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MODIFIED STEROID HORMONES—XLV[1]

17α-ACETOXY-6-METHYLPREGNA-4,6-14-TRIENE-3,20-DIONE AND RELATED COMPOUNDS

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Abstract—Routes to 17α-acetoxy-6-methylpregna-4,6,14-triene-3,20-dione, 17α,21-diacetoxy-6-methylpregna-4,6,14-triene-3,20-dione and related compounds, are described.

WE REPORT herein the preparation, for biological study, of 17α-acetoxy-6-methylpregna-4,6,14-triene-3,20-dione and some of its derivatives, which compounds may be regarded as structurally related to the progestagen, megestrol acetate (17α-acetoxy-6-methylpregna-4,6-diene-3,20-dione).[2]

The starting material, 14α,17α,21- trihydroxypregn-4-ene-3,20-dione (14α-hydroxy Compound S),[3] employed for the presently described series of transformations, was of microbiological origin and contained ca. 15% of a contaminant, probably 7α,14α-dihydroxy compound S. This impurity was eliminated at an early stage by one or other procedures best fitted to particular synthetic routes explored, which are conveniently presented in Sections (a) and (b) below.

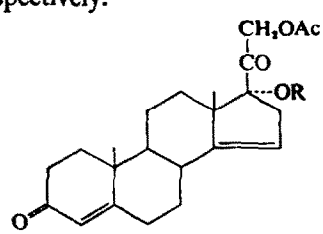
Section (a). Crude 14α-hydroxy compound S (V; R=OH) was purified as the 21-monoacetate[4,5] (V; R = OAc), thereby effectively removing the contaminant referred to above, and was then converted into 21-acetoxy-17α-hydroxypregna-4,14-diene-3,20-dione[4] (I; R = H) by selective dehydration with toluene-*p*-sulphonic acid in boiling benzene. Enforced acetylation gave the 17α,21-diacetate (I; R = Ac), readily transformed by enol etherification with trimethylorthoformate into 17α,21-diacetoxy-3-methoxypregna-3,5-14-trien-20-one (II; R = H). In analogy with the behaviour of other 3-alkoxy-3,5-dienes,[6] the last compound on treatment with the Vilsmeier reagent prepared from phosgene and dimethylformamide passed into the 6-formyl-3-methyl enol ether (II; R = CHO) having the UV and IR absorption spectral characteristics (Experimental) expected for this type of chromophore. Transfer hydrogenation of compound (II; R = CHO) in ethanol, employing a 5% Pd—C catalyst and cyclohexene as hydrogen donor, followed a previously established[7] pattern, and afforded 17α,21-diacetoxy-6α-methylpregna-4,14-diene-3,20-dione (III),

[1] Part XLIV, F. K. Butcher, G. Cooley, M. T. Davies and V. Petrow, *Tetrahedron* **22**, 377 (1966).
[2] B. Ellis, D. N. Kirk, V. Petrow, B. Waterhouse and D. M. Williamson, *J. Chem. Soc.* 2828 (1960).
[3] We thank Dr. de Flines of the Royal Netherlands Fermentation Industries Ltd. for a generous gift of this material with which we were able to carry out much of the work described herein.
[4] B. M. Bloom, E. J. Agnello and G. D. Laubach, *Experientia* **12**, 27 (1956).
[5] S. H. Epstein, P. D. Meister, D. H. Peterson, H. C. Murray, H. M. Leigh Osborn, A. Weintraub, L. M. Reincke and R. C. Meeks, *J. Amer. Chem. Soc.* **80**, 3382 (1958).
[6] 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).
[7] D. Burn, D. N. Kirk and V. Petrow, *Tetrahedron* **21**, 1619 (1965).

dehydrogenated by chloranil to 17α,21-diacetoxy-6-methylpregna-4,6,14-triene-3,20-dione (IV), the 21-acetoxy-Δ^{14}-derivative of megestrol acetate.

Section (b). Pathways to 17α-hydroxypregna-4,14-diene-3,20-dione (VI; R = H), an essential intermediate required for conversion into the title compounds, were investigated with the following results. Mesylation of 14α-hydroxy compound S afforded a crude product, which, without purification, was demesylated by treatment with hot sodium iodide–acetic acid. Fractional crystallization of the mixture thus obtained gave 17α-hydroxypregna-4,14-diene-3,20-dione (VI; R = H) in reasonable yield, and a minor proportion of 17α-hydroxypregna-4,6,8(14)-triene-3,20-dione (VII; R = H), the identity of which was confirmed by conversion into the known 17α-acetoxy derivative[8] (VII; R = Ac). Compound VII(R = H) evidently arose from the contaminant (probably 7α,14α-dihydroxy compound S) present in the crude 14α-hydroxy compound S used as starting material for the foregoing reaction sequence. In a second route to the required intermediate (VI; R = H), the purified 21-mesylate (V; R = OMesyl) of 14α-hydroxy compound S was transformed by hot acetone–sodium iodide into the 21-iodo analogue (V; R = I), and thence by reduction with sodium metabisulphite[9] into 14α,17α-dihydroxypregna-4-ene-3,20-dione (V; R = H). Dehydration of the last compound with toluene-*p*-sulphonic acid in boiling benzene then gave 17α-hydroxypregna-4,14-diene-3,20-dione (VI; R = H) in good overall yield. Enforced acetylation furnished the 17α-acetoxy derivative[8] (VI; R = Ac) which formed a 3-methyl enol ether (VIII; R = H). Formylation with the Vilsmeier reagent then gave the 6-formyl 3-enol ether (VIII; R = CHO) which was reduced with lithium borohydride to the corresponding 6-hydroxymethyl 3-enol ether (VIII; R = CH_2OH). This compound like others of its type,[6] underwent facile dehydration on treatment with aqueous acetic acid, to give 17α-acetoxy-6-methylenepregna-4,14-diene-3,20-dione (IX), isomerized by Pd charcoal and sodium acetate in ethanol[7] to the title compound (X). An alternative route to 17α-acetoxy-6-methyl-pregna-4,6,14-triene-3,20-dione (X) involved reduction of the 6-formyl 3-enol ether (VIII; R = CHO) in ethanol with Pd-charcoal and cyclohexene,* followed by chloranil dehydrogenation of the resulting 17α-acetoxy-6α-methylpregna-4,14-diene-3,20-dione (XI).

Dehydrogenation of the last compound (XI) and of the title compound (X) with 2,3-dichloro-5,6-dicyano-*p*-benzoquinone[10] gave 17α-acetoxy-6α-methylpregna-1,4,14-triene-3,20-dione (XII) and 17α-acetoxy-6-methylpregna-1,4,6,14-tetraene-3,20-dione (XIII), respectively.



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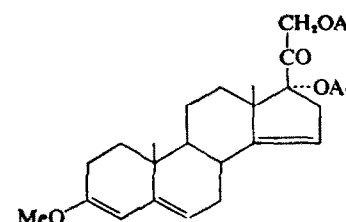


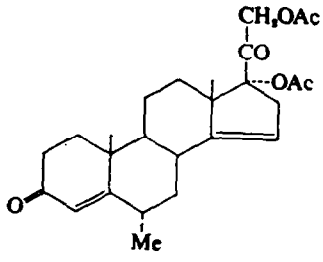
II

* It is noteworthy that in this transfer hydrogenation reaction, 17α-acetoxy-3-methoxy-6-methyl-pregna-3,5,14-trien-20-one was formed together with XI (cf Ref[7]).

[8] F. Bohlmann, V. Hinz and B. Diedrich, *Chem. Ber.* **96**, 1316 (1963).

[9] Cf. P. L. Julian and W. J. Karpel, *J. Amer. Chem. Soc.* **72**, 362 (1950).

[10] D. Burn, D. N. Kirk and V. Petrow, *Proc. Chem. Soc.* 14 (1960).



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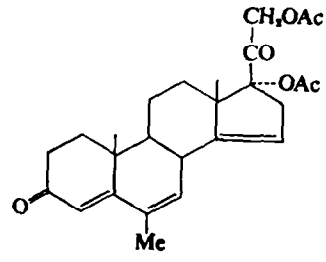

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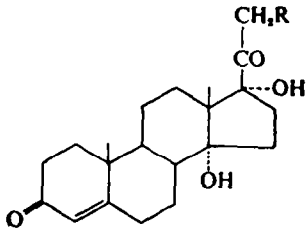

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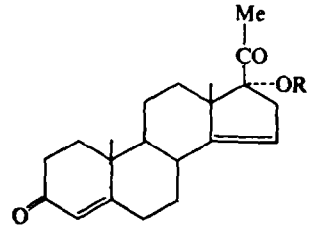

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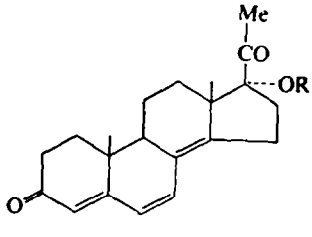

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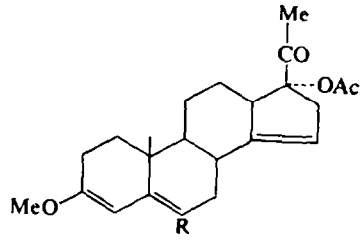

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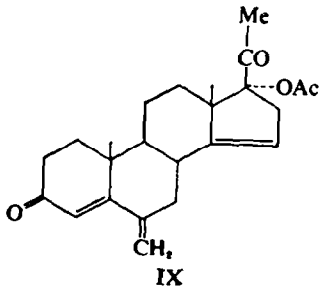

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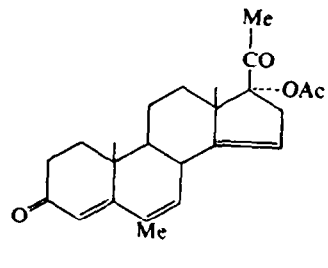

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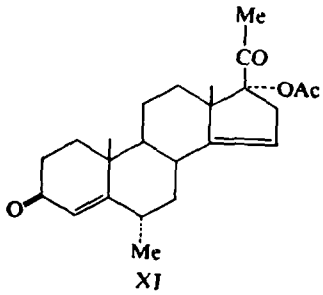

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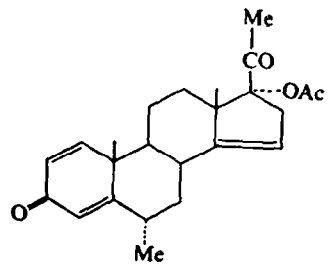
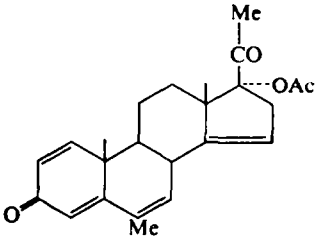


XII



XIII

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 range 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. The spectroscopic determinations were carried out under the direction of Mr. M. T. Davies, B.Sc., F.R.I.C. The 14α-hydroxy Compound S employed was of microbiological origin and had m.p. 217–222° (after softening at 210°), $[\alpha]_D$ +168°, $\nu_{max}^{CH_2Cl_2}$ 3598, 3480, 1715, 1668 and 1619 cm^{-1}.

17α-21-*Diacetoxypregna*-4,14-*diene*-3,20-*dione* (I; R = Ac)

21-Acetoxy-17α-hydroxypregna-4,14-diene-3,20-dione (4·65 g) was dissolved in a mixture of redistilled AcOH (100 ml), Ac_2O (19 ml) and toluene-*p*-sulphonic acid (3·5 g). The solution was stored under N_2 for 16 hr at room temp, then poured into water, and the product crystallized from MeOH. The 17α,21-diacetate (2·9 g) formed plates, m.p. 193·5–194°, $[\alpha]_D$ −0·5°, λ_{max} 238 mμ (ε, 17,700), $\nu_{max}^{CS_2}$ 1756, 1741, 1681 and 1230 cm^{-1}, τ 9·01, 8·79, 7·92, 7·85, 7·66, 5·12, 4·8 and 4·22. (Found: C, 70·1; H, 7·7. $C_{25}H_{32}O_6$ requires: C, 70·1; H, 7·5%.)

In other experiments in which glacial AcOH (not redistilled) was employed in the reaction mixture, the product consisted largely of 3,17α,21-*triacetoxypregna*-3,5,14-*trien*-20-*one*, needles (from aqueous MeOH), m.p. 129·5–130°, $[\alpha]_D$ −168°, λ_{max} 234 mμ (ε, 19,670), $\nu_{max}^{CS_2}$ 1762, 1742, 1230, 1215 and 1200 cm^{-1}. (Found: C, 68·95; H, 7·6. $C_{27}H_{34}O_7$ requires: C, 68·9; H, 7·3%.)

17α,21-*Diacetoxy*-3-*methoxypregna*-3,5,14-*trien*-20-*one* (II; R = H)

17α,21-Diacetoxypregna-4,14-diene-3,20-dione (22·8 g) in dry dioxan (400 ml), MeOH (2 ml), and trimethylorthoformate (20 ml) was treated with H_2SO_4 (0·75 g) in dioxan (15 ml). Pyridine (15 ml) was added after 30 min, followed by water (3 l.), and the mixture set aside overnight. The product was purified from MeOH containing a trace of pyridine to give the 3-methyl enol ether (14·6 g), needles, m.p. 137·5–138°, $[\alpha]_D$ −168° (in $CHCl_3$ containing trace of pyridine), λ_{max} 240 mμ (ε, 21,290), $\nu_{max}^{CCl_4}$ 1755, 1738, 1656 and 1629 cm^{-1}. (Found: C, 70·1; H, 7·6. $C_{26}H_{34}O_6$ requires: C, 70·6; H, 7·7%.)

17α,21-*Diacetoxy*-6-*formyl*-3-*methoxypregna*-3,5,14-*trien*-20-*one* (II; R = CHO)

The foregoing compound (1·35 g) in ethylene dichloride (6·25 ml containing 1 drop of pyridine) was added to an ice-cooled Vilsmeier reagent prepared from redistilled dimethylformamide (1·25 ml), ethylene dichloride (5 ml) and phosgene in ethylene dichloride (10 ml of 10% w/v solution). The stirred mixture was allowed to reach room temp during 2 hr, and then poured into a solution of AcONa (2 g) in water (3 ml) and MeOH (12·5 ml). The mixture was stirred a further 10 min, and the product isolated with ether. Purified from MeOH, the 6-formyl derivative formed plates (1 g), m.p. 176·5°, $[\alpha]_D$ −153°, λ_{max} 219 mμ (ε, 11,500) and 321 mμ (ε, 15,340), $\nu_{max}^{CH_2Cl_2}$ 1751, 1737, 1663, 1615 and 1585 cm^{-1}. (Found: C, 68·4; H, 7·1. $C_{27}H_{34}O_7$ requires: C, 68·9; H, 7·3%.)

17α,21-*Diacetoxy*-6α-*methylpregna*-4,14-*diene*-3,20-*dione* (III)

A mixture of the foregoing compound (1 g), cyclohexene (2 ml) and 5% Pd–charcoal (300 mg) in EtOH (40 ml) was heated for 2 hr under reflux. The catalyst was removed, and the filtrate evaporated to dryness *in vacuo*. Residual cyclohexene was removed by four successive treatments of the product with small amounts of EtOH and evaporation of the solvent. Crystallization from EtOH gave 17α,21-diacetoxy-6α-methylpregna-4,14-diene-3,20-dione (0·4 g), plates, m.p. 188–189°, $[\alpha]_D$ −11°, λ_{max} 239 mμ (ε, 15,220), $\nu_{max}^{CCl_4}$ 1755, 1740, 1680 and 1610 cm^{-1}. (Found: C, 70·7; H, 7·8. $C_{26}H_{34}O_6$ requires: C, 70·6; H, 7·7%.)

17α,21-*Diacetoxy*-6-*methylpregna*-4,6,14-*triene*-3,20-*dione* (IV)

A mixture of the foregoing compound (1 g), chloranil (1 g) and *p*-nitrophenol (0·1 g) in redistilled sec-butanol (16 ml) was heated for 8 hr under reflux, then set aside overnight. Following the addition of ether, the mixture was washed with dilute aqueous alkali, water, dried and the solvents removed. Crystallization of the residue from MeOH gave the trienedione (200 mg), prisms, m.p. 183–185°, $[\alpha]_D$ +54°, λ_{max} 284 mμ (ε, 16,690), $\nu_{max}^{CCl_4}$ 1754, 1743, 1667, 1630 and 1371 cm^{-1}. (Found: C, 70·6; H, 7·0. $C_{26}H_{32}O_6$ requires: C, 70·9; H, 7·3%.)

17α,21-*Diacetoxy*-6-*methylenepregna*-4,14-*diene*-3,20-*dione*

The 6-formyl intermediate (II; R = CHO; 0·8 g) in dry tetrahydrofuran (8 ml) was treated with lithium borohydride (125 mg), the mixture stirred for 10 min, and then poured into water. The product was isolated with ether, and warmed for a few min with 90% AcOH (4 ml). Addition of water gave a solid which was purified from MeOH. 17α,21-Diacetoxy-6-methylenepregna-4,14-diene-3,20-dione (0·6 g) formed plates, m.p. 205–208°, $[\alpha]_D$ +143·5°, λ_{max} 260 mμ (ε, 7,140), $\nu_{max}^{CCl_4}$ 1755, 1741, 1677, 1628 and 1371 cm^{-1}. (Found: C, 70·4; H, 7·3. $C_{28}H_{32}O_6$ requires: C, 70·9; H, 7·3%.)

21-*Methanesulphonyloxy*-14α,17α-*dihydroxypregn*-4-*ene*-3,20-*dione* (V; R = OSO_2Me)

Methanesulphonyl chloride (1 ml) in pyridine (2·5 ml) was added dropwise to a stirred suspension of 14α-hydroxy-Compound S (3·8 g) in pyridine (11·5 ml) at 0°, and the mixture stirred for 3 hr at this temp. The product obtained on pouring the mixture into cold water was purified from EtOH to give the 21-mesylate (2·5 g), needles, m.p. 168–170° (dec), $[\alpha]_D$ +141°, λ_{max} 239·5 mμ (ε, 15,420), $\nu_{max}^{CH_2Cl_2}$ 3590, 3450, 1741, 1669 and 1618 cm^{-1}. (Found: C, 59·5; H, 7·1; S, 7·7. $C_{22}H_{32}O_7S$ requires: C, 60·0; H, 7·3; S, 7·3%.)

17α-*Hydroxypregna*-4,14-*diene*-3,20-*dione* (VI; R = H) and 17α-*hydroxypregna*-4,6,8(14)-*triene*-3,20-*dione* (VII; R = H)

The total crude product (17 g) from a 21-mesylation expt. (see foregoing preparation), and NaI (8·5 g) in AcOH (88 ml) were heated for 30 min under reflux. After addition of water, the product was isolated with $CHCl_3$ and fractionated from acetone. Purification of the less soluble fraction from acetone–hexane gave 17α-hydroxypregna-4,14-diene-3,20-dione (4·9 g), plates, m.p. 194°, $[\alpha]_D$ +72°, λ_{max} 239 mμ (ε, 15,550), $\nu_{max}^{CH_2Cl_2}$ 3620, 3530 (OH doublet), 1715, 1701 (C_{20} doublet), 1671 and 1621 cm^{-1}, τ 9·07, 8·78, 7·74, 7·36, 4·74 and 4·22. (Found: C, 76·8; H, 8·55. $C_{21}H_{30}O_3$ requires: C, 76·8; H, 8·6%.)

The more soluble fraction was recrystallized from acetone, giving 17α-hydroxypregna-4,6,8(14)-triene-3,20-dione (0·45 g), yellow prisms, m.p. 236°, $[\alpha]_D$ +770°, λ_{max} 348 mμ (ε 24,710), $\nu_{max}^{CH_2Cl_2}$ 3590, 3500, 1710, 1683, 1670 and 1589 cm^{-1}. (Found: C, 77·6; H, 8·5. $C_{21}H_{28}O_3$ requires: C, 77·3; H, 8·0%.) Acetylation, employing toluene-*p*-sulphonic acid and redistilled AcOH and Ac_2O, gave 17α-acetoxypregna-4,6,8(14)-triene-3,20-dione, prisms (from acetone–hexane), m.p. 194°, $[\alpha]_D$ +526°, λ_{max} 350 mμ (ε 33,130), $\nu_{max}^{CH_2Cl_2}$ 1737, 1717, 1650 and 1592 cm^{-1}. (Found: C, 74·4; H, 7·6. Calc. for $C_{23}H_{28}O_4$: C, 75·0; H, 7·7%.) [Lit.[8] gives m.p. 193–194°, $\lambda_{max}^{Et_2O}$ 342 (ε 27,800), $\nu_{max}^{CHCl_3}$ 1750, 1650 and 1600 cm^{-1}.]

21-*Chloro*-14α,17α-*dihydroxypregn*-4-*ene*-3,20-*dione* (V; R = Cl)

A solution of purified V (R = OSO_2Me; 1 g) and LiCl (1 g) in redistilled dimethylformamide (20 ml) was heated for 1 hr under reflux. The product obtained on addition of water was purified

from EtOH to give the 21-chloro derivative (0·75 g), prisms, m.p. 218·5–219° (dec), $[\alpha]_D$ +187°, λ_{max} 240 mμ (ε 14,900), $\nu_{max}^{CH_2Cl_2}$ 3604, 3475, 1736, 1666 and 1618 cm^{-1}. (Found: C, 65·6; H, 7·5; Cl, 9·35. $C_{21}H_{29}O_4Cl$ requires: C, 66·2; H, 7·7; Cl, 9·3%.) Attempts to convert this compound into the 21-iodo analogue (*vide infra*) were unsuccessful.

21-*Iodo*-14α,17α-*dihydroxypregn*-4-*ene*-3,20-*dione* (V; R = I)

A solution of purified V (R = OSO_2Me; 1 g) and NaI (1 g) in acetone (30 ml) was heated for 2 hr under reflux. After the addition of excess $Na_2S_2O_3$aq, the mixture was poured into water and the product washed, dried and crystallized from acetone–hexane. The 21-iodo compound (0·85 g) formed prisms, m.p. 120–124° (dec), $[\alpha]_D$ +171°, λ_{max} 240 mμ (ε 17,400), $\nu_{max}^{CH_2Cl_2}$ 3620, 3470, 1720 1667 and 1617 cm^{-1}, τ 9·20, 8·80, 5·79 and 4·27. (Found: C, 53·9; H, 6·5; I, 26·1. $C_{21}H_{29}O_4I$ requires: C, 53·4; H, 6·2; I, 26·9%.)

14α,17α-*Dihydroxypregn*-4-*ene*-3,20-*dione* (V; R = H)

The foregoing 21-iodo derivative (crude, obtained from 10 g of V; R = OSO_2Me) in $CHCl_3$ (150 ml) was shaken vigorously with aqueous sodium metabisulphite (50 ml of 10%), then allowed to stand for 30 min. The mixture was again shaken, and the procedure repeated until the organic layer remained permanently colourless. The organic phase was then washed with dil Na_2CO_3aq, water, dried, and the solvent removed. Purification of the residue from CH_2Cl_2–acetone gave 14α,17α-dihydroxypregna-4-ene-3,20-dione (5·8 g), prisms, m.p. 239·5° $[\alpha]_D$ +156°, λ_{max} 240 mμ (ε 16,300), $\nu_{max}^{CH_2Cl_2}$ 3620, 3480, 1710, 1666 and 1616 cm^{-1}. (Found: C, 72·3; H, 8·6. $C_{21}H_{30}O_4$ requires: C, 72·8; H, 8·7%.)

Dehydration of the compound by heating it with toluene-*p*-sulphonic acid in benzene (cf. Bloom *et al.*[4]) gave 17α-hydroxypregna-4,14-diene-3,20-dione (80% yield), identical in every respect with a sample prepared by the method described above.

17α-*Acetoxypregna*-4,14-*diene*-3,20-*dione* (VI; R = Ac)

A solution of VI (R = H; 19·5 g) and toluene-*p*-sulphonic acid (3·6 g) in redistilled AcOH (240 ml) and Ac_2O (120 ml) was set aside for 6 hr at room temp. The product obtained on pouring the mixture into water was dried and crystallized from acetone–hexane to give 17α-acetoxypregna-4,14-diene-3,20-dione (8·65 g), needles, m.p. 210–212°, $[\alpha]_D$ +12°, λ_{max} 239 mμ (ε 16,370), $\nu_{max}^{CCl_4}$ 1743, 1724, 1681, and 1622 cm^{-1}, τ 9·10, 8·82, 7·92, 4·80 and 4·22. (Found: C, 73·9: H, 8·2. Calc. for $C_{23}H_{30}O_4$: C, 74·5; H, 8·2%.) (Bohlmann *et al.*[8] give m.p. 222°.)

From the acetone–hexane mother-liquor there was obtained 3,17α-*diacetoxypregna*-3,5,14-*trien*-20-*one* (2·5 g), needles (from aqueous MeOH containing a trace of pyridine), m.p. 194·5°, $[\alpha]_D$ −211° (in $CHCl_3$ containing 0·2% pyridine), λ_{max} 234 mμ (ε 22,800), $\nu_{max}^{CCl_4}$ 1761, 1738, and 1721 cm^{-1}, τ 9·09, 8·99, 7·92, 7·88, 4·8, 4·6 and 4·25. (Found: C, 72·2; H, 7·8. $C_{25}H_{32}O_6$ requires: C, 72·8; H, 7·8%.) Mineral acid hydrolysis gave VI (R = Ac) in high yield.

17α-*Acetoxy*-3-*methoxypregna*-3,5,14-*trien*-20-*one* (VIII; R = H)

17α-Acetoxypregna-4,14-diene-3,20-dione (2·2 g) in dry dioxan (50 ml), MeOH (0·2 ml), and trimethylorthoformate (2 ml) was treated with H_2SO_4 (75 mg) in dioxan (1·5 ml). Pyridine (1·5 ml) was added after 30 min, followed by water (350 ml). The precipitated solid was purified from MeOH containing a trace of pyridine to give the 3-methyl enol ether (1·45 g), golden blades, m.p. 214°, $[\alpha]_D$ −225° (in $CHCl_3$ containing a trace of pyridine), λ_{max} 239 mμ (ε 18,400), $\nu_{max}^{CCl_4}$ 1740, 1722, 1655, 1630 and 1370 cm^{-1}. (Found: C, 74·4; H, 8·0. $C_{24}H_{32}O_4$ requires: C, 75·0; H, 8·4%.)

The analogous 3-*ethyl enol ether* was prepared in a similar way. It crystallized from EtOH containing a trace of pyridine, flat needles, m.p. 166–166·5°, $[\alpha]_D$ −224° (in $CHCl_3$ containing pyridine), λ_{max} 240 mμ (ε 18,400), $\nu_{max}^{CCl_4}$ 1740, 1722, 1656, 1629 and 1371 cm^{-1}. (Found: C, 75·1: H, 8·5. $C_{25}H_{34}O_4$ requires: C, 75·3; H, 8·6%.)

17α-*Acetoxy*-6-*formyl*-3-*methoxypregna*-3,5,14-*trien*-20-*one* (VIII; R = CHO)

Compound VIII (R = H; 1·2 g) was formylated with the Vilsmeier reagent by the procedure described for the preparation of II (R = CHO). The 6-formyl derivative (1·0 g) crystallized from

acetone–MeOH, yellow rods, m.p. 199–199·5°, $[\alpha]_D$ −183°, λ_{max} 218·5 mμ (ε 10,900) and λ_{max} 320 (ε 14,500), $\nu_{max}^{CCl_4}$ 1739, 1720, 1660 and 1619 cm^{-1}. (Found: C, 72·4; H, 7·7. $C_{25}H_{32}O_5$ requires: C, 72·8; H, 7·8%.)

The analogous 6-*formyl* 3-*ethyl enol ether*, prepared in a similar way, crystallized from EtOH, pale yellow needles, m.p. 170–174°, $[\alpha]_D$ −188°, λ_{max} 219 mμ (ε 11,050) and 321 mμ (ε 14,760), $\nu_{max}^{CCl_4}$ 1741, 1721, 1661 and 1619 cm^{-1}. (Found: C, 73·4; H, 8·0. $C_{26}H_{34}O_5$ requires: C, 73·2; H, 8·0%.)

17α-*Acetoxy*-6-*hydroxymethyl*-3-*methoxypregna*-3,5,14-*trien*-20-*one* (VIII; R = CH_2OH)

The intermediate VIII (R = CHO; 6·4 g) in dry tetrahydrofuran (50 ml) was treated with lithium borohydride (1 g), the mixture stirred for 10 min, and then poured into cold water. The precipitated solid was purified from MeOH containing a trace of pyridine to give the 6-hydroxymethyl derivative (4·1 g), needles, m.p. 122·5–123° or 153–155°, $[\alpha]_D$ −213°, λ_{max} 249 mμ (ε 17,500), $\nu_{max}^{CCl_4}$ 3605, 1743, 1725, 1650 and 1622 cm^{-1}. (Found: C, 72·6; H, 8·5. $C_{25}H_{34}O_5$ requires: C, 72·4; H, 8·3%.)

17α-*Acetoxy*-6-*methylenepregna*-4,14-*diene*-3,20-*dione* (IX)

A solution of the foregoing compound (3·95 g) in AcOH (30 ml) was warmed to 50°, and gradually diluted with water. The product which separated was purified from EtOH to give the 6-methylene derivative (2·5 g), prisms, m.p. 166–167°, $[\alpha]_D$ +122°, λ_{max} 260 mμ (ε 10,250), $\nu_{max}^{CCl_4}$ 1745, 1726 and 1681 cm^{-1}. (Found: C, 75·7; H, 8·0. $C_{24}H_{30}O_4$ requires: C, 75·4; H, 7·9%.)

17α-*Acetoxy*-6-*methylpregna*-4,6,14-*triene*-3,20-*dione* (X)

(a) A stirred mixture of the foregoing compound (2 g), AcONa (1 g) and 5% Pd–C (0·35 g) was heated for 24 hr under reflux. After removal of the catalyst, the filtrate was concentrated under red. press., then diluted with water. The product was purified from EtOH to give 17α-acetoxy-6-methylpregna-4,6,14-triene-3,20-dione (1·2 g), plates, m.p. 214–215°, $[\alpha]_D$ −25°, λ_{max} 285 mμ (ε 21,700), $\nu_{max}^{CCl_4}$ 1741, 1724, 1669 and 1632 cm^{-1} τ 9·03, 8·88, 8·07, 7·93, 7·91, 4·65, 4·06 and 3·75. (Found: C, 75·2; H, 8·0. $C_{24}H_{30}O_4$ requires: C, 75·4; H, 7·9%.)

(b) A mixture of 17α-acetoxy-6α-methylpregna-4,14-diene-3,20-dione (see below; 1·25 g), chloranil (1·25 g) and *p*-nitrophenol (110 mg) in sec butanol (18·8 ml) was heated for 7½ hr under reflux. After addition of ether (300 ml), the mixture was washed several times with dil KOHaq, then with water, dried, and the solvents were removed. Crystallization of the residue from MeOH gave the trienedione (0·33 g), identical in every respect with a specimen prepared by method (a) above.

Transfer hydrogenation of VIII (R = CHO)

A mixture of VIII (R = CHO; 27·7 g), 5% Pd–C (8·4 g) and cyclohexene (56 ml) in EtOH (1·12 l.) was heated for 2 hr under reflux. The catalyst was removed, and water added to the hot filtrate until solid began to separate. When cool, this was collected to give "Solid A" (12 g). Extraction of the aqueous ethanolic mother-liquor with ether gave a second material, "Solid B" (10 g). A portion of "Solid A" was purified from MeOH containing a trace of pyridine to give 17α-*acetoxy*-3-*methoxy*-6-*methylpregna*-3,5,14-*trien*-20-*one*, pale yellow needles, m.p. 187–190·5, $[\alpha]_D$ −228° (in $CHCl_3$ containing a trace of pyridine), λ_{max} 245 mμ (ε 18,300), $\nu_{max}^{CCl_4}$ 3065 (weak, Δ^{14}), 1737, 1720, 1654 and 1625 cm^{-1}, τ 9·10, 9·05, 8·29, 7·91, 6·38 (OMe), 4·76 and 4·53. (Found: C, 75·0; H, 8·5. $C_{25}H_{34}O_4$ requires: C, 75·3; H, 8·6%.) A second portion (5·5 g) of "Solid A" in MeOH (280 ml) was treated with conc. HCl(1 ml), the mixture warmed briefly and then poured into water. Purification of the product from acetone–hexane gave 17α-acetoxy-6α-*methylpregna*-4,14-*diene*-3,20-*dione* (3·6 g), blades, m.p. 184–187°, $[\alpha]_D$ −34·5°, λ_{max} 238 mμ (ε 15,500), $\nu_{max}^{CCl_4}$ 1740, 1722, 1679 and 1612 cm^{-1} τ 9·08, 8·95, 8·78, 8·71, 7·92, 4·7 and 4·25. (Found: C, 75·1; H, 8·4. $C_{24}H_{32}O_4$ requires: C, 75·0; H, 8·4%.) Chromatographic purification of "Solid B" gave a further quantity (6 g) of the last compound.

17α-*Acetoxy*-6α-*methylpregna*-1,4,14-*triene*-3,20-*dione* (XII)

A solution of XI (2 g) and 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ; 2 g) in dry benzene (28 ml) was heated for 19 hr under reflux. The solid which had formed was removed, and more benzene was added to the filtrate. The solution was washed with dil NaOHaq, then with water, and

the solvent was removed under red. press. Purification of the residue from acetone–hexane gave the trienedione (0·8 g), prismatic needles, m.p. 191–194°, $[\alpha]_D$ −90°, λ_{max} 242 mμ (ε 14,300). (Found: C, 75·1; H, 7·5. $C_{24}H_{30}O_4$ requires: C, 75·4; H, 7·9%.)

17α-*Acetoxy*-6-*methylpregna*-1,4,6,14-*tetraene*-3,20-*dione* (XIII)

Compound X (5 g) was dehydrogenated with DDQ (5 g) by the method described in the foregoing experiment. The tetraenedione (4 g) crystallised from ether, in prisms, m.p. 201–202·5°, $[\alpha]_D$ −72°, λ_{max} 226 mμ (ε 11,400), 252 mμ (ε 8,560) and 296 mμ (ε 12,900), $\nu_{max}^{CCl_4}$ 1738, 1720, 1658, 1653 and 1615 cm^{-1}, τ 9·02, 8·80, 8·0, 7·94, 7·93, 7·90, 4·68, 3·85, 3·75, 3·58 and 2·96. (Found: C, 75·7; H, 7·5 $C_{24}H_{28}O_4$ requires: C, 75·8; H, 7·4%.)