9α-Methylhydrocortisone (XVIa). Thirty-four milligrams of 9α-methyl-17,20;20,21-bismethylenedioxy-4-pregnene-11β-ol-3-one was suspended in 2 ml. of 50% acetic acid and treated at 100° for 2.5 hr. It was then evaporated *in vacuo* and extracted with ethyl acetate and with methylene chloride, washed with a saturated sodium bicarbonate solution, dried and evaporated. Trituration of the resulting oil with methanol–methylene chloride gave 26 mg. of 9α-methylhydrocortisone (XVIa), m.p. 220–230°.

Anal. Calcd. for $C_{22}H_{32}O_5$: C, 70.18; H, 8.57. Found: C, 70.42; H, 8.73. λ_{max} 244 mμ ε 14,300. λ_{max}^{Nujol} 2.8, 5.80, 6.0, 6.15, 7.2 μ.

9α-Methyl-4-pregnene-3,20-dione-11β,17α,21-triol-21-acetate (XVIb). Two hundred twenty-four milligrams of 9α-methyl-4-pregnene-3,20-dione-11β,17α,21-triol was combined with 1 ml. of pyridine and 1 ml. of acetic anhydride and allowed to stand at room temperature for 18 hr. It was then diluted with water, extracted with methylene chloride and the organic phase washed with 2.5*N* hydrochloric acid, a saturated solution of sodium bicarbonate, dried and evaporated to dryness *in vacuo*. Trituration with acetone afforded crystals which upon recrystallization from acetone-ether yielded 136 mg. of analytically pure 9α-methyl-4-pregnene-3,20-dione-11β,17α,21-triol-21-acetate, m.p. 235–238.

Anal. Calcd. for $C_{24}H_{34}O_6$: C, 68.87; H, 8.19. Found: C, 69.16; H, 8.15. λ_{max} 243 mμ, ε 16,500. $\lambda_{max}^{CHCl_3}$ 2.9, 5.75, shoulder 5.80, 6.04, 6.26, 8.2 μ.

9α-Methylprednisolone acetate (XVII). Fifty milligrams of 9α-methylhydrocortisone acetate (XVIb) was dissolved in 2.2 ml. of *t*-butyl alcohol. To this solution was added 0.04 ml. of glacial acetic acid, 30 mg. of selenium dioxide, 50 mg. of mercury and 50 mg. of mercuric oxide. This reaction mixture was refluxed with stirring for 3.5 hr. After cooling, the mixture was filtered through Supercel and washed with additional *t*-butyl alcohol. The *t*-butyl alcohol was then concentrated to dryness and the residue dissolved in ethyl acetate. The organic phase was washed with a saturated solution of sodium thiosulfate until no more color was removed and with a 10% sodium bicarbonate solution. After drying over magnesium sulfate and concentrating *in vacuo*, the resulting 40 mg. of oil was chromatographed on acid-washed alumina. Elution of the column with ether-chloroform (1:4) and chloroform yielded 9α-methylprednisolone acetate (XVII), m.p. 228–230°.

Anal. Calcd. for $C_{24}H_{32}O_6$: C, 69.21; H, 7.74. Found: C, 69.02; H, 7.91. λ_{max}^{Nujol} 2.8, 5.70, 5.79, 6.01, 6.18, 6.25, 8.05 μ. λ_{max} 244 mμ, ε 14,000.

Acknowledgment. The authors are indebted to Dr. N. R. Trenner and Mr. B. H. Arison for the nuclear magnetic resonance data reported, to Mr. James Wittick and associates for ultraviolet spectra and Mr. R. N. Boos and associates for microanalytical data.

RAHWAY, N. J.

[CONTRIBUTION FROM THE COBB CHEMICAL LABORATORY, UNIVERSITY OF VIRGINIA]

Rearranged Steroid Systems. I. Studies in the Pregnane Series[1,2]

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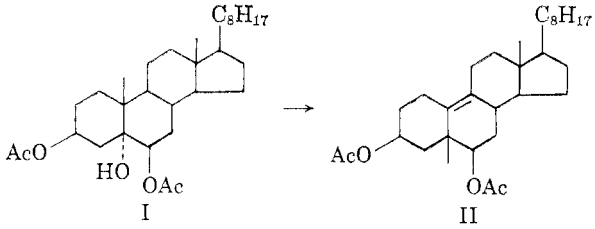
Pregnenolone and prenenolone methyl ether have been converted to 19-nor-5-methyl steroids by the Westphalen rearrangement. An attempt to carry pregnenolone ethylene ketal through a similar series of reactions was unsuccessful. An isomeric substance, obtained in the preparation of pregnenolone methyl ether, was identified as the 17α-epimer.

In 1915, Westphalen[5] obtained a dehydration product from cholestane-3β,5α,6β-triol diacetate (I) by treating this compound with acetic anhydride and sulfuric acid. The product was shown by later workers[6] to have structure II, the C-10 methyl group having migrated to the C-5 position. Spectrographic[7] and chemical[8] evidence are in accord with assigning the 9,10 position to the double bond, while the probable *beta* orientation of the C-5 methyl group is supported by optical rotatory dispersion measurements.[9]



I II

This C-10 to C-5 methyl shift, commonly referred to as the Westphalen rearrangement, has been investigated mainly in the cholestane series[10] and to a lesser extent with androgen derivatives.[11] The current interest in 19-nor steroids as progestational, antiestrogen and cancer agents led us to extend this rearrangement to some

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(2) Supported by Grant CY-3377 of the National Cancer Institute, U. S. Public Health Service.

(3) Postdoctoral Research Associate, 1957–58.

(4) Postdoctoral Research Associate, 1959–60.

(5) T. Westphalen, *Ber.*, **48**, 1064 (1915).

(6) H. Lettré and M. Müller, *Ber.*, **70**, 1947 (1937); V. A. Petrow, O. Rosenheim, and W. W. Starling, *J. Chem. Soc.*, 677 (1938); V. Petrow, *J. Chem. Soc.*, 998 (1939).

(7) P. Bladen, H. B. Henbest, and G. W. Wood, *J. Chem. Soc.*, 2737 (1952).

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(10) For additional references, see M. Davis and V. Petrow, *J. Chem. Soc.*, 2211 (1951); Y. F. Shealy and R. M. Dodson, *J. Org. Chem.*, **16**, 1427 (1951); C. A. Grob and E. Schumacher, *Helv. Chim. Acta*, **41**, 924 (1958).

(11) (a) M. Davis and V. Petrow, *J. Chem. Soc.*, 2973 (1949); (b) 1185 (1950).

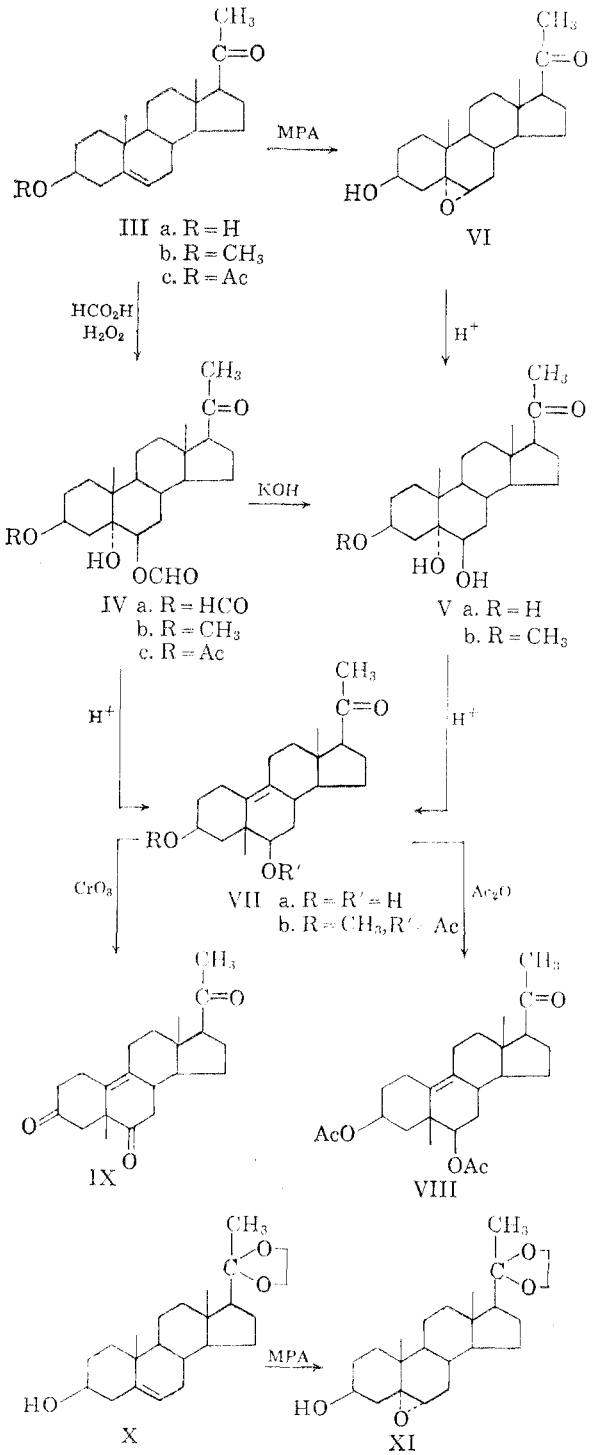


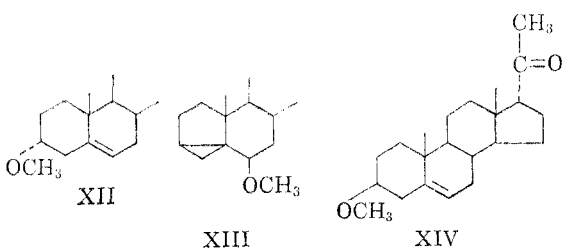
Figure 1

20-ketopregnanes, and the transformations reported in the present paper are shown in Fig. 1.

When pregnenolone (IIIa) was treated with hydrogen peroxide and formic acid, the 5α-hydroxy-3β,6β-diformate IVa was obtained. This diester was readily hydrolyzed in base to yield the known 3β,5α,6β-triol Va. A similar series of reactions on pregnenolone acetate (IIIc) gave the same triol (Va) *via* the 3β-acetoxy-5α-hydroxy-6β-formate IVc. The triol was prepared by still another method, albeit in poorer yield, by the acid hydrolysis of pregnenolone α-epoxide (VI).

When the triol Va was treated with acetic anhydride containing a trace of sulfuric acid a product was obtained which yielded a small amount of diol VIIa on hydrolysis. The latter compound gave a positive Tortelli-Jaffé Test, a negative color reaction with trichloroacetic acid and exhibited a strongly dextrorotatory optical rotation, properties characteristic of 19-nor-5-methyl steroids.[6,8,10] A much higher yield of the diol VIIa (43%) could be obtained by carrying out the rearrangement directly on the diformate IVa. In general, the rearrangements were accompanied by the formation of minor amounts of other products, as well as tarry material. Decomposition could be kept to a minimum by carrying out the reaction at 0°. However, even at this temperature by-products were formed. Usually these were not further identified because they were obtained in low yield and have been investigated to some extent in another series.[9] The diol VIIa was readily acetylated to yield the diacetate VIII and underwent oxidation with chromic acid, giving the triketone IX.

The rearrangement was also found to occur quite readily with 3-methoxy derivatives. When pregnenolone methyl ether (IIIb) was prepared from the tosylate by a modification of the method described by Butenandt and Grosse,[12] a second product was isolated which showed a high negative optical rotation and which was isomeric with IIIb. The infrared spectra of the two compounds were very similar, suggesting only a minor structural difference. A high negative optical rotation was inconsistent with the 3α-methoxy structure XII[13] and a direct comparison with an authentic sample of 6β-methoxy-i-pregnan-20-one[12] (XIII) showed the two substances to be different. The compound was identified as the 17α-epimer XIV from its optical



rotatory dispersion curve which exhibits a negative Cotton effect[14] (Fig. 2).

The pregnenolone methyl ether (IIIb) was converted to the diol Vb through the 5α-hydroxy-6β-formoxy derivative IVb. Rearrangement of the diol was effected with acetic anhydride–sulfuric

(12) A. Butenandt and W. Grosse, *Ber.*, 70, 1446 (1937).
(13) W. Klyne, *The Chemistry of the Steroids*, John Wiley & Sons, Inc., New York, 1957, pp. 53 ff.
(14) C. Djerassi, *Optical Rotatory Dispersion*, McGraw-Hill Book Co., Inc., New York, 1960, p. 51.

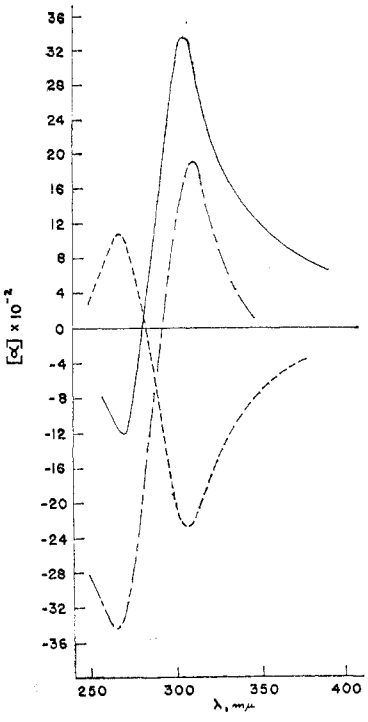


Fig. 2. Rotatory dispersion curves: (———) 3β,6β-dihydroxy-5β-methyl-19-nor-9-pregnen-20-one (VIIa); (— - —) 17β-pregnenolone methyl ether (IIIb); (- - - -) 17α-pregnenolone methyl ether (XIV)

acid, yielding the rearranged product as the 6β-acetate VIIb.

In an attempt to diminish interference from the 20-keto group, the ketal X[15] was converted to the 5,6-epoxide XI[16] with monoperphthalic acid. However, attempts to open the epoxide ring under basic conditions were unsuccessful. The epoxide VI was likewise recovered unchanged under basic hydrolysis conditions. *Beta* hydroxyl attack is undoubtedly hindered by steric interference of the C-10 methyl group.

EXPERIMENTAL[17]

3β,6β-Diformoxy-5α-hydroxypregnan-20-one (IVa). A solution of 10.0 g. of pregnenolone (IIIa) in 100 ml. of 98% formic acid was cooled in ice and 10 ml. of 30% hydrogen peroxide was added dropwise with stirring. Forty-five minutes after the beginning of the addition a crystalline product separated. The mixture was stirred for an additional 3 hr. 15 min. with occasional chilling in ice. Sixty milliliters of water was then added and the solid collected by filtration. The yield of *3β,6β-diformoxy-5α-hydroxypregnan-20-one* was 8.16 g. (64%), m.p. 227–230°. For analysis, the compound was recrystallized from acetone, m.p. 229–230°, $[\alpha]_D$ −9.0° (c = 1.04).

Anal. Calcd. for $C_{23}H_{34}O_6$: C, 67.95; H, 8.43. Found: C, 67.98; H, 8.38.

When 90% formic acid[18] was used, the yield was 59%.

3β-Acetoxy-5α-hydroxy-6β-formoxypregnan-20-one (IVc). Ten milliliters of 30% hydrogen peroxide was added to a stirred solution of 10.5 g. of pregnenolone acetate[19] in 60 ml. of carbon tetrachloride and 80 ml. of 98% formic acid. The mixture was heated at 40–45° for 1 hr. and then at 50–55° for 6.5 hr. It was then poured into a saturated solution of aqueous sodium chloride and extracted with ether. The extracts were washed with a saturated solution of sodium bicarbonate, dried (sodium sulfate), and the solvent removed. The remaining white solid was recrystallized from aqueous ethanol, yielding 7.2 g. (59%) of 3β-acetoxy-5α-hydroxy-6β-formoxypregnan-20-one (IVc), m.p. 218–220°, $[\alpha]_D$ −9.6° (c = 0.99) [lit.,[20] m.p. 215–217°, $[\alpha]_D$ ± 0° (chloroform)].

Anal. Calcd. for $C_{24}H_{36}O_6$: C, 68.54; H, 8.63. Found: C, 68.58; H, 8.45.

Pregnenolone α-epoxide (VI). A solution of 4.50 g. of monoperphthalic acid in 50 ml. of ether was added to a solution of 10.0 g. of pregnenolone (IIIa) in 50 ml. of chloroform and 25 ml. of ether, and the mixture let stand for 22 hr. in a refrigerator (0°). The solid (phthalic acid) which had separated was filtered off, and the filtrate washed thoroughly with 5% aqueous sodium carbonate, water, ferrous sulfate solution, and again with water. The organic phase was dried over sodium sulfate and the solvent removed. The remaining crude product was triturated with 10 ml. of acetone and filtered, yielding 8.70 g. of crystalline solid, m.p. 170–178°. Recrystallization from methanol gave 6.73 g. (64%) of pregnenolone α-epoxide, m.p. 180–182°. Recrystallization from ethyl acetate and then acetone raised the melting point to 185–187°. $[\alpha]_D^{30}$ + 6.8° (c = 1.05) [lit., m.p. 185–187°[21]; 188–190°, $[\alpha]_D$ + 17° (chloroform)[22]].

Anal. Calcd. for $C_{21}H_{32}O_3$: C, 75.86; H, 9.70. Found: C, 75.76; H, 9.48.

The infrared spectrum showed a doublet in the carbonyl region at 1712 and 1699 cm.$^{-1}$

3β,5α,6β-Trihydroxypregnan-20-one (Va.) (a) *From hydrolysis of 3β-acetoxy-5α-hydroxy-6β-formoxypregnan-20-one* (IVc). A solution of 0.5 g. of the diester, 0.5 g. of potassium hydroxide, and 10 ml. of methanol was refluxed for 6 hr. The reaction mixture was poured into water, extracted with chloroform, and the organic phase dried over sodium sulfate. Removal of the solvent left a solid residue which was recrystallized from acetone, yielding 0.18 g. (43%) of 3β,5α,-6β-trihydroxypregnan-20-one (Va), m.p. 256–258° (lit., m.p. 256–258°,[19] 252–255°[18]).

Anal. Calcd. for $C_{21}H_{34}O_4$: C, 71.96; H, 9.78. Found: C, 71.70; H, 9.46.

(b) *From hydrolysis of 3β,6β-diformoxy-5α-hydroxypregnan-20-one* (IVa). Employing the same conditions described above for the 3β-formoxy-6β-acetoxy compound, the hydrolysis of 0.16 g. of the 3β,6β-diformate IVa yielded 0.045 g. (33%) of the triol Va, m.p. 252–253°, unchanged on admixture with a sample of the triol prepared above.

(15) P. Ziegler and K. R. Bharucha, *Chem. and Ind. (London)*, 1955, 1351.

(16) The epoxide ring is assigned the *alpha* configuration from analogy with similar epoxidations and from its optical rotation which lacks the dextrorotatory shift characteristic of *beta* epoxidation. *Cf.* Fieser and Fieser, *Steroids*, Reinhold Publishing Corporation, New York, 1959, pp. 193 ff.

(17) All melting points are uncorrected. All rotations were determined in chloroform at room temperature unless otherwise stated. Infrared spectra were determined on a Perkin-Elmer model 21 spectrophotometer and ultraviolet spectra on a Perkin-Elmer model 4000A Spectracord. A Rudolph Photoelectric Spectropolarimeter was used for the optical rotatory dispersion measurements. Microanalyses were carried out by Mrs. M. Logan and Mrs. D. Ellis.

(18) O. Mancera, G. Rosenkranz, and C. Djerassi, *J. Org. Chem.*, 16, 192 (1951).

(19) M. Ehrenstein, *J. Org. Chem.*, 4, 506 (1939).

(20) A. Bowers, E. Denot, R. Urquiza, and L. M. Sanchez-Hidalgo, *Tetrahedron*, 8, 116 (1960).

(21) Y. Urusibara, M. Chuman, and S. Wada, *Bull. Chem. Soc. Japan*, 24, 83 (1951).

(22) A. Bowers, E. Donet, M. B. Sanchez-Hidalgo, and H. R. Ringold, *J. Am. Chem. Soc.*, 81, 5233 (1959).

(c) *From acid hydrolysis of pregnenolone α-epoxide* (VI). A solution of 5.00 g. of the epoxide in 70 ml. of methanol and 50 ml. of 2*N* sulfuric acid was refluxed for 3 hr. The methanol was partly removed by distillation, chloroform was added, and the layers were separated. The organic phase was washed with 5% aqueous sodium carbonate and water, and dried over sodium sulfate. Removal of the solvent left an oil which crystallized when treated with ether, yielding 1.25 g. (24%) of 3β,5α,6β-trihydroxypregnan-20-one (Va), m.p. 200–212°. Recrystallization from ethanol raised the melting point to 245–252°. The infrared spectrum was identical with those of the products obtained in (a) and (b) above. Evaporation of the ether filtrate left a yellow oil which yielded small amounts of two additional solids after chromatography, m.p.'s 150–160 and 142–146°. These were not further characterized.

Basic hydrolysis of pregnenolone α-epoxide proved unsuccessful. Thus, when 0.50 g. of the epoxide in 6 ml. of 5% methanolic potassium hydroxide was refluxed for 2 hr. on a steam bath, 0.45 g. of starting material was the only identifiable substance recovered.

3β,6β-Dihydroxy-5β-methyl-19-nor-9-pregnen-20-one (VIIa). (a) *From 3β,6β-diformoxy-5α-hydroxypregnan-20-one* (IVa). A stirred suspension of 8.00 g. of the diformate IVa in 80 ml. of acetic anhydride was cooled in an ice bath and a solution of 6 drops of concd. sulfuric acid in 5 ml. of acetic anhydride added. After 45 min., the mixture had turned brown and the solid had partly dissolved. Two drops of sulfuric acid was added and the temperature was allowed to rise to 16°. After 30 min., the solid had completely dissolved. The dark brown solution was taken up in benzene–ethyl acetate, washed with dilute aqueous sodium bicarbonate, and then water. Removal of the solvent from the dried (sodium sulfate) organic phase left an oil, which was refluxed with 60 ml. of 5% methanolic potassium hydroxide for 1 hr. on a steam bath. After removal of the methanol, the residue was dissolved in ethyl acetate and washed thoroughly with water. The organic layer was dried over sodium sulfate and the solvent removed, leaving an oil which was treated twice with a hot mixture of toluene–petroleum ether (1:1). The remaining semicrystalline solid was crystallized from ethyl acetate, yielding 2.78 g. (43%) of *3β,6β-dihydroxy-5β-methyl-19-nor-9-pregnen-20-one* (VIIa), m.p. 152–155°. For analysis, a sample was recrystallized from ethyl acetate, m.p. 158–159°, $[\alpha]_D$ + 218° (*c* = 1.0), Tortelli-Jaffé test (+), Trichloroacetic acid test (−), not precipitated with digitonin. RD in methanol (*c* = 0.011), 24°; $[\alpha]_{589}$ +253°, $[\alpha]_{305}$ +3371°, $[\alpha]_{270}$ −1213°, $[\alpha]_{260}$ −812° (l = 1 dm.) (Fig. 2).

Anal. Calcd. for $C_{21}H_{32}O_3$: C, 75.86; H, 9.70. Found: C, 75.67; H, 9.67.

Chromatography of the mother liquors on alumina yielded additional product (VIIa), 0.76 g., m.p. 160–161° eluted with ethyl acetate and 0.31 g., m.p. 140–145° eluted with ethyl acetate–methanol. Further elution with ethyl acetate–methanol yielded a different solid, 0.05 g., m.p. 179–180°, $[\alpha]_D$ + 62.7°, Tortelli-Jaffé test delayed and faint (+), which was not further characterized.

Anal. Calcd. for $C_{21}H_{32}O_3$: C, 75.86; H, 9.70. Found: C, 75.30; H, 9.61.

(b) *From 3β,5α,6β-trihydroxypregnan-20-one* (Va). To a hot suspension (steam bath) of 1.0 g. of triol (Va) in 10 ml. of acetic anhydride was added 0.2 g. of potassium hydrogen sulfate. The organic material dissolved readily, accompanied by the development of a slight brown color. After 10 min. the solution was chilled in ice and a solution of 2 drops of sulfuric acid in several milliliters of acetic anhydride slowly added. Several seconds of heating on a steam bath turned the solution dark brown. It was quickly cooled in ice and the acetic anhydride was removed by vacuum distillation. The oily residue was dissolved in ethyl acetate, washed successively with 5% sodium carbonate solution and water, and dried over sodium sulfate. Removal of the solvent left an oil which was refluxed for 1 hr. with 20 ml. of a 5% solution of potassium hydroxide in aqueous methanol and let stand at room temperature overnight. After removal of the methanol, the product was taken up in an ether–ethyl acetate mixture and washed thoroughly with water. Removal of the solvent left a glass which crystallized when treated with ethyl acetate to give 0.12 g. (13%) of *3β,6β-dihydroxy-5β-methyl-19-nor-9-pregnen-20-one* (VIIa), m.p. 156–157.5°. The infrared spectrum was identical with that of the product (VIIa) obtained in part (a).

No attempt was made to develop conditions for optimum yields in this reaction because it was found that rearrangement of the diformate IVa provided a better route to VIIa [see (a) above].

3β,6β-Diacetoxy-5β-methyl-19-nor-9-pregnen-20-one (VIII). A solution of 0.5 g. of the diol VIIa in 8 ml. of pyridine and 4 ml. of acetic anhydride was allowed to stand at room temperature for 3 days. The addition of 50 ml. of water produced an oil which was separated from the supernatant liquid by decantation. After drying over potassium hydroxide in a vacuum desiccator, the oil crystallized from methanol. Recrystallization from this solvent yielded 0.13 g. (21%) of 3β,6β-diacetoxy-5β-methyl-19-nor-9-pregnen-20-one (VIII) as colorless plates, m.p. 129.5–130.5° (micro hot stage), $[\alpha]_D$ + 152.7° (*c* = 1.02), Tortelli-Jaffé test (+), Trichloroacetic acid test (−). Davis and Petrow[11a] reported m.p. 120° and Tortelli-Jaffé test (−).

Anal. Calcd. for $C_{25}H_{36}O_5$: C, 72.08; H, 8.71. Found: C, 72.11; H, 8.50.

An additional 0.24 g. (39%), m.p. 123–125°, was obtained as a second crop. The semicarbazone was recrystallized from methanol, m.p. 212.5–215° dec. (lit.,[11a] m.p. 213–219°).

Anal. Calcd. for $C_{26}H_{39}O_5N_3$: C, 65.93; H, 8.30; N, 8.87. Found: C, 65.93; H, 7.99; N, 9.20.

Pregnenolone tosylate. Sixty grams of *p*-toluenesulfonyl chloride was added to a solution of 30.0 g. of pregnenolone (IIIa) in 180 ml. of warm pyridine. The mixture was warmed *gently* until the solid dissolved, and allowed to stand overnight at room temperature. The mixture, containing some crystalline material, was poured into water, and the oil which separated soon solidified. After cooling in an ice bath the mixture was filtered, and the colorless solid obtained was recrystallized from acetone, yielding 39.0 g. (88%) of pregnenolone tosylate, m.p. 137.5–138° (lit.,[12] m.p. 139–140°).

Pregnenolone methyl ether (IIIb) and 17α-pregnenolone methyl ether (XIV).[23] A solution of 10.0 g. of pregnenolone *p*-toluenesulfonate in 80 ml. of absolute methanol was refluxed for 4 hr. The pregnenolone methyl ether, which crystallized on cooling, was filtered off. When water was added to the mother liquor, a crude solid was obtained which yielded additional methyl ether IIIb when recrystallized from petroleum ether (b.p. 30–60°). Recrystallization of the combined crops from aqueous methanol gave 6.07 g. (87%) of pregnenolone methyl ether, m.p. 124–125° (lit.,[12] m.p. 123–124°). RD in methanol (*c* = 0.05), 24°, $[\alpha]_{345}$ +160°, $[\alpha]_{311}$ +1920° $[\alpha]_{265}$ −3440°, $[\alpha]_{250}$ −2920° (l = 0.1 dm.) (Fig. 2).

The solvent was removed from the petroleum ether mother liquor, and the solid residue was recrystallized from absolute methanol, yielding 0.80 g. (11%) of *17α-pregnenolone methyl ether* (XIV), m.p. 131–132°, $[\alpha]_D^{26}$ −154° (*c* = 1.4). RD in methanol (*c* = 0.06), 24°, $[\alpha]_{350}$ −900°, $[\alpha]_{305}$ −2250°, $[\alpha]_{269}$ + 1083°, $[\alpha]_{250}$ + 267° (l = 0.1 dm.) (Fig. 2).

Anal. Calcd. for $C_{22}H_{34}O_2$: C, 79.89; H, 10.37. Found: C, 79.62; H, 10.11.

Because of the large difference in the optical rotations of IIIb and XIV, equilibration of these two isomers was easily followed by observing the rotation change with a polarimeter. Thus, when a solution of 1.0 g. of XIV and 0.5 g. of *p*-toluenesulfonic acid in 9.7 ml. of methanol was kept at 50°, equilibrium was attained in 2.25 hr. The equilibrated mixture contained approximately 15% of XIV and 85% of IIIb, as de-

(23) This experiment was performed by D. Savage.

termined from the optical rotation values of the mixture and of the pure isomers.

3β-Methoxy-5α-hydroxy-6β-formoxypregnan-20-one (IVb). Three milliliters of 30% hydrogen peroxide was slowly added at room temperature to a stirred mixture of 2.50 g. of pregnenolone methyl ether (IIIb) in 15 ml. of carbon tetrachloride and 20 ml. of 98% formic acid. After maintaining the temperature at 40–45° for 1 hr. and then at 50–55° for 6 hr., the mixture was cooled and poured into saturated sodium chloride solution. The water solution was extracted with ether, and the organic phase washed with dilute aqueous sodium bicarbonate until the washings were basic. The solvent was removed from the dried (sodium sulfate) organic layer and the remaining oil crystallized from acetone petroleum ether (b.p. 30–60°), giving 2.40 g. (80%) of *3β-methoxy-5α-hydroxy-6β-formoxypregnan-20-one* (IVb), m.p. 180–182°, $[\alpha]_D$ + 5° (c = 7.0).

Anal. Calcd. for $C_{23}H_{36}O_5$: C, 70.37; H, 9.24. Found: C, 70.37; H, 9.19.

3β-Methoxy-5α,6β-dihydroxypregnan-20-one (Vb). To a stirred solution of 7.90 g. of pregnenolone methyl ether (IIIb) in 48 ml. of carbon tetrachloride and 64 ml. of 98% formic acid were added 9.6 ml. of 30% hydrogen peroxide. The reaction was run and worked up in the manner described above, except that the oil which was obtained was refluxed for 4 hr. with a solution of 9.0 g. of potassium hydroxide in 200 ml. of methanol. The reaction mixture was poured into water and extracted with chloroform. The organic phase was dried over sodium sulfate, the solvent removed, and the residue recrystallized from aqueous acetone. The *3β-methoxy-5α,6β-dihydroxypregnan-20-one* (Vb) was obtained as colorless crystals, 5.50 g. (63%), m.p. 191–193°, $[\alpha]_D$ +39.3° (c = 0.98).

An analytical sample, prepared from another run, had m.p. 192–194°.

Anal. Calcd. for $C_{22}H_{36}O_4$: C, 72.49; H, 9.96. Found: C, 72.52; H, 10.10.

3β-Methoxy-5β-methyl-6β-acetoxy-19-nor-9-pregnen-20-one (VIIb). A stirred solution of 500 mg. of the diol Vb in 9 ml. of acetic anhydride (warmed to dissolve) was cooled in an ice bath and 0.9 ml. of a solution of 1 drop of concd. sulfuric acid in 1.0 ml. of acetic anhydride was added. After 1.25 hr., the dark mixture was diluted with benzene and washed with 10% aqueous sodium carbonate and with water. The organic phase was dried (Drierite-magnesium sulfate) and the solvent removed, leaving 450 mg. of a brown oil, which was chromatographed on 12 g. of alumina. Elution with benzene–petroleum ether yielded 70 mg. of an oil which solidified on standing. Recrystallization from methanol gave 50 mg. of colorless solid, m.p. 127.5–128°, Tortelli-Jaffé test (−), trichloroacetic acid test (yellow-pink). This substance was not further identified.

The desired product was obtained on elution with benzene as 110 mg. (21%) of pale yellow needles, m.p. 128–132°, Tortelli-Jaffé test (+). Recrystallization from acetone-water and finally pure acetone gave 74 mg. of *3β-methoxy-5β-methyl-6β-acetoxy-19-nor-9-pregnen-20-one* (VIIb), m.p. 138–139°, $[\alpha]_D$ +155° (c = 0.99), Trichloroacetic acid test (−).

Anal. Calcd. for $C_{24}H_{36}O_4$: C, 74.19; H, 9.34. Found: C, 73.76; H, 9.26.

5β-Methyl-19-nor-9-pregnene-3,6,20-trione (IX). A solution of 61 ml. of 2% chromic acid in glacial acetic acid was added dropwise over a 1-hr. period to a stirred solution of 1.90 g. of diol VIIa in 50 ml. of glacial acetic acid. The mixture was allowed to stir for 22 hr. at room temperature, and the acetic acid then removed by distillation. The remaining oil was taken up in ethyl acetate, washed with water, and dried (sodium sulfate). Removal of the solvent left an oil which crystallized from methanol, giving 0.68 g. (36%) of *5β-methyl 19-nor-9-pregnene-3,6,20-trione* (IX), m.p. 163–167°. Recrystallization from ethanol-water and finally pure ethanol provided an analytical sample, m.p. 167–169° $[\alpha]_D^{28}$ +7.8 (c, = 1.09), Tortelli-Jaffé test (+), $\lambda_{max}^{CH_3OH}$ 292 mμ (ϵ = 167).

Anal. Calcd. for $C_{21}H_{28}O_3$: C, 76.79; H, 8.59. Found: C, 76.49; H, 8.52.

Pregnenolone ethylene ketal (X). A vigorously stirred mixture (two layers) of 3.00 g. of pregnenolone (IIIa), 25 ml. of ethylene glycol, 50 ml. of toluene, and 0.03 g. of *p*-toluenesulfonic acid was refluxed for 5 hr. the water formed being collected in a Dean-Stark water separator. Five milliliters of 5% methanolic potassium hydroxide were added to the warm solution and the mixture then poured into an equal amount of water. Extraction with ether caused some solid to separate, which was removed by filtration and recrystallized from methanol, yielding 1.30 g. (35%) of pregnenolone ethylene ketal (X), m.p. 162–164°.

Two drops of pyridine were added to the filtrate, the solution was dried, and the solvent removed under vacuum. The semicrystalline residue was combined with some additional solid which separated from the aqueous layer on letting stand at room temperature overnight and the mixture was recrystallized from methanol. This yielded an additional 1.20 g. (32%) of ketal, X, m.p. 161–163° (lit., 164–167°;[15] 163–166°, $[\alpha]_D^{26}$ − 39 ± 2°[24]).

Pregnenolone ethylene ketal oxide (XI), *and attempted hydrolysis of the epoxide ring under alkaline conditions.* A solution of 1.2 g. of pregnenolone ethylene ketal (X) in 25 ml. of chloroform was chilled in ice and 1.4 g. of monoperphthalic acid in 30 ml. of ether added. The clear solution was let stand in a refrigerator for 18 hr., then washed thoroughly with 5% sodium carbonate solution, water, ferrous sulfate solution, and again with water. The organic layer was dried over sodium sulfate, the solvent removed, and the solid product recrystallized from ethanol, yielding 0.70 g. (56%) of *pregnenolone ethylene ketal α-epoxide* (XI), m.p. 183–185°, $[\alpha]_D$ −51.2 (c = 0.94).

Anal. Calcd. for $C_{23}H_{36}O_4$: C, 73.36; H, 9.64. Found: C, 73.17; H, 9.67.

When the ketal epoxide was refluxed for 2 hr. with methanolic potassium hydroxide or heated on a steam bath for 2.5 hr. with aqueous methanolic sodium bicarbonate, mainly starting material was recovered.

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