## Petrow and Williamson.

## 3595

## Modified Steroid Hormones. Part XI.\* 721. $16\alpha$ -Methyldeoxycorticosterone Acetate.

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16 $\alpha$ -Methyldeoxycorticosterone acetate (II; R = OAc, R' = H), required for studies of the effect of the  $16\alpha$ -methyl substituent upon mineralocorticoid activity, has been obtained by conventional routes from  $3\beta$ -hydroxy-16 $\alpha$ methylpregn-5-en-20-one (I; R = H) and  $16\alpha$ -methylprogesterone (II; R = $\mathbf{R}' = \mathbf{H}$ ).

4-Chloro- (II; R = H, R' = Cl) and 21-fluoro-16 $\alpha$ -methylprogesterone (II; R = F, R' = H) have also been prepared.

WE found previously <sup>1</sup> that  $6\alpha$ -methylation of diverse steroid types often leads to enhancement of progestational, anabolic, and glucocorticoid activity with a concomitant decrease in mineral corticoid activity, when present. The effect of  $6\alpha$ -methylation in antagonising  $Na^+$  retention and  $K^+$  excretion, however, though marked, is not entirely sufficient to eliminate undesirable water-retaining properties completely from certain steroidal structures. As complete elimination of mineralocorticoid activity accompanies 16amethoxylation of deoxycorticosterone,<sup>2</sup> it seemed likely that mineralocorticoid activity was highly susceptible to  $16\alpha$ -substitution. We therefore turned our attention to  $16\alpha$ methylation. Our primary object was to obtain qualitative information of the effect of this on the Na<sup>+</sup>-retaining and K<sup>+</sup>-excreting properties of deoxycorticosterone.<sup>†</sup>



Bromination of pregnan-20-one derivatives leads normally to 17,21-dibromides. An exception was encountered during the halogenation of  $3\beta$ -hydroxy- $16\alpha$ -methoxypregn-5en-20-one,<sup>2</sup> substitution occurring exclusively at position 21. This result was originally ascribed to the deactivating influence of the methoxyl group on the 17-hydrogen atom. Work to be described here and in subsequent publications, however, shows clearly the overriding steric rôle of the 16-substituent in shielding the 17-position from reagent attack with consequential reaction at position 21. Thus, careful bromination of  $3\beta$ -hydroxy- $16\alpha$ methylpregn-5-en-20-one (I; R = H) with 2 mols. of bromine led smoothly to the formation of 5,6,21-tribromo-3β-hydroxy-16α-methyl-5α-pregnan-20-one in excellent yield. Treatment with sodium iodide followed by acetolysis gave 21-acetoxy- $3\beta$ -hydroxy- $16\alpha$ methylpregn-5-en-20-one (I; R = OAc), which was converted into the required 21acetoxy-16 $\alpha$ -methylpregn-4-ene-3,20-dione (II; R = OAc, R' = H) by Oppenauer oxidation. The last compound was additionally prepared from  $16\alpha$ -methylprogesterone (II;

\* Part X, J., 1959, 788.

 $\dagger$  Since completion of the present study, the preparation of 16 $\alpha$ -methyl-corticoids has been reported by two separate groups <sup>3</sup> who, like ourselves, have found that in general 16α-methylation decreases mineralocorticoid activity.

<sup>1</sup> (a) Burn, Ellis, Petrow, Stuart-Webb, and Williamson, J., 1957, 4092; (b) Ackroyd, Adams, Ellis, Petrow, and Stuart-Webb, *ibid.*, p. 4099; (c) Grenville, Patel, Petrow, Stuart-Webb, and Williamson, *ibid.*, p. 4105; (d) Cooley, Ellis, Kirk, and Petrow, *ibid.*, p. 4112; (e) Barton, Ellis, and Petrow, J., 1959, 478.

<sup>2</sup> Cooley, Ellis, and Petrow, J., 1954, 1813.

<sup>3</sup> Arth, Johnston, Fried, Spooncer, Hoff, and Sarett, J. Amer. Chem. Soc., 1958, **80**, 3160; Arth, Fried, Johnston, Hoff, Sarett, Silber, Stoerk, and Winter, *ibid.*, p. 3161; Oliveto, Rausser, Nussbaum, Gebert, Hershberg, Tolksdorf, Eisler, Perlman, and Pechet, *ibid.*, p. 4428; Oliveto, Rausser, Weber, Nussbaum, Gebert, Coniglio, Hershberg, Tolksdorf, Eisler, Perlman, and Pechet, *ibid.*, p. 4428; Oliveto, Rausser, Weber, Nussbaum, Gebert, Coniglio, Hershberg, Tolksdorf, Eisler, Perlman, and Pechet, *ibid.*, p. 4431; Taub, Nussbaum, Gebert, Washing, Washing, Coniglio, Hershberg, Tolksdorf, Eisler, Perlman, and Pechet, *ibid.*, p. 4431; Taub, Nussbaum, Gebert, Washing, Marking, Marking Hoffsommer, Slates, and Wendler, ibid., p. 4435; Oliveto, Rausser, Herzog, Hershberg, Tolksdorf, Eisler, Perlman, and Pechet, ibid., p. 6687.

R = R' = H) via the intermediate 2,21-diethoxalyl derivatives.<sup>4</sup> This was transformed into 2-ethoxalyl-21-iodo-16 $\alpha$ -methylpregn-4-ene-3,20-dione by reaction with iodine. Acetolysis followed by removal of the 2-ethoxalyl residue furnished the required ketone (II; R = OAc, R' = H).

4-Chloro-16 $\alpha$ -methylprogesterone (II; R = H, R' = Cl) was readily obtained by direct chlorination <sup>5</sup> of 16 $\alpha$ -methylprogesterone, followed by dehydrohalogenation of the intermediate 4 $\xi$ ,5 $\xi$ -dichloride. The preparation of the 21-chloro-analogue (II; R = Cl, R' = H), in contrast, proved surprisingly difficult, reaction of 21-ethoxalyl-16 $\alpha$ -methylprogesterone <sup>6</sup> with chlorine yielding products which could not be obtained analytically pure. 21-Fluoro-16 $\alpha$ -methylprogesterone (II; R = F, R' = H) was obtained by Oppenauer oxidation of 21-fluoro-16 $\alpha$ -methylpregnenolone (I; R = F), readily formed by reaction of the corresponding iodide (I; R = I) with silver fluoride in aqueous aceto-nitrile.<sup>7</sup>

## EXPERIMENTAL

Rotations were determined in a 1 dm. tube for chloroform solutions unless otherwise stated. Ultraviolet absorption spectra (for ethanol solutions) were kindly determined by Mr. M. T. Davies, B.Sc. Alumina (B.D.H. chromatography grade) was used throughout.

5,6,21-Tribromo-3 $\beta$ -hydroxy-16 $\alpha$ -methylpregnan-20-one.—Bromine (9.6 g.) in acetic acid (30 ml.) was added dropwise to a stirred suspension of 3 $\beta$ -hydroxy-16 $\alpha$ -methylpregn-5-en-20-one (I; R = H) (9.9 g.) in ether (300 ml.) during 30 min. After being stirred for a further 30 min., the mixture was washed with sodium hydrogen carbonate solution and water, and the ether layer was dried (Na<sub>2</sub>SO<sub>4</sub>). Evaporation under reduced pressure at <30°, followed by crystallisation from methanol, gave 5,6,21-tribromo-3 $\beta$ -hydroxy-16 $\alpha$ -methylpregnan-20-one, needles, m. p. 160—162°, [ $\alpha$ ]<sub>D</sub> +93° (c 0.776) (Found: C, 46.2; H, 5.9; Br, 43.3. C<sub>22</sub>H<sub>33</sub>O<sub>2</sub>Br<sub>3</sub> requires C, 46.4; H, 5.8; Br, 42.2%).

21-Iodo-3 $\beta$ -hydroxy-16 $\alpha$ -methylpregn-5-en-20-one (I; R = I).—The foregoing tribromide (3.3 g.) in benzene (100 ml.) was treated with sodium iodide (6.6 g.) in absolute alcohol (45 ml.), and the mixture left overnight at room temperature. Water was added and the benzene layer was separated, washed with 3% sodium thiosulphate solution, then with water, and dried. Evaporation of the benzene under reduced pressure at <40° left a residue which crystallised from methanol to give 21-iodo-3 $\beta$ -hydroxy-16 $\alpha$ -methylpregn-5-en-20-one, prisms, m. p. 136—137°, [ $\alpha$ ]<sub>p</sub><sup>21</sup> +85° (c 0.518) (Found: C, 57.8; H, 7.2; I, 28.3. C<sub>22</sub>H<sub>33</sub>O<sub>2</sub>I requires C, 57.9; H, 7.3; I, 27.8%).

21-Acetoxy-3 $\beta$ -hydroxy-16 $\alpha$ -methylpregn-5-en-20-one (I; R = OAc).—3 $\beta$ -Hydroxy-21-iodo-16 $\alpha$ -methylpregn-5-en-20-one (I; R = I) (3 g.) in acetone (30 ml.) was added to potassium hydrogen carbonate (6 g.) and glacial acetic acid (3.8 ml.), and the mixture boiled under reflux for 24 hr. Water was added and the precipitated solids were collected, washed with water, dried, and crystallised from methanol, yielding 21-acetoxy-3 $\beta$ -hydroxy-16 $\alpha$ -methylpregn-5-en-20-one, needles, m. p. 152—154°,  $[\alpha]_{\rm D}^{21}$  +14° (c 0.592) (Found: C, 73.9; H, 9.3. C<sub>24</sub>H<sub>36</sub>O<sub>4</sub> requires C, 74.2; H, 9.3%).

21-Acetoxy-16 $\alpha$ -methylpregn-4-ene-3,20-dione (II; R = OAc, R = H).—(a) The compound (I; R = OAc) (3 g.) was boiled in cyclohexanone (45 ml.) until 10 ml. of distillate had been collected. Aluminium t-butoxide (3 g.), dissolved in dry toluene (25 ml.), was then added and the mixture heated under reflux for 45 min. Rochelle salt solution was added and the mixture steam-distilled for 6 hr. The product was isolated with ether and crystallised from aqueous methanol, to give 21-acetoxy-16 $\alpha$ -methylpregn-4-ene-3,20-dione, needles, m. p. 136—138°,  $[\alpha]_{\rm p}^{23}$  + 160° (c 0.706)  $\lambda_{\rm max}$  240 mµ ( $\epsilon$  16,155) (Found: C, 74.5; H, 8.8; C<sub>24</sub>H<sub>34</sub>O<sub>4</sub> requires C, 74.5; H, 8.8%).

(b)  $16\alpha$ -Methylprogesterone (II; R = R' = H) (3.3 g.) in t-butyl alcohol (100 ml.) was mixed with ethyl oxalate (11.7 g.) at 70°. When the temperature had fallen to 55°, a solution of sodium methoxide (2.7 g.) in methanol (12 ml.) was added and the mixture stirred for 15 min. To this mixture containing the sodium dienolate of 2,21-diethoxalyl-16 $\alpha$ -methylpregn-4-ene-3,20-dione a solution of acetic acid (3 g.) in methanol (160 ml.) was added, followed by iodine

<sup>6</sup> B.P. 738,445.

<sup>4</sup> B.P. 775,411.

<sup>&</sup>lt;sup>5</sup> Kirk, Patel, and Petrow, J., 1956, 1184.

<sup>7</sup> Jacobsen and Jensen, Chem. and Ind., 1957, 172.

 $(5\cdot 1 \text{ g.})$  in methanol (100 ml.). The mixture was stirred for  $2\frac{1}{2}$  hr. at room temperature and the resulting 2,21-diethoxalyl-21-iodo-16 $\alpha$ -methylpregn-4-ene-3,20-dione treated with potassium acetate (39 g.) and left at room temperature for 24 hr. The mixture was then poured into icewater (1 1.) containing sodium thiosulphate (4.5 g.) and concentrated sulphuric acid (6 ml.). The precipitate of 21-acetoxy-2-ethoxalyl-16 $\alpha$ -methylprogesterone was collected, washed with water, and dried. It was dissolved in methanol (120 ml.) containing sodium acetate (5 g.) and treated with bromine (2.5 g.) in methanol (25 ml.) at 0°. Sodium methoxide (0.845 g.), in methanol (5 ml.) was then added and the mixture stirred whilst it came to room temperature. Glacial acetic acid (8 ml.) and zinc dust (3.5 g.) were added and the mixture was stirred for 1 hr. The suspended matter was next removed and the filtrate poured into water (1 1.). The precipitate of 21-acetoxy-16 $\alpha$ -methylprogesterone was collected, washed with water, and dried. The crude product was chromatographed on alumina (110 g.). Benzene-acetone (9:1) eluates gave 21-acetoxy-16 $\alpha$ -methylpregn-4-ene-3,20-dione as needles, m. p. and mixed m. p. 134—136° (from methanol). The product gave a purple colour with the tetrazolium reagent.

4-Chloro-16α-methylpregn-4-ene-3,20-dione (II; R = H, R' = Cl).—16α-Methylprogesterone (II; R = R' = H) (1 g.) in ether (50 ml.) was treated with a 0.84M-solution of chlorine in propionic acid (4·2 ml.) at  $-30^{\circ}$  and left in the dark for 18 hr. at this temperature. More ether was added and the acids were washed out with water. The ether was evaporated under reduced pressure at  $<30^{\circ}$ . The residue crystallised from methanol in needles, m. p. 168—170° (Found: Cl, 16·4. Calc for C<sub>22</sub>H<sub>32</sub>O<sub>2</sub>Cl<sub>2</sub>: Cl, 17·8%). This crude 4ξ,5ξ-dichloride (250 mg.) was dissolved in benzene (3 ml.) containing pyridine (0·5 ml.) and left at room temperature for 4 hr. The product was isolated with ether and crystallised from methanol, to give 4-chloro-16α-methylpregn-4-ene-3,20-dione, needles, m. p. 180—182°, [α]<sub>D</sub><sup>22</sup> + 175° (c 1·148), λ<sub>max</sub>. 254—256 mμ, (ε 13,900) (Found: C, 72·9; H, 8·7; Cl, 9·8. C<sub>22</sub>H<sub>31</sub>O<sub>2</sub>Cl requires C, 72·8; H, 8·5; Cl, 9·8%).

21-Chloro-16α-methylpregn-4-ene-3,20-dione (II; R = Cl, R' = H).—16α-Methylprogesterone (3·3 g.) in dry benzene (75 ml.) was added rapidly to a mixture of dry sodium methoxide (0·59 g.), dry benzene (20 ml.), and ethyl oxalate (2·7 ml.) which had been stirred at room temperature until a clear solution was obtained and had then been diluted with absolute alcohol (1 ml.). After being stirred at room temperature for 2 hr., the mixture was diluted with dry ether (250 ml.) and after a further 45 minutes' stirring the precipitated sodium enolate of 21-ethoxalyl-16α-methylpregn-4-ene-3,20-dione was collected and dried. It was dissolved in methanol (100 ml.) and treated dropwise with a solution of chlorine in dimethylformamide (45 ml.) containing 0·027 g. of chlorine/ml., during 1 hr. at  $-20^{\circ}$ . The mixture was stirred at this temperature for a further 60 min., then treated with 3·4N-methanolic sodium methoxide (4·8 ml.) at 0° for 1 hr. A saturated salt solution was then added and the product isolated with benzene and chromatographed on alumina. Benzene eluates gave slightly impure 21-chloro-16α-methylpregn-4-ene-3,20-dione which crystallised from methanol in needles, m. p. 178— 180°, [ $\alpha$ ]<sub>D</sub><sup>24</sup> +171° (c 0·498)  $\lambda_{max}$ . 243 mµ ( $\epsilon$  14,350) (Found: C, 71·9; H, 8·5; Cl, 10·4. Calc. for C<sub>22</sub>H<sub>31</sub>O<sub>2</sub>Cl: C, 72·8; H, 8·5; Cl, 9·8%).

21-Fluoro-3 $\beta$ -hydroxy-16 $\alpha$ -methylpregn-5-en-20-one (I; R = F).—To 3 $\beta$ -hydroxy-21-iodo-16 $\alpha$ -methylpregn-5-en-20-one (I; R = I) (1.6 g.) in acetonitrile (50 ml.) were added aqueous silver fluoride solution (50% w/v) (5 ml.) and sufficient distilled water to give a clear solution. The whole was kept at 50° for 40 hr., then filtered, and water was added to the filtrate. The precipitate was collected and crystallised from methanol, to give 21-fluoro-3 $\beta$ -hydroxy-16 $\alpha$ methylpregn-5-en-20-one, prisms, m. p. 190—192°,  $[\alpha]_{\rm p}^{20}$  +10° (c 0.514) (Found: C, 75.5; H, 9.4. C<sub>22</sub>H<sub>33</sub>O<sub>2</sub>F requires C, 75.8; H, 9.5.

21-Fluoro-16 $\alpha$ -methylpregn-4-ene-3,20-dione (II; R = F, R' = H).—Oxidation of compound (I; R = F) (0.9 g.) in cyclohexanone (12 ml.) with aluminium t-butoxide (1.0 g.) in toluene (8 ml.) for 45 min. under reflux, followed by steam-distillation in the presence of Rochelle salt solution, gave an oil which was isolated with chloroform. Crystallisation from acetone-hexane gave 21-fluoro-16 $\alpha$ -methylpregn-4-ene-3,20-dione, prisms, m. p. 139—140°, [ $\alpha$ ]<sub>p</sub><sup>23</sup> +177° (c 0.34)  $\lambda_{max}$ . 240 mµ ( $\epsilon$  16,350) (Found: C, 76.4; H, 9.2; F, 5.1. C<sub>22</sub>H<sub>31</sub>O<sub>2</sub>F requires C, 76.2; H, 8.9; F, 5.5%).

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