(ϵ 2780); $\lambda_{\max}^{\text{NaOH}}$ 245 mμ (ϵ 7352), and 303 mμ (ϵ 4168)[17]; $\lambda_{\max}^{\text{KBr}}$ 2.95 (OH), 3.26 (vinyl CH_2), 5.76 (carbonyl), 6.08 (isolated C=C), 6.16, 6.27, 6.61 (aromatic C=C), and 11.14 and 11.42 μ (isolated aromatic ring H).

Anal. Calcd. for $C_{22}H_{28}O_2$: C, 81.43; H, 8.69. Found: C, 81.49; H, 8.54.

The acetate, *2-(α-methylallyl)estrone acetate,* melted at 134.5°; $\lambda_{\max}^{\text{KBr}}$ 3.27 (vinyl CH_2), 5.67 (acetate carbonyl), 5.75 (carbonyl), 6.08 (isolated C=C), 6.67 (aromatic C=C), and 8.20–8.25 μ (acetate C—O).

Anal. Calcd. for $C_{24}H_{29}O_3$: C, 78.86; H, 7.99. Found: C, 78.79; H, 8.59.

Acknowledgment. The author gratefully acknowledges the technical assistance of Mrs. Sylvia Capetillo for the ultraviolet spectroscopic determinations.

Houston 25, Tex.

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(17) The solvent used for these measurements was 0.1*N* sodium hydroxide in 70% ethyl alcohol.

[Contribution from Merck Sharp & Dohme Research Laboratories, Division of Merck & Co., Inc.]

Alkylated Adrenal Steroids. Dexamethasone-17 Methyl Ether

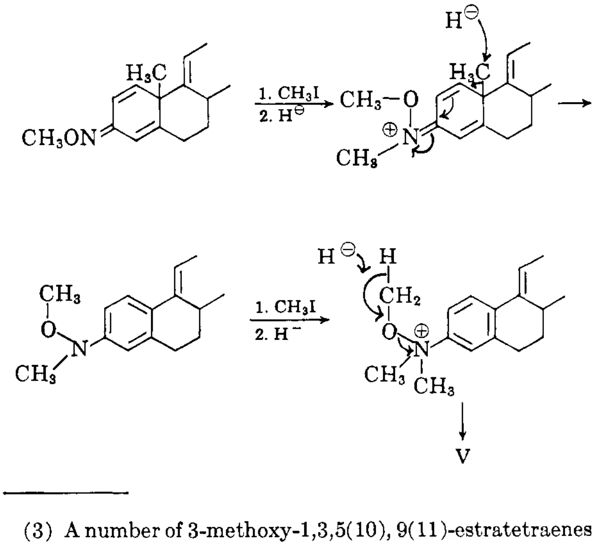
J. H. FRIED and A. N. NUTILE

Received September 27, 1961

Dexamethasone-17 methyl ether has been prepared. Two A-ring aromatization reactions occurring during the course of the present work have been discussed, and the possible utility of the C-3 methoximes of 1,4-dienone-3-ones as base stable protecting groups has been indicated.

Since the biological effect of a 17-methoxy substituent in the anti-inflammatory series is unknown, it became of interest to prepare the 17-methyl ether (IX) of dexamethasone (9α-fluoro-16α-methyl - 1,4 - pregnadiene - 11β,17α,21 - triol-3,20-dione). A readily available synthetic intermediate was 16α-methyl-1,4,9(11)-pregnatriene-17α,21-diol-3,20-dione 21-acetate (I).[1] This compound was converted to the side chain protected C-20,21-acetonide (II). It was then necessary to find a protecting group for the A-ring dienone that would be able to withstand sodium hydride and methyl iodide in refluxing xylene, the conditions required to methylate the sterically hindered hydroxyl at C-17.

Although a number of base stable derivatives of C-3 ketones and enones in the steroid series are known, no convenient protecting group is available for the corresponding 1,4-diene-3-ones.[2] It was found that the dienone methoxime III was relatively stable under these methylating conditions and afforded the corresponding 17-methyl ether IV in 60% yield. In addition to IV, a more polar compound, V, was isolated in 4.5% yield. The analytical data obtained for compound V yielded the empirical formula $C_{27}H_{39}O_3N$. The infrared spectrum, $\lambda_{\max}$ 6.18 and 6.58 μ; ultraviolet spectrum,[3] $\lambda_{\max}$ 288, 317 mμ; E 24,500, 6300; and NMR spectrum:[4] four vinyl protons τ 2.45, 2.61 (H_1); 3.35, 3.51 (H_2); 3.67 (H_4); 4.07 (H_{11}) and two *N*-methyl groups τ 7.18; are in accord with structure V. The additional vinyl proton must arise during the aromatization reaction. Therefore, expulsion rather than migration of the angular methyl at C-19 must have occurred during the course of this transformation. A mechanism in accord with these facts can be written as follows:



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(1) Unpublished results of Dr. R. Hirschmann of these laboratories. Obtained by mesyl chloride–pyridine dehydration of 16α-methylprednisolone 21-acetate. *Cf.* G. E. Arth, D. B. R. Johnston, J. Fried, W. W. Spooncer, D. R. Hoff, and L. H. Sarett, *J. Am. Chem. Soc.*, **80**, 3160 (1958). This compound was also converted to the corresponding 9β,11β-oxide. *Cf.* G. E. Arth, J. Fried, D. B. R. Johnston, D. R. Hoff, L. H. Sarett, R. H. Silber, H. C. Stoerk, and C. A. Winter, *J. Am. Chem. Soc.*, **80**, 3161 (1958). These compounds have also been reported by E. P. Oliveto, R. Rausser, L. Weber, A. L. Nussbaum, W. Gebert, C. T. Coniglio, E. B. Hershberg, S. Tolksdorf, M. Eisler, P. L. Perlman, and M. M. Pechet, *J. Am. Chem. Soc.*, **80**, 4431 (1958).

(2) *Cf.* L. F. Fieser and M. Fieser, *Natural Products Related to Phenanthrene,* Reinhold Publishing Co., New York, 1959.

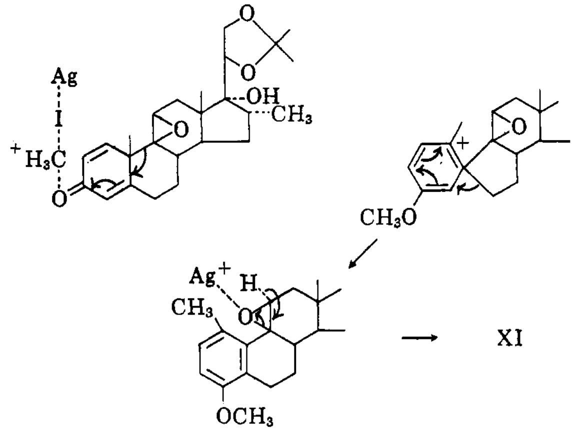
(3) A number of 3-methoxy-1,3,5(10), 9(11)-estratetraenes have ultraviolet absorption λmax 264, 299 mμ; E *ca* 18,000, 3000. L. Dorfman, *Chem. Revs.*, **53**, 129 (1953). A bathochromic shift of nitrogen compared to oxygen would not be unexpected.

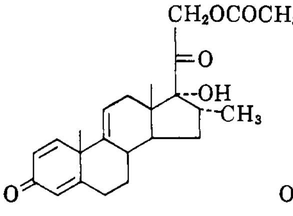
Hydrolysis of the C-20,21-acetonide protecting group in IV with *p*-toluenesulfonic acid in acetone afforded the diol VI. The C-3 methoxime, however, proved to be extremely stable toward a number of acidic hydrolytic reagents. Eventually the free C-3 ketone was obtained by conversion of the methoxime to the semicarbazone followed by aqueous acetic acid hydrolysis[5] to yield VII.

Selective acetylation of VII at C-21, followed by oxidation of the C-20 hydroxyl[6] afforded VIII. Finally VIII was transformed to dexamethasone-17-methyl ether IX by converting the 9,11-double bond sequentially to the bromohydrin, oxide, and fluorohydrin.[7–9]

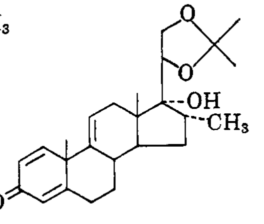
In an earlier attempt to obtain IX, methyl ether formation at C-17 was studied with the 9,11-oxide X.[1] The C-17 hydroxyl was inert to methyl iodide and silver oxide methylation; instead a low yield of the 11-keto-anisole XI was formed during the course of the reaction. The NMR spectrum of XI requires two vicinal aromatic protons τ 2.94, 3.08; 3.27, 3.43. The methyl and methoxyl groups must therefore be placed at C-1 and C-4 since substitution at C-1, C-2 and C-3, C-4 can be ruled out on the basis of the mechanism of the dienone-phenol rearrangement.[10] However, the evidence was insufficient to allow a decision between the remaining two structures XIa and XIb. A possible mechanism for this transformation proceeds *via* dienone-phenol rearrangement, followed by rearrangement of the 9,11-oxide facilitated by stabilization of the intermediate cation by the newly formed anisole ring.

It may be noted that the hydroxyl at C-17 in compound X is remarkably stable toward methyla-

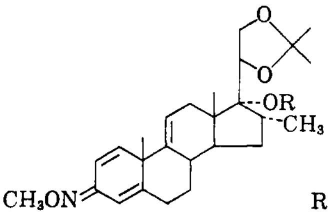




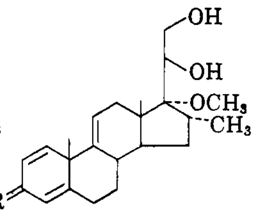
I



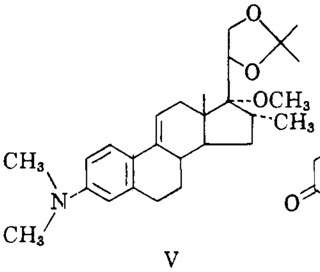
II



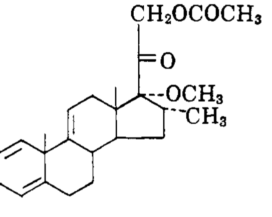
III. R = H
IV. R = OCH_3



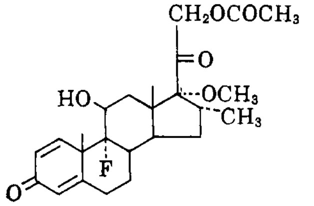
VI. R = $NOCH_3$
VII. R = O



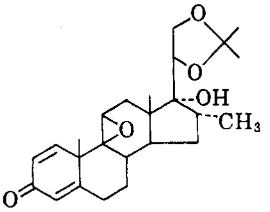
V



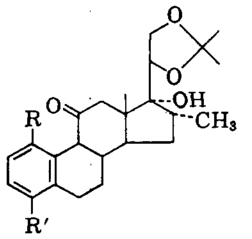
VIII



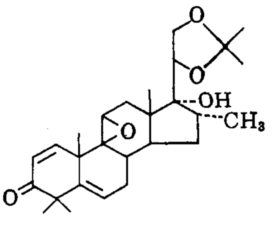
IX



X



XIa. R = CH_3; R′ = OCH_3
b. R = OCH_3; R′ = CH_3



XII

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(4) Nuclear magnetic resonance spectra were run on a Varian 60 mc. spectrometer at a concentration of *ca.* 20 mg. in 0.3 ml. of deuterochloroform. $\tau = \gamma/60 + 3.6$ where γ is the observed band position in c.p.s. relative to benzene as external standard. *cf.* G. V. D. Tiers, *J. Phys. Chem.*, **62**, 1151 (1958).

(5) Private communication from Dr. D. Taub. *Cf.* D. Taub, R. D. Hoffsommer, H. L. Slates, C. H. Kuo, and N. L. Wendler, *J. Am. Chem. Soc.*, **82**, 4012 (1960).

(6) L. H. Sarett, *J. Am. Chem. Soc.*, **68**, 2478 (1946).

(7) Josef Fried and E. F. Sabo, *J. Am. Chem. Soc.*, **76**, 1455 (1954); **79**, 1130 (1957).

(8) R. F. Hirschmann, R. Miller, J. Wood, and R. E. Jones, *J. Am. Chem. Soc.*, **78**, 4956 (1956).

(9) Compound IX was tested in the Merck Institute for Therapeutic Research and was found to be 0.15 × dexamethasone acetate in the systemic granuloma assay. Modification of the method of R. Meier, W. Schuler, and P. Desaulles, *Experientia*, **6**, 469 (1950). Intact male Holtzman rats (*ca.* 125 g.) are dosed orally each day for one week. We are indebted to Dr. S. L. Steelman for carrying out this determination.

(10) R. B. Woodward and T. Singh, *J. Am. Chem. Soc.*, **72**, 494 (1950).

tion. It is unaffected under conditions sufficient to methylate III, although the A-ring dienone is dimethylated at C-4 in the process. This may be attributed to the cage-like structure of X which effectively shields the hydroxyl against approach of the alkylating agent.

EXPERIMENTAL[11]

16α-Methyl-20β,21-isopropylidenedioxy-1,4,9(11)-pregnatriene-17α-ol-3-one (II). A solution consisting of 2.3 g. of sodium in 100 ml. of methanol and 40 g. of 16α-methyl-1,4-9(11)-pregnatriene-17α,21-diol-3,20-dione 21-acetate in 1 l. of methanol was allowed to stand at room temperature under nitrogen for 15 min. After addition of 8 ml. of glacial acetic acid and concentration *in vacuo* at room temperature, filtration afforded 27 g. of 16α-methyl-1,4,9(11)-pregnatriene-17α-21-diol-3,20-dione.

This material in 1 l. of methanol was cooled to 5° and 4.2 g. of sodium borohydride in 3 ml. of water was added with stirring. The mixture was maintained at 5°, under nitrogen for 3 hr., brought to pH 6 with 2.5 N hydrochloric acid, diluted with water, and concentrated *in vacuo* at room temperature. The product was isolated by extraction with ethyl acetate and then refluxed for 3 hr. with 900 ml. of 1:1 aqueous methanol and 30 g. potassium carbonate to cleave borate esters. The reaction mixture was concentrated *in vacuo* and an ethyl acetate extract was dried and concentrated to yield 15.4 g. (43%) of 16α-methyl-1,4,9(11)-pregnatriene-17α,20β,21-triol-3-one, m.p. 195–206°. A sample for analysis was crystallized from ethyl acetate, m.p. 211–215°; $\alpha^{26}\mathrm{D}$ −45° (c 1.0, chloroform); ultraviolet: $\lambda_{\max}^{\mathrm{CH_3OH}}$ 240 mμ, ϵ 14,900.

Anal. Calcd. for $C_{22}H_{30}O_4 \cdot CH_3OH$: C, 70.74; H, 8.78. Found: C, 70.79; H, 8.54.

A mixture of 15.3 g. of the triol, 3 g. of p-toluenesulfonic acid and 300 ml. of acetone was stirred at room temperature under nitrogen for 15 min. Isolation and crystallization from ethyl acetate afforded 12.58 g. (76%) of 16α-methyl-20β,21-isopropylidenedioxy-1,4,9(11)-pregnatriene-17α-ol-3-one, m.p. 158–160°. Recrystallization from ethyl acetate afforded a sample for analysis, m.p. 156–157°C; $\alpha^{25}\mathrm{D}$ −16°, (c 0.9, chloroform); ultraviolet: $\lambda_{\max}^{\mathrm{CH_3OH}}$ 238 mμ, ϵ 15,200.

Anal. Calcd. for $C_{25}H_{34}O_4$: C, 75.34; H, 8.60. Found: C, 74.98; H, 8.68.

16α-Methyl-17α-methoxy-20β,21-isopropylidenedioxy-1,4,9(11)-pregnatriene-3-one 3-methoxime (IV) *and 3-dimethylamino-16α-methyl-17α-methoxy-20β,21-isopropylidenedioxy-1,3,5(10),9(11):19-norpregnatetraene* (V). A solution consisting of 11.2 g. of 16α-methyl-20β,21-isopropylidenedioxy-1,4,9(11)-pregnatriene-17α-ol-3-one and 2.75 g. of methoxylamine hydrochloride in 50 ml. of pyridine was allowed to stand at room temperature under nitrogen overnight. The reaction mixture was poured into water and extracted with chloroform. The chloroform extract was washed with aqueous sodium bicarbonate and water, dried over sodium sulfate, and concentrated *in vacuo*, to yield 11.7 g. of 16α-methyl-20β,21-isopropylidenedioxy-1,4,9(11)-pregnatriene-17α-ol-3-one 3-methoxime as a colorless oil. The product showed absorption in the ultraviolet $\lambda_{\max}^{\mathrm{CH_3OH}}$ 248, 274 mμ, ϵ 12,300, 15,000.

Anal. Calcd. for $C_{26}H_{37}O_4N$: C, 73.03; H, 8.72; N, 3.28. Found: C, 72.35; H, 8.41; N, 3.17.

A solution of 24 g. of 16α-methyl-20β,21-isopropylidenedioxy-1,4,9(11)-pregnatriene-17α-ol-3-one 3-methoxime (III) prepared as above in 450 ml. of xylene was dried by azeotropic distillation, and 12.3. g of 53% sodium hydride in oil suspension was added. The mixture was refluxed under nitrogen for 1.5 hr. and a total of 42.5 ml. of methyl iodide, dried by percolating through a tube filled with calcium chloride, was added to the refluxing solution over a period of 4 hr. and reflux was continued for an additional 7 hr. The solution was cooled, diluted with water, and acidified to pH 3 with 2.5 N hydrochloric acid. A benzene extract was washed with saturated aqueous sodium bicarbonate and water, dried over sodium sulfate, and concentrated *in vacuo*. Chromatography on 1800 g. of acid-washed alumina (Merck) and elution with ether–petroleum ether (2:8) afforded 11.0 g. of 16α-methyl-17α-methoxy-20β,21-isopropylidenedioxy-1,4,9(11)-pregnatriene-3-one 3-methoxime as a colorless oil, ultraviolet: $\lambda_{\max}^{\mathrm{CH_3OH}}$ 249, 274 mμ, ϵ 11,000, 15,200. Further elution with ether–petroleum ether (4:6 and 5:5) afforded 5.0 g. of recovered starting material III. Elution with ether afforded 1.03 g. of 3-dimethylamino-16α-methyl-17α-methoxy-20β,21-isopropylidenedioxy-1,3,5(10),9(11)-19-norpregnatetraene (V), m.p. 190–202°. A sample for analysis was crystallized from ethyl acetate, m.p. 209–212°; ultraviolet: $\lambda_{\max}^{\mathrm{CH_3OH}}$ 288 mμ, ϵ 24,500; inf. 317 mμ, ϵ 6300; $\alpha^{25}\mathrm{D}$ +68° (c 1.2, chloroform).

Anal. Calcd. for $C_{27}H_{39}O_3N$: C, 76.19; H, 9.24; N, 3.29; mol. wt. 426. Found: C, 76.19; H, 9.34; N, 3.23. Potentiometric titration with perchloric acid in acetic acid. Found: Equiv. wt. 432.

16α-Methyl-17α-methoxy-1,4,9(11)-pregnatriene-20β,21-diol-3-one (VII). A solution consisting of 5.8 g. of 16α-methyl-17α-methoxy-20β,21-isopropylidenedioxy-1,4,9(11)-pregnatriene 3-one 3-methoxime (IV) and 2.3 g. of p-toluenesulfonic acid in 230 ml. methanol and 60 ml. of water was refluxed under nitrogen for 2 hr. The reaction was cooled, diluted with water, and concentrated *in vacuo*. An ethyl acetate extract was washed with saturated aqueous sodium bicarbonate solution and water, dried over sodium sulfate, and concentrated *in vacuo* to yield 5.3 g. of 16α-methyl-17α-methoxy-1,4,9(11)-pregnatriene-20β,21-diol-3-one 3-methoxime VI as a gum. The crude material dissolved in 530 ml. of ethanol was refluxed with 20 g. of semicarbazide hydrochloride and 53 ml. of water for 22 hr. under nitrogen. The solution was cooled and filtered. The filtrate was neutralized with saturated aqueous sodium bicarbonate solution, diluted with water, and concentrated *in vacuo*. An ethyl acetate extract was washed with water, dried, and concentrated *in vacuo*, to yield 2.27 g. of 16α-methyl-17α-methoxy-1,4,9(11)-pregnatriene-20β,21-diol-3-one 3-semicarbazone, m.p. 250–257° dec.; ultraviolet: $\lambda_{\max}^{\mathrm{CH_3OH}}$ 242, 293 mμ, ϵ 11,200, 20,800. A solution consisting of 3.5 g. of the semicarbazone prepared as above in 65 ml. of glacial acetic acid, and 65 ml. of water was heated on the steam bath under nitrogen for 4.5 hr. The reaction mixture was cooled, diluted with water, and extracted with ethyl acetate. The ethyl acetate extract was washed with saturated aqueous sodium bicarbonate solution and water, dried, and concentrated *in vacuo*. Chromatography on 235 g. of ethyl acetate-treated alumina and elution with chloroform and chloroform-acetone mixtures afforded 500 mg. of 16α-methyl-17α-methoxy-1,4,9(11)-pregnatriene-20β,21-diol-3-one (VII), m.p. 209–217°. A sample for analysis was crystallized from ethyl acetate, m.p. 219–222°; $\alpha^{25}\mathrm{D}$ −3° (c 0.7, chloroform); ultraviolet: $\lambda_{\max}^{\mathrm{CH_3OH}}$ 240 mμ, ϵ 15,500.

Anal. Calcd. for $C_{23}H_{32}O_4$: C, 74.16; H, 8.66. Found: C, 74.21; H, 8.69.

16α-Methyl-17α-methoxy-1,4,9(11)-pregnatriene-21-ol-3,20-dione 21-acetate (VIII). A solution consisting of 1.92 g. of 16α-methyl-17α-methoxy-1,4,9(11)-pregnatriene-20β,21-diol-3-one (VII) prepared as above in 15 ml. of freshly distilled tetrahydrofuran, 2.53 ml. of 20% acetic anhydride in tetrahydrofuran, and 0.47 ml. of dry pyridine was allowed to stand at room temperature overnight under nitrogen. Ten drops of water were added and the mixture stirred for 10 min., subsequently diluted with benzene, and concen-

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[11] Melting points were determined on a Kofler micro hot stage and are corrected. We wish to thank R. Boos and his associates for microanalyses, A. Kalowsky for ultraviolet absorption spectra, R. Walker and N. Allen for the infrared spectra and B. Arison and Dr. N. R. Trenner for the NMR spectra herein reported.

trated in high *vacuo* at room temperature. Chromatography on 80 g. of alumina treated with ethyl acetate and elution with ether–petroleum ether (7:3) and ether afforded 650 mg. of 16α-methyl-17α-methoxy-1,4,9(11)-pregnatriene-20β,21-diol-3-one 21-acetate VIII, m.p. 171–177°. Further elution with chloroform–acetone mixtures afforded 770 mg. of recovered VII. A sample for analysis was crystallized from ethyl acetate–ether, m.p. 174–177°; α^{25}D −85° (*c* 0.95, chloroform); ultraviolet: $\lambda_{\max}^{CH_3OH}$ 244 mμ, ϵ 15,200.

Anal. Calcd. for $C_{25}H_{34}O_5$: C, 72.43; H, 8.27. Found: C, 72.41; H, 8.52.

A solution consisting of 475 mg. of chromium trioxide in 8.8 ml. of water and 7.8 ml. of glacial acetic acid was added to 856 mg. of the 21-acetate prepared as above in 78 ml. of acetic acid. The reaction mixture was allowed to stand at room temperature for 1 hr. followed by the addition of aqueous sodium sulfite until the color of the solution changed from green to blue. The reaction mixture was then concentrated at 30° to a small volume, poured into water, and extracted with chloroform. The chloroform extract was washed with saturated aqueous sodium bicarbonate solution and water, and concentrated *in vacuo*. Crystallizations from ethyl acetate–ether afforded 470 mg. of 16α-methyl-17α-methoxy-1,4,9(11)-pregnatriene-21-diol-3,20-dione 21-acetate, m.p. 135–139°. Chromatography of mother liquors on 12 g. acid-washed alumina (Merck) and elution with ether afforded an additional 130 mg. of product, m.p. 136–139°.

A sample for analysis was crystallized from ethyl acetate–ether, m.p. 142–145°; ultraviolet: $\lambda_{\max}^{CH_3OH}$ 238 mμ, ϵ 16,000; α^{27}D + 38° (*c* 0.9, chloroform).

Anal. Calcd. for $C_{25}H_{32}O_5$: C, 72.79; H, 7.82. Found: C, 72.45; H, 7.83.

16α-Methyl-17α-methoxy-9α-fluoro-1,4-pregnadiene-11β,-21-diol-3,20-dione 21-acetate (IX). A solution consisting of 570 mg. of 16α-methyl-17α-methoxy-1,4,9(11)-pregnatriene-21-ol-3,20-dione 21-acetate (VIII) and 370 mg. of *N*-Gromosuccinimide, in 9.2 ml. of acetone was cooled to 0°, and 1.84 ml. of 0.2 *N* aqueous perchloric acid was added. The reaction mixture was allowed to stir for 2 hr. at 0°, followed by the addition of a few drops of allyl alcohol to destroy unchanged *N*-bromosuccinimide. The solution was poured into ice water and filtered to yield 765 mg. of 16α-methyl-17α-methoxy-9α-bromo-1,4-pregnadiene-11β,21-diol-3,20-dione 21-acetate, m.p. 196–200° dec.

Anal. Calcd. for $C_{24}H_{33}O_6Br$: Br, 15.6. Found: Br, 16.0.

A solution consisting of 755 mg. of the bromohydrin and 2.1 ml. of 1 *N* sodium methoxide in 17 ml. of methanol was allowed to stand for 8 min. under an atmosphere of nitrogen. The reaction mixture was neutralized with a few drops of acetic acid and poured into ice water. The oxide was isolated by extraction with chloroform. Reacetylation at C-21 was carried out with 5 ml. of pyridine and 4.5 ml. of acetic anhydride at room temperature overnight. The crude product was chromatographed on 30 g. of acid-washed alumina (Merck). Elution with ether–chloroform mixtures afforded 498 mg. of 16α-methyl-17α-methoxy-9β,11β-oxido-1,4-pregnadiene-20-ol-3,20-dione 21-acetate as an oil; ultraviolet: $\lambda_{\max}^{CH_3OH}$ 248 mμ, ϵ 14,400.

A solution of 360 mg. of the oxide in 14.5 ml. of chloroform was cooled to −40° and added to a solution consisting of 8 g. of anhydrous hydrofluoric acid in 35 ml. of tetrahydrofuran cooled to −80°. The mixture was allowed to stand at 0° for 3.5 hr. and poured into a mixture consisting of 75 g. of potassium carbonate, chloroform, water, and ice. The product was isolated by extraction with chloroform and crystallized from ethyl acetate–ether to yield 236 mg. of 16α-methyl-17α-methoxy-9α-fluoro-1,4-pregnadiene-11β,21-diol-3,20-dione 21-acetate IX, m.p. 182–186°. An additional 60 mg. of IX was obtained on chromatography of the mother liquors. A sample for analysis was crystallized from ethyl acetate, m.p. 183–186°; α^{25}D +80° (*c* 0.8, chloroform); ultraviolet: $\lambda_{\max}^{CH_3OH}$ 238 mμ, ϵ 15,900.

Anal. Calcd. for $C_{25}H_{33}O_6F$: C, 66.95; H, 7.44. Found: C, 66.76; H, 7.20.

16α-Methyl-9β,11β-oxido-20β,21-isopropylidenedioxy-1,4-pregnadiene-17α-ol-3-one (X). The deacetylation, reduction, and acetonide formation procedures described for the synthesis of II were used to convert 20.0 g. of 16α-methyl-9β,-11β-oxido-1,4-pregnadiene-17α,21-diol-3,20-dione 21-acetate to 11 g. of 16α-methyl-9β,11β-oxido-20β,21-isopropylidenedioxy-1,4-pregnadiene-17α-ol-3-one, m.p. 220–226°. Crystallization from ethyl acetate afforded a sample for analysis, m.p. 221–224°; α_D +10° (*c* 1.1, chloroform); ultraviolet: $\lambda_{\max}^{CH_3OH}$ 250 mμ, ϵ 15,000.

Anal. Calcd. for $C_{25}H_{34}O_5$: C, 72.43; H, 8.27. Found: C, 72.59; H, 8.02.

4,4,16α-Trimethyl-9β,11β-oxido-20β,21-isopropylidenedioxy-1,5-pregnadiene-17α-ol-3-one (XII). A suspension consisting of 510 mg. of 16α-methyl-9β,11β-oxido-20β,21-isopropylidenedioxy-1,4-pregnadiene-17α-ol-3-one, 70 mg. of 53% sodium hydride in mineral oil, 5 ml. of methyl iodide, and 1 drop of *t*-butyl alcohol in 20 ml. of dry xylene was refluxed for 5.5 hr. and allowed to stand at room temperature overnight. After addition of 5 ml. of methanol, the reaction mixture was poured into ice water and extracted with benzene. The benzene solution was dried, concentrated *in vacuo* and chromatographed on 50 g. of acid-washed alumina (Merck). Elution with ether–petroleum ether mixtures afforded 238 mg. of 4,4,16α-trimethyl-9β,11β-oxido-20β,21 - isopropylidenedioxy - 1,5 - pregnadiene - 17α-ol-3-one. Crystallization from ether gave a sample for analysis, m.p. 181–183°; α_D +15° (*c* 1.1, chloroform); ultraviolet: $\lambda_{\max}^{CH_3OH}$ 225 mμ, ϵ 6900.

Anal. Calcd. for $C_{27}H_{38}O_5$: C, 73.27; H, 8.65. Found: C, 72.93; H, 8.74.

Further elution with chloroform–ether mixtures afforded 75 mg. of recovered X.

1,16α-Dimethyl-4-methoxy-20β,21-isopropylidenedioxy-1,3,5(10) - pregnatriene - 17α - ol - 11 - one (XIa) *or 4,16α-dimethyl - 1 - methoxy - 20β,21-isopropylidenedioxy - 1,3,5-(10)pregnatriene-17α-ol-11-one* (XIb). A suspension consisting of 1.0 g. of 16α-methyl-9β,11β-oxido-20β,21-isopropylidenedioxy-1,4-pregnadiene-17α-ol-3-one (X) and 4.0 g. of silver oxide[12] in 50 ml. of methyl iodide was shaken in a sealed ampoule for 19 hr. at 130°. The reaction mixture was filtered, concentrated *in vacuo*, and chromatographed on 50 g. of acid-washed alumina (Merck). Elution with ether–petroleum ether (7:3) afforded 238 mg.of a crude product which was combined with 137 mg. of material prepared as above and rechromatographed to yield 38 mg. of XIa or b after crystallization from methanol, m.p. 202–206°; ultraviolet: $\lambda_{\max}^{CH_3OH}$ 282–293 mμ, ϵ 2600. Calcd. for $C_{25}H_{36}O_5$: C, 72.86; H, 8.47. Found: C, 73.21; H, 8.62.

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[12] B. Helferich and W. Klein, *Ann.*, **450**, 219 (1926).