Tetrahedron, 1966, Vol. 22, pp. 365 to 367. Pergamon Press Ltd. Printed in Northern Ireland

MODIFIED STEROID HORMONES—XLII[1]

PARTIAL SYNTHESIS OF 17α-ACETOXY-6-ACETOXYMETHYLPREGNA-4,6-DIENE-3,20-DIONE AND ITS 2α-ACETOXY DERIVATIVE, TWO ACETYLATED METABOLITES OF MEGESTROL ACETATE

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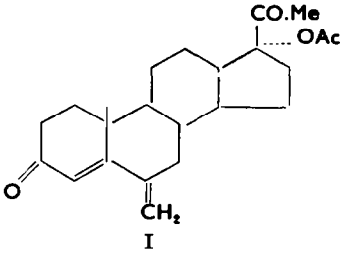
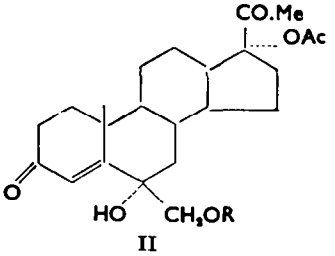
(*Received* 31 *July* 1965)

Abstract—The isolation from rabbit urine of two major metabolites of megestrol acetate (17α-acetoxy-6-methylpregna-4,6-diene-3,20-dione[2]) has been reported,[3] and evidence presented[3] for their identity with 17α-acetoxy-6-hydroxymethylpregna-4,6-diene-3,20-dione and 17α-acetoxy-2α-hydroxy-6-hydroxymethylpregna-4,6-diene-3,20-dione, respectively. The present communication records the partial synthesis of 17α-acetoxy-6-acetoxymethylpregna-4,6-diene-3,20-dione (III; R = Ac, R^1 = H) and its 2α-acetoxy derivative (III; R = Ac, R^1 = α-OAc) used in the foregoing identification studies.

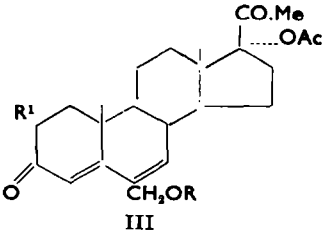
ADDITION of osmium tetroxide to 17α-acetoxy-6-methylenepregn-4-ene-3,20-dione[4] (I) in pyridine afforded in good yield a crystalline steroid-osmium tetroxide-pyridine complex, cleaved by hydrogen sulphide in dioxan[5] to 17α-acetoxy-6α-hydroxy-6β-hydroxymethylpregn-4-ene-3,20-dione (II; R = H). The C_6-hydroxyl group present in this intermediate has been assinged the α-(equatorial) configuration on the basis of



I



II



III

[1] Part XLI, M. T. Davies, B. Ellis, D. N. Kirk and V. Petrow, *Tetrahedron* **21**, 3185 (1965).
[2] B. Ellis, D. N. Kirk, B. Waterhouse and D. M. Williamson, *J. Chem. Soc.* 2828 (1960).
[3] J. M. Cooper, H. E. H. Jones and A. E. Kellie, *Steroids* **6**, 255 (1965).
[4] D. Burn, G. Cooley, M. T. Davies, J. W. Ducker, B. Ellis, P. Feather, A. K. Hiscock, D. N. Kirk, A. P. Leftwick, V. Petrow and D. M. Williamson, *Tetrahedron* **20**, 597 (1964).
[5] D. H. R. Barton and D. Elad, *J. Chem. Soc.* 2085 (1956).

physical data discussed in Part XLIII.[6] The diol (II; R = H) formed (a) an isopropylidenedioxy derivative by acid-catalysed condenstation with acetone, and (b) the 6β-acetoxymethyl derivative (II; R = Ac) on acetylation. Treatment of the diol (II; R = H) with perchloric acid in acetic acid–acetic anhydride, or of the 6β-acetoxymethyl derivative (II; R = Ac) with thionyl chloride in pyridine gave, in each case, a crude dehydration product which could not be purified satisfactorily, but from which 17α-acetoxy-6-hydroxymethylpregna-4,6-diene-3,20-dione (III; R = R^1 = H) was isolated following hydrolysis with hot methanolic hydrochloric acid. Acetylation of the last compound gave 17α-acetoxy-6-acetoxymethylpregna-4,6-diene-3,20-dione (III; R = Ac, R^1 = H).

Direct acetoxylation of a Δ^4-3-ketosteroid with lead tetra-acetate leads generally to a mixture of the corresponding 2α- and 2β-acetoxy derivatives.[7] This reaction, to our knowledge, has not hitherto been extended to 4,6-diene-3-ketones substituted or unsubstituted at C_6. We have now found that lead tetra-acetate converts compound III(R = Ac, R^1 = H) into an amorphous solid from which 2β,17α-diacetoxy-6-acetoxymethylpregna-4,6-diene-3,20-dione (III; R = Ac, R^1 = β-OAc) may be isolated in 20% yield by a simple crystallization procedure. The 2α-acetoxy epimer could not be isolated from the other products of this reaction. Prolonged treatment of the 2β-acetoxy derivative (III; R = Ac, R^1 = β-OAc) with hot potassium acetate–acetic acid effected its epimerization[8] to 2α,17α-diacetoxy-6-acetoxymethylpregna-4,6-diene-3,20-dione (III; R = Ac, R^1 = α-OAc). The constitutions assigned to the last two compounds are based upon physical data, which, together with a detailed discussion, are presented in Part XLIV.[9]

EXPERIMENTAL

Optical rotations were determined at concentrations of ca. 1% in A.R. $CHCl_3$ at laboratory temp. UV spectra refer to solutions in spectro-grade EtOH. IR spectra were determined with a Hilger H800 spectrophotometer fitted with CaF_2 and NaCl prisms for the frequency ranges 4000–1300 and 1350–650 cm^{-1} respectively, the solvents used being as indicated. NMR spectra were determined at 40 Mc/s with a Perkin–Elmer permanent magnet spectrometer, employing a crystal calibrated decade field shift. Solutions were in $CDCl_3$ containing tetramethylsilane as internal reference.

17α-Acetoxy-6α-hydroxy-6β-hydroxymethylpregn-4-ene-3,20-dione (II; R = H)

A mixture of 17α-acetoxy-6-methylenepregn-4-ene-3,20-dione[4] (2·7 g) and osmium tetroxide (2 g) in dry pyridine (40 ml) was kept for 4 days at room temp. The complex (3·3 g, m.p. 212–225°) which separated was suspended in dry dioxan (120 ml) and a stream of H_2S passed through the suspension for 5 min. The mixture was filtered, the residue washed with dioxan, and the combined filtrate and washings evaporated *in vacuo*. The residual material was treated with a few ml EtOH, and the solvent removed *in vacuo*. This treatment was repeated to give a crystalline product which was purified from EtOH. The *diol* formed prisms (0·8 g), m.p. 219–220°, $[\alpha]_D$ +37°, λ_{max} 243·5 mμ (ε 13,850), $\nu_{max}^{CH_2Cl_2}$ 3578, 3442, 1730, 1716, 1668 and 1607 cm^{-1}, τ 9·32, 8·78, 7·95, 7·89, 7·40, 6·38 and 3·64. (Found: C, 68·2; H, 8·2. $C_{24}H_{34}O_6$ requires: C, 68·9; H, 8·2%.)

The *isopropylidenedioxy derivative*, prepared by treating the foregoing compound (0·33 g) in acetone (20 ml) with 2 drops of conc. HCl and allowing the mixture to stand for 18 hr at room temp, separated

[6] Part XLIII, D. Burn, G. Cooley, M. T. Davies, B. Ellis, V. Petrow and J. P. Yardley, *Tetrahedron* **22**, 369 (1966).

[7] See F. Sondheimer, St. Kaufmann, J. Roms, H. Martinez and G. Rosenkranz, *J. Amer. Chem. Soc.* **75**, 4712 (1953) and references cited therein.

[8] R. L. Clarke, K. Dobriner, A. Mooradian and C. M. Martini, *J. Amer. Chem. Soc.* **77**, 661 (1955).

[9] Part XLIV, F. K. Butcher, G. Cooley, M. T. Davies and V. Petrow, *Tetrahedron* **22**, 377 (1966).

from acetone–hexane in blades (0·35 g), m.p. 207–208°. $[\alpha]_D$ +46°, λ_{max} 242 mμ (ε 13,480), $\nu_{max}^{CCl_4}$ 1741, 1720, 1660 and 1612 cm^{-1}. (Found: C, 70·5; H, 8·4. $C_{27}H_{38}O_6$ requires: C, 70·7; H, 8·35%.)

The *6β-acetoxymethyl derivative* (II; R = Ac) crystallized from EtOH in needles, m.p. 175–175·5°, $[\alpha]_D$ +29°, λ_{max} 241 mμ (ε 14,050), $\nu_{max}^{CCl_4}$ 3595, 3470, 1743, 1723, 1685 and 1609 cm^{-1}, τ 9·30, 8·76 7·95, 7·89, 7·56, 6·02 [and 5·58 (quartet)] and 3·62. (Found: C, 68·3; H, 8·1. $C_{36}H_{56}O_7$ requires: C, 67·8; H, 7·9%.)

17α-Acetoxy-6-hydroxymethylpregna-4,6-diene-3,20-dione (III; R = R^1 = H)

(a) A solution of II(R = H; 0·4 g) in acetic acid (10 ml) and acetic anhydride (2·5 ml) was treated with 2 drops 72% perchloric acid, and the mixture set aside for 45 min at room temp. It was poured into water, and the precipitate dissolved in MeOH (5 ml) to which conc. HCl (0·04 ml) had been added. The solution was refluxed for 1½ hr, water (20 ml) was added, and the mixture filtered rapidly. The filtrate deposited *17α-acetoxy-6-hydroxymethylpregna-4,6-diene-3,20-dione* (51 mg), needles, m.p. 125–127°, $[\alpha]_D$ +16°, λ_{max} 284 mμ (ε 21,900), $\nu_{max}^{CCl_4}$ 3625, 3435, 1745, 1724, 1670 and 1633 cm^{-1}, τ 9·255, 8·88, 7·94, 7·91, 5·69, 4·17 and 3·79. (Found: C, 69·3; H, 7·9. $C_{24}H_{32}O_6 \cdot H_2O$ requires: C, 68·9; H, 8·2%.) Crystallization from benzene gave the anhydrous compound, blades, m.p. 206°, $[\alpha]_D$ +11·5°, λ_{max} 284 mμ (ε 23,600). (Found: C, 71·55; H, 8·1. $C_{24}H_{32}O_6$ requires: C, 71·95; H, 8·05%.)

(b) Thionyl chloride (0·7 ml) was added dropwise during 10 min to a solution of II(R = Ac; 1·15 g) in dry pyridine (11·5 ml) at −5°. After a further 10 min at this temp, the mixture was poured into water, and the precipitate collected and air dried. Its solution in MeOH (11·5 ml) and conc. HCl (0·1 ml) was refluxed for 1½ hr, diluted with water to 100 ml, and filtered hot. The filtrate was stored for 18 hr at 0° to give III(R = R^1 = H; 0·22 g), needles, m.p. 125–127°, not depressed in admixture with a specimen prepared by method (a) above.

17α-Acetoxy-6-acetoxymethylpregna-4,6-diene-3,20-dione (III; R = Ac, R^1 = H)

This was prepared by acetylation of the foregoing compound, crystallized from acetone–hexane, in needles, m.p. 191°, $[\alpha]_D$ +21°, λ_{max} 280 mμ (ε 23,900), $\nu_{max}^{CH_2Cl_2}$ 1730, 1712, 1659, 1629 and 1584 cm^{-1}, τ 9·266, 8·89, 7·94, 7·90, 5·28, 4·08 and 3·70. (Found: C, 70·1; H, 7·8. $C_{26}H_{34}O_6$ requires: C, 70·55; H, 7·7%.)

2β,17α-Diacetoxy-6-acetoxymethylpregna-4,6-diene-3,20-dione (III; R = Ac, R^1 = β-OAc)

The foregoing compound (1·8 g) in glacial acetic acid (26·7 ml) was treated with lead tetra-acetate (2·8 g) and the mixture heated for 2½ hr at 100°. Dilution with water gave an amorphous solid which was crystallized from MeOH. The *2β-acetoxy derivative* separated in dense flat diamond-shaped crystals (0·35 g), m.p. 204°, $[\alpha]_D$ −37·5°, λ_{max} 286 mμ (ε 22,700). (Found: C, 67·2; H, 7·2. $C_{28}H_{36}O_8$ requires: C, 67·2; H, 7·25%.)

2α,17α-Diacetoxy-6-acetoxymethylpregna-4,6-diene-3,20-dione (III; R = Ac, R^1 = α-OAc)

A solution of the foregoing compound (0·2 g) and potassium acetate (0·5 g) in glacial acetic acid (7·5 ml) was heated for 18½ hr at 100°. The mixture was poured into water, and the precipitate purified from aqueous acetic acid to give the *2α-acetoxy derivative* (90 mg), needles, m.p. 110°, $[\alpha]_D$ +5°, λ_{max} 280 mμ (ε 21,200). (Found: C, 67·1; H, 7·3. $C_{28}H_{36}O_8$ requires: C, 67·2; H, 7·25.)