Reduction of a small sample of 17β-hydroxyestrane-2-one (VIa) with sodium borohydride in ethanol water for 2 hr. afforded from benzene–petroleum ether hexagonal *prisms*, m.p. 208–210°, identical with the estrane 2α,17β-diol (VIb) obtained above by mixed melting point and infrared spectra comparison.

Estrane-17β-ol (VIc). (a) *By Huang-Minlon reduction of 17β-hydroxyestrane-3-one* (V). To a solution of 50 mg. of 17β-hydroxyestrane-3-one (V) in 7 cc. of ethanol and 7 cc. of diethylene glycol 5 cc. of hydrazine hydrate was added. After refluxing for 30 min., 0.3 g. of solid potassium hydroxide was added and refluxing was continued for another 15 min. The condenser was then removed and the temperature of the solution was allowed to rise to 190°. Refluxing was then continued for 2.5 hr., at which point water was added and the mixture was extracted with ether. After washing with 5% hydrochloric acid, 5% sodium bicarbonate, and water, the ether was dried and evaporated. The residue weighing 28 mg. was purified by sublimation at 90°, and subsequent crystallization from dilute ethanol. The estrane-17β-ol (VIc) melted 130–133° (needles); $[\alpha]_D$ −8°.

Anal. Calcd. for $C_{18}H_{30}O$: C, 82.39; H, 11.52. Found: C, 81.99; H, 11.51.

(b) *By Huang-Minlon reduction of 17β-hydroxyestrane-2-one* (VIa). Reduction of 17β-hydroxyestrane-2-one (VIa) by the same procedure as above, gave crystals, m.p. 128–130°, identical by mixed melting point and infrared spectra comparison with estrane-17β-ol (VIc).

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16α-Methylated Adrenal Hormones. 17α-Hydroxylation by the Glyoxylate Process

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The glyoxylate process has been utilized for the introduction of a C-17 hydroxyl group in the 16-alkyl-20-ketopregnane series. Thus, the 3α-hydroxy-16α-methyl-11,20-dioxo-21-pregnaneglyoxylic acid (III) has been converted in good yield to 3α,17α-dihydroxy-16α-methylpregnane-11,20-dione[1] (VI).

One of the difficult problems encountered in the synthesis of 16-alkylated cortical steroids was the introduction of the C-17 hydroxy group. Apparently an alkyl substituent in the 16- position exerts a steric effect which renders the enol-acetylation procedure of Gallagher[2] very impractical.[3] It has been found that the utilization of the 20-keto-21-glyoxylate (III) offers an excellent route for the introduction of the 17α-hydroxy group. This method was based on the procedure of Hogg and Nathan.[4]

This glyoxylate procedure was admirably suited for the synthesis of 3α,17α-dihydroxy-16α-methylpregnane-11,20-dione (VI),[5] a key intermediate for the preparation of Decadron® (16α-methyl-9α-fluoroprednisolone).

The condensation of diethyl oxylate in ether with 3α-hydroxy-16α-methyl-11,20-dione using sodium methylate was very facile. The resulting sodium salt of the glyoxylate II was hydrolyzed in aqueous methanol without purification to give the 21-glyoxylic acid (III), m.p. 243°, $\lambda_{max}^{CH_3OH}$ 293 (10,200).

The treatment of III with acetic anhydride and either perchloric or 2,4-dinitrobenzenesulfonic acid at 25° gave an excellent conversion to the enol lactone acetate IV as a mixture of geometrical isomers, m.p. 165–175°, $\lambda_{max}^{CH_3CN}$ 297 mμ (22,800). Epoxidation of this isomeric mixture of IV with perbenzoic acid afforded the epoxy lactone V in quantitative yield, m.p. 225–227°, $\lambda_{max}^{CH_3CN}$ 226 mμ (11,400). The hydrolysis of V under mild conditions in aqueous ethanol yielded the desired 3α,17α-dihydroxy-16α-methylpregnane-11,20-dione (VI) in an 80% yield, m.p. 191–193°.

We cannot understand the experience of the Ciba group[3] who found that the application of this procedure to a similar series of 16α-methylated steroids did not give the desired enol lactone acetate (compare IV). These authors imply that the selective enol lactone acetate formation ($\Delta^{17,20}$) from the glyoxylic acid III is inhibited because of steric interaction of the 16-methyl substituent and the grouping at C-20. That this explanation is not completely valid, is attested to by the synthesis of VI and also by the application of this approach by Hoffsommer *et al.*[6] to the synthesis of 3α,17α-dihydroxy-16,16-dimethylpregnane-11,20-dione—a compound in which this type of steric effect should be enhanced. Perhaps the reason for the divergence is because of minor differences in procedure.

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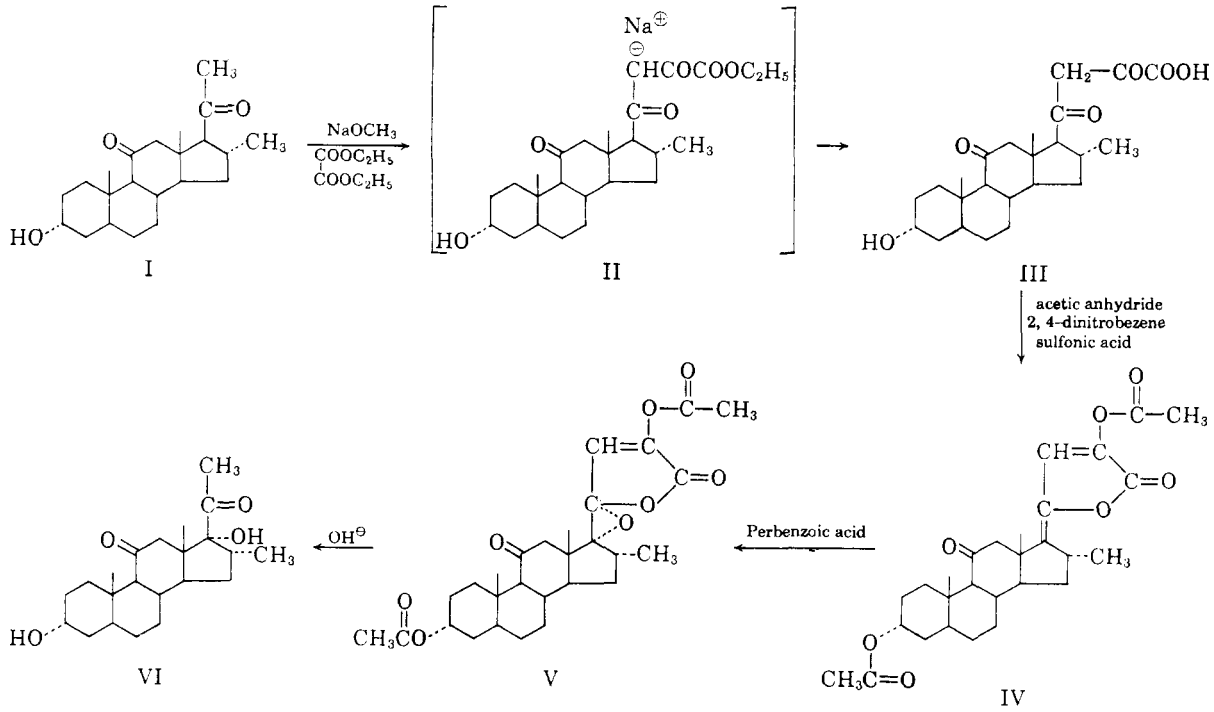

EXPERIMENTAL[7]

3α-Hydroxy-16α-methyl-11,20-dioxo-21-pregnaneglyoxylic acid (III). To a slurry of 1.8 g. of sodium methoxide in 50 ml. of ether was added slowly 5.7 ml. of diethyl oxylate while keeping the temperature below 20°. The 3α-hydroxy-16α-methylpregnane-11,20-dione (I) (5.0 g.) was then added and the mixture heated at reflux for 2 hr. The slurry was cooled to 20–25° and 100 ml. of ether added with stirring to complete the precipitation of the sodium enolate. The ether was removed and the glyoxylic acid ester hydrolyzed at 20–25° by dissolving in 25 ml. of methanol and adding 200 ml. of aqueous 0.5*N* sodium hydroxide. The mixture was stirred at 20–25° for 6 hours and filtered to remove a slight turbidity. The filtrate was acidified to *p*H 2 by the addition of 2.5*N* HCl with good stirring. The keto acid was filtered, washed with four 20-ml. portions of water and dried in vacuum at 60° to give 5.1 g. of III (94.6%), m.p. 214°. Recrystallization from aqueous ethanol (92% recovery) raised the melting point to 243°; $\lambda_{max}^{CH_3OH}$ 293 mμ (10,200); $[\alpha]_D^{25}$ + 74.4° (*c* 1.0, dioxane).

Anal. Calcd. for $C_{24}H_{34}O_6$ (418.5): C, 68.87; H, 8.19. Found: C, 68.64; H, 8.43.

3α-23-Diacetoxy-16α-methyl-21-normethyl-11-oxo-17(20), 22-choladieno-24(20)-lactone (IV).[8] A mixture of 10 g. of the glyoxylic acid III, 100 ml. of acetic anhydride, and 500 mg. of 2,4-dinitrobenzenesulfonic acid was stirred at 25° for 2 hr. Sodium acetate (500 mg.) was added and the mixture concentrated in vacuum at 50°. The residue was taken up in 100 ml. of benzene and washed with 2 portions of 2.5*N* sodium hydroxide to remove the remaining acetic anhydride. The benzene solution was washed with water, dried, and concentrated in vacuum to dryness. Crystallization from 40 ml. of absolute ethanol gave 9.8 g. (85%) of IV; m.p. 165–175°; $\lambda_{max}^{CH_3CN}$ 297 mμ (22,800); $\lambda_{max}^{CHCl_3}$ 5.65, 5.75, 5.87, 6.20 μ; $[\alpha]_D^{24}$ + 42° (*c* 1.0, $CHCl_3$).

(7) Melting points are uncorrected.

Anal. Calcd. for $C_{28}H_{36}O_7$ (484.6): C, 69.40; H, 7.49. Found: C, 69.32; H, 7.48.

3α-23-Diacetoxy-16α-methyl-21-normethyl-17(20)-oxido-11-oxo-22-cholano-24(20)-lactone (V).[8] The enol lactone (IV) (12.7 g.) was added to 157 ml. of 0.50*M* perbenzoic acid in benzene and allowed to stand at 25° for 140 hours. The solution was cooled to 15°, and 15% sodium bisulfite solution was added to neutralize the excess peracid. The organic layer was separated and washed with saturated sodium bicarbonate solution and water. The benzene solution was dried over anhydrous sodium sulfate, filtered, and concentrated to 30 ml. The product was crystallized by adding 80 ml. of petroleum ether, filtered, and washed with petroleum ether to yield 12.8 g. (98%), m.p. 225–227°, $\lambda_{max}^{CH_3CN}$ 226 mμ (11,400); $\lambda_{max}^{CHCl_3}$ 5.6–5.62, 5.8, 5.85, 6.07 μ; $[\alpha]_D^{24}$ +75.2° (*c* 1.0, $CHCl_3$).

Anal. Calcd. for $C_{28}H_{36}O_8$ (500.6): C, 67.18; H, 7.25. Found: C, 67.03; H, 7.30.

3α,17α-Dihydroxy-16α-methylpregnane-11,20-dione (VI). To a suspension of 12.0 g. of V in 80 ml. of ethanol was added, with maintenance of temperature between 10–20°, 51 ml. of 1*N* sodium hydroxide over 30 min. The solution was stirred at 22–25° for 18 hours during which time the product (VI) separated. After filtration and washing with two 25-ml. portions of water, the wet cake was extracted into 150 ml. of ethyl acetate. The organic layer, after washing with water, was dried and concentrated in vacuum to 25 ml. After aging at 5° for 3 hours, the product was filtered, washed with cold ethyl acetate, and dried in vacuum to give 6.92 g. (79%), m.p. 191–193°; $[\alpha]_D^{24}$ +30.3° (*c* 1.0, $CHCl_3$); $\lambda_{max}^{CHCl_3}$ 2.9, 5.85 μ.

Anal. Calcd. for $C_{22}H_{34}O_4$: C, 72.89; H, 9.45. Found: C, 72.85; H, 9.33.

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(8) This preparation gives a mixture of geometrical isomers.