxidized at room temperature for 18 hr. with the chromium trioxide–pyridine complex[14] (from 0.1 g. of chromium trioxide and 3 ml. of pyridine). Isolation was effected by adding toluene and ether to the reaction mixture and filtering to remove the insoluble material. The organic layer was washed twice with water and dried (sodium sulfate), and the solvent was removed *in vacuo*. The crystalline residue was triturated with ether and the residue crystallized from acetone–Skellysolve B to give 55 mg., m.p. 245–250°. Final crystallization from acetone–Skellysolve B gave **15b**, m.p. 245–250°; ν_{max}^{Nujol} 1785, 1715, 1675, 1639, 1605, 1230, 1205, 1160, 1140, 1075 cm.$^{-1}$; λ_{max}^{EtOH} 238.5 mμ (ε 15,650).

O.r.d. (*c* 0.1, dioxane); $[M]_{460}$ −97°, $[M]_{325}$ +4270°, $[M]_{310}$ +1742°.

Anal. Calcd. for $C_{24}H_{28}O_4$: C, 75.76; H, 7.42. Found: C, 75.58; H, 6.90.

17α-Hydroxy-6α-methyl-9,11β-oxido-3,20-dioxopregna-1,4-dien-16α-acetic Acid, γ-Lactone (16b). From 15b.—The $\Delta^{9(11)}$-lactone **15b** (610 mg.) was dissolved in *t*-butyl alcohol (27 ml.) and methylene chloride (15 ml.) and to this stirred solution were added N-bromoacetamide (0.33 g.) dissolved in 6 ml. of *t*-butyl alcohol and 70% perchloric acid (1.7 ml.) dissolved in 9 ml. of water. This mixture was stirred for 20 min. at room temperature and then a solution of sodium sulfite (0.5 g.) in 10 ml. of water was added, and the solvent was evaporated below 50°. The crystalline solid which formed was collected by filtration, washed with water and dried *in vacuo* to give 0.6 g. of bromohydrin, m.p. 199–201°. The crude bromohydrin was heated to reflux in acetone (50 ml.) with potassium acetate (0.6 g.) for 18 hr. After cooling, the insoluble material was collected by filtration and washed with methylene chloride, and the filtrate was evaporated to dryness *in vacuo* and chromatographed on Florisil (100 g.). Elution was effected with increasing per cents of acetone in Skellysolve B. Crystalline material was obtained from the 10% acetone–Skellysolve B eluates. Combination of these fractions and crystallization from acetone–Skellysolve B gave the 9,11β-oxide **16b**, 0.36 g., m.p. 253–256°. Further crystallization from acetone–Skellysolve B gave m.p. 250–255°; ν_{max}^{Nujol} 3070, 1780, 1715, 1670, 1635, 1623, 1610, 1235, 1209, 1179, 1156, 1135, 1035, cm.$^{-1}$.

Anal. Calcd. for $C_{24}H_{28}O_5$: C, 72.70; H, 7.12. Found: C, 72.34; H, 7.35.

From 16a.—To a solution of 65 mg. of the oxidolactol **16a** (described later) in 2 ml. of pyridine was added the chromium

trioxide–pyridine complex[14] from chromium trioxide (100 mg.) and 2 ml. of pyridine, and the mixture was allowed to stand 18 hr. at room temperature. The insoluble material was removed by filtration through Celite and washed with toluene–ether (1:1). The organic extracts were washed with water and dried (sodium sulfate). Removal of the solvent gave material which was crystallized from acetone–Skellysolve B to give **16b**. The infrared spectrum of this material was identical with that of the sample previously prepared.

9α-Fluoro-11β,17α-dihydroxy-6α-methyl-3,20-dioxopregna-1,4-dien-16α-acetic Acid, γ-Lactone (17b).—The 9,11β-oxide **16b**, (0.65 g.) was dissolved in methylene chloride (10 ml.), and this solution was added to a mixture of hydrogen fluoride (5.6 g.) and tetrahydrofuran (9.9 g.). The reaction mixture was allowed to stand for 18 hr. at 0–5°. Isolation was effected by pouring the reaction mixture into ice–sodium carbonate solution and extracting with additional methylene chloride. The combined extracts were washed with water and dried (sodium sulfate), and the solvent was removed. Crystallization of the residue from acetone–Skellysolve B gave the 9α-fluoro compound, 0.44 g., m.p. 300–301°. Further crystallization gave **17b**, m.p. 308–310°; ν_{max}^{Nujol} 3500, 1779, 1717, 1669, 1632, 1615, 1240, 1214, 1179, 1156, 1144, 1065 cm.$^{-1}$; λ_{max}^{EtOH} 239 mμ (ε 15,350).

O.r.d. (*c* 0.1, dioxane); $[M]_{460}$ 156°, $[M]_{325}$ 4870°, $[M]_{305}$ 1205°.

The n.m.r. spectrum (observed in d_7 dimethylformamide) showed a singlet at 60 c.p.s. (C-18-methyl); a doublet (J = 6) at 71, 64 c.p.s. (6α-methyl-H); a singlet at 133 c.p.s. (C-21-H); multiplet at 160 c.p.s. (lactone CH_2).

Anal. Calcd. for $C_{24}H_{29}O_5F$: C, 69.23; H, 6.97; F, 4.57. Found: C, 69.21; H, 7.53; F, 4.42.

9α-Bromo-11β,17α-dihydroxy-6α-methyl-3,20-dioxopregna-1,4-dien-16α-acetaldehyde, γ-Lactol. A. Prior Protection of the Lactol.—A mixture of 17α-hydroxy-6α-methyl-3,20-dioxopregna-1,4,9(11)-triene-16α-acetaldehyde, γ-lactol (**15a**) (0.36 g.), pyridine (10 ml.) and acetic anhydride (3 ml.) was allowed to stand 18 hr. at room temperature. Isolation was effected by pouring this reaction mixture into ice–water and collecting the crystalline solid by filtration. After washing with water and drying *in vacuo*, the total crude acetate weighed 0.35 g. and had m.p. 208–210°. The infrared spectrum showed no OH absorption and 1740-, 1235-cm.$^{-1}$ absorption for the acetate. This material was dissolved in 9 ml. of methylene chloride and 15 ml. of *t*-butyl alcohol and was stirred for 20 min. at room temperature with N-bromoacetamide (0.19 g.) in 4 ml. of *t*-butyl alcohol and 70% perchloric acid (0.95 ml.) dissolved in 4.9 ml. of water. Then an aqueous solution of 0.3 g. of sodium sulfite in 2 ml. of water was added and the solvent was evaporated *in vacuo* keeping the bath temperature below 50°. Crystalline material was obtained which was collected by filtration, washed with water, and dried *in vacuo*. This material (0.35 g., m.p. 235° dec.) showed no ester absorption in the infrared and is formulated as lactol bromohydrin.

B. Direct Reaction.—The $\Delta^{9(11)}$-lactol **15a** (0.4 g.) in 18 ml. of *t*-butyl alcohol and 10 ml. of methylene chloride was converted directly to the bromohydrin as described for the lactol acetate in method A, employing the following scale: N-bromoacetamide (0.25 g.) in 6 ml. of *t*-butyl alcohol; 70% perchloric acid (1.1 ml.) in 6 ml. of water. Isolation as in the earlier example gave 0.48 g. of the lactol bromohydrin, m.p. *ca.* 220° dec.,

9α-Fluoro-11β,17α-dihydroxy-6α-methyl-3,20-dioxopregna-1,4-diene-16α-acetaldehyde, Cyclic Hemiacetal (17a).—The total crude lactol bromohydrin (method B, 0.75 g.) obtained from the $\Delta^{9(11)}$ compound was heated to reflux in acetone (40 ml.) with potassium acetate (0.75 g.) for 18 hr. Isolation was effected, after cooling, by filtration and evaporation *in vacuo*. The resulting 9,11β-oxide **16a** was dissolved in methylene chloride (75 ml.) and chromatographed on Florisil (100 g.) made up in Skellysolve B. Crystalline material was obtained from the 10–15% acetone–Skellysolve B eluates; these fractions were combined (0.663 g.) and crystallized from acetone–Skellysolve B to give **16a**, 0.308 g., m.p. 206–210°, and 0.166 g., m.p. 205–212°.

A solution of the 9,11-oxidolactol **16a** (0.271 g.) was allowed to stand for 18 hr. at room temperature with 6 ml. of pyridine and 2.5 ml. of acetic anhydride. Isolation was effected by pouring the reaction mixture into water and collecting the crystalline solid which formed by filtration. After washing with water this material was dried *in vacuo* and crystallized from acetone–Skellysolve B to give the lactol acetate (0.203 g.), m.p. 215–222°. This material was dissolved in 10 ml. of methylene chloride and added to a cooled mixture of hydrogen fluoride (3.95 g.) and tetrahydrofuran (7.11 g.). This mixture was allowed to stand for 18 hr. at +5° and then for 30 min. at room temperature. After pouring the reaction mixture into ice–sodium carbonate solution the organic material was isolated with additional methylene chloride. The organic extracts were washed with water and dried (sodium sulfate), and the solvent was removed to give an oil (0.219 g.) showing no acetate absorption in the infrared. This material was dissolved in methylene chloride (40 ml.) and chromatographed on Florisil (50 g.). Crystalline material (106 mg.), obtained from the 20–25% acetone–Skellysolve B eluates, was crystallized from methanol to give 38 mg. Recrystallization from acetone–Skellysolve B gave **17a**, m.p. 270–272°; ν_{max}^{Nujol} 3510, 3380, 1685, 1655, 1600, 1525, 1242, 1223, 1196, 1160, 1091, 1073, 1055, 1020, 1010 cm.$^{-1}$; λ_{max}^{EtOH} 239 mμ (ε 14,750).

Anal. Calcd. for $C_{24}H_{31}O_5F$: C, 68.90; H, 7.42; F, 4.54. Found: C, 68.41; H, 7.43; F, 4.57.

The n.m.r. spectrum (observed in d_6 dimethyl sulfoxide) showed a singlet at 48 c.p.s. (C-18-methyl); 127 c.p.s. (21-H); 317, 326 c.p.s. (broad, hemiacetal H) (see Fig. 4).

Alternatively the 9,11-oxidolactol **16a** (0.26 g.) in 10 ml. of methylene chloride was added to a mixture of hydrogen fluoride (5.17 g.) and tetrahydrofuran (9.3 g.), and this reaction mixture was allowed to stand for 18 hr. at 5°. Isolation of the fluorohydrin was effected as previously described, and the total crude material was dissolved in methylene chloride (40 ml.) and chromatographed on 50 g. of Florisil. The crystalline material eluted with 20% acetone–Skellysolve B was combined (0.14 g.) and crystallized from acetone–Skellysolve B to give **17a**, 46 mg., m.p. 263–268°.

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