802. *Modified Steroid Hormones. Part XXX.*[1] *Some 16α,17α-Methylenepregnen-20-ones and Derived Compounds.*

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The preparation of some 16α,17α-methylenepregnen-20-one derivatives, required for biological study, is reported.

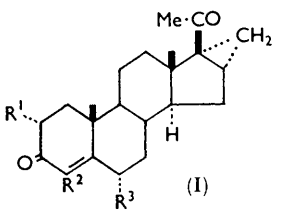
The observation[2] that 16α,17α-methylenepregn-4-ene-3,20-dione[3] possesses progestational activity prompted us to prepare some related 16α,17α-methylenepregnen-20-ones embodying structural modifications known to influence biological activity.

16α,17α-Methylenepregn-4-ene-3,20-dione[3] (I; $R^1 = R^2 = R^3 = H$) was converted into 16α,17α-methylenepregna-1,4-diene-3,20-dione by reaction with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone.[4] The isomeric 16α,17α-methylenepregna-4,6-diene-3,20-dione was obtained by Oppenauer oxidation of 3β-hydroxy-16α,17α-methylenepregn-5-en-20-one[3] with benzoquinone as hydrogen-acceptor. Addition of chlorine to the double bond of the αβ-unsaturated ketone (I; $R^1 = R^2 = R^3 = H$), under experimental conditions developed previously in these laboratories,[5] afforded an intermediate 4,5-dichloro-compound which passed into 4-chloro-16α,17α-methylenepregn-4-ene-3,20-dione (I; $R^1 = R^3 = H$, $R^2 = Cl$) on treatment with pyridine. Hydroxylation of 3β-hydroxy-16α,17α-methylenepregn-5-en-20-one was achieved by the preparation of the corresponding 5,6-epoxides (isolated but not characterised), followed by their hydrolysis with hot aqueous-acetonic periodic acid,[6] to give 3β,5α,6β-trihydroxy-16α,17α-methylenepregnan-20-one. Oxidation of the last compound afforded 5α-hydroxy-16α,17α-methylenepregnane-3,6,20-trione, which, with alkali, suffered dehydration to 16α,17α-methylenepregn-4-ene-3,6,20-trione.

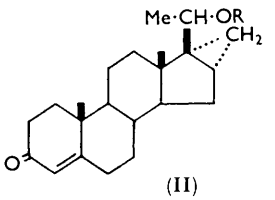
The introduction of a 2α-methyl substituent into 16α,17α-methylenepregn-4-ene-3,20-dione required prior protection of the 20-oxo-function. Reduction of the diketone (I; $R^1 = R^2 = R^3 = H$) with lithium aluminium hydride, followed by oxidation of the resulting pregn-4-ene-3,20-diol with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone,[7] gave 20β-hydroxy-16α,17α-methylenepregn-4-en-3-one (II; R = H) which formed a more

[1] Part XXIX, *J.*, 1962, 4995.
[2] G.P. 1,096,902.
[3] Sandoval, Rosenkranz, and Djerassi, *J. Amer. Chem. Soc.*, 1951, **73**, 2383.
[4] Burn, Kirk, and Petrow, *Proc. Chem. Soc.*, 1960, 14.
[5] Kirk, Patel, and Petrow, *J.*, 1956, 1184.
[6] Fieser and Rajagopalan, *J. Amer. Chem. Soc.*, 1949, **71**, 3938.
[7] Burn, Petrow, and Weston, *Tetrahedron Letters*, 1960, No. 9, p. 14.

dextrorotatory [8] monoacetate (II; R = Ac). Condensation of the ketone (II; R = H) with ethyl formate and sodium hydride in benzene gave a sodio-derivative, which, on reaction with methyl iodide followed by hydrolysis of the 2-ester grouping and subsequent oxidation of the 20β-hydroxyl group, was converted into the required 2α-methyl-16α,17α-methylenepregn-4-ene-3,20-dione (I; R^1 = Me, R^2 = R^3 = H).



(I)



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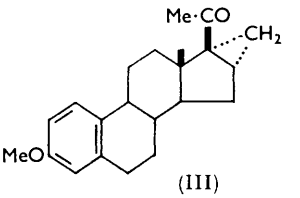

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Catalytic hydrogenation of 16α,17α-methylenepregn-4-ene-3,20-dione to a saturated 5β-pregnane derivative could not be accomplished satisfactorily. The required compound, 16α,17α-methylene-5β-pregnane-3,20-dione, was ultimately obtained by hydrogenation of the unsaturated ketone (II; R = H) in pyridine with a palladium–charcoal catalyst and oxidation of the resulting 20β-hydroxy-16α,17α-methylene-5β-pregnan-3-one with chromium trioxide–pyridine.

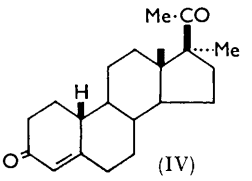
6α-Methyl-16α,17α-methylenepregn-4-ene-3,20-dione (I; R^1 = R^2 = H, R^3 = Me) was prepared by standard procedures involving the reaction of 6α-methylpregna-4,16-diene-3,20-dione [9] with diazomethane to give the corresponding 16,17-pyrazoline derivative, and elimination of nitrogen from the last compound by treating it in acetone solution with boron trifluoride–ether complex.[10] Dehydrogenation with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone and with chloranil gave 6α-methyl-16α,17α-methylenepregna-1,4-diene-3,20-dione and 6-methyl-16α,17α-methylenepregna-4,6-diene-3,20-dione, respectively. The last compound, also obtained by an alternative route from 6-methylpregna-4,6,16-triene-3,20-dione by way of a 16,17-pyrazoline, passed into 6-methyl-16α,17α-methylenepregna-1,4,6-triene-3,20-dione on reaction with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone.

21-Acetoxy-16α,17α-methylenepregn-4-ene-3,11,20-trione was obtained from 21-acetoxypregna-4,16-diene-3,11,20-trione [11] through a 16,17-pyrazoline intermediate. Another preparation of the same methylene derivative has since been described in the patent literature.[12]

An attempt was made to convert 3-methoxy-16α,17α-methylene-19-norpregna-1,3,5(10)-trien-20-one (III), prepared from 3-methoxy-19-norpregna-1,3,5(10),16-tetraen-20-one [13] through a 16,17-pyrazoline intermediate, into the corresponding 19-norpregn-4-en-3-one. For this purpose, the compound was reduced with lithium in liquid ammonia to a total crude product which lacked infrared carbonyl absorption. After treatment with dilute acid followed by regeneration of the 20-oxo-function by oxidation with the Jones reagent,[14] a crystalline substance was obtained which showed infrared bands at 1679 and 1621 (4-en-3-one) and at 1706 $cm.^{-1}$. The position of the latter carbonyl band is inconsistent with a 16α,17α-cyclomethylene-20-one formulation for which an absorption at 1688—1691 $cm.^{-1}$ would be expected.[3] The compound differs from 16α-methyl-19-norpregn-4-ene-3,20-dione.[13] We assign to it the constitution 17α-methyl-19-norpregn-4-ene-3,20-dione (IV) on the basis of the following model transformations. The 3β-tetrahydropyranyl ether derived from 3β-hydroxy-16α,17α-methylenepregn-5-en-20-one was reduced by lithium in

[8] See Fieser and Fieser, " Steroids," Reinhold Publ. Corp., New York, 1959, p. 614.
[9] Burn, Ellis, Petrow, Stuart-Webb, and Williamson, *J.*, 1957, 4092.
[10] Nominé and Bertin, *Bull. Soc. chim. France*, 1960, 550.
[11] Allen and Bernstein, *J. Amer. Chem. Soc.*, 1955, **77**, 1028; McGuckin and Mason, *ibid.*, p. 1822.
[12] U.S.P. 3,032,567.
[13] Burn and Petrow, *J.*, 1962, 364.
[14] Bowden, Heilbron, Jones, and Weedon, *J.*, 1946, 39; Djerassi, Engle, and Bowers, *J. Org. Chem.*, 1956, **21**, 1547.

liquid ammonia, and the total product, which lacked infrared carbonyl absorption, was first oxidised with chromium trioxide–pyridine to regenerate the 20-oxo-function and then treated with acid to regenerate the 3β-hydroxyl group. Acetylation then furnished a crystalline compound having (i) carbonyl absorption at 1703 cm.$^{-1}$, characteristic of a



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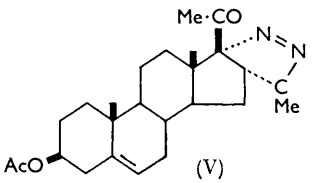

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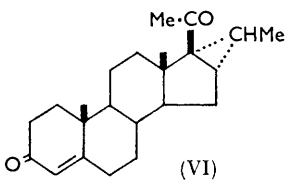

(VI)

saturated 20-ketone, and (ii) other physical constants in excellent agreement with those reported [15] for 3β-acetoxy-17α-methylpregn-5-en-20-one.

Subsequent model experiments revealed the stability to lithium–liquid ammonia of the 20β-hydroxy-16α,17α-methylene-system. Accordingly, 3-methoxy-16α,17α-methylene-19-norpregna-1,3,5(10)-triene-20-one (III) was converted, by reduction with lithium aluminium hydride, into material believed to consist largely of its 20β-hydroxy-derivative (not purified and characterised). Treatment of this product with lithium in liquid ammonia, followed by acid hydrolysis and oxidation, afforded the required 16α,17α-methylene-19-norprogesterone (infrared band at 1686 cm.$^{-1}$, consistent with a 16α,17α-methylene-20-one structure).

Finally, 16α,17α-ethylidenepregn-4-ene-3,20-dione (VI) was prepared by the reaction sequence: (i) addition of diazoethane to 3β-acetoxypregna-5,16-dien-20-one to give the substituted pyrazoline (V), (ii) elimination of nitrogen by treatment with boron trifluoride–ether complex in acetone followed by hydrolysis of the product to 16α,17α-ethylidene-3β-hydroxypregn-5-en-20-one, and (iv) Oppenauer oxidation.

Experimental

Optical rotations were measured for chloroform solutions. Ultraviolet absorption spectra (in EtOH) were kindly determined by Mr. M. T. Davies, B.Sc.

16α,17α-*Methylenepregna*-1,4-*diene*-3,20-*dione*.—A mixture of 16α,17α-methylenepregn-4-ene-3,20-dione [3] (1·5 g.) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (1·7 g.) in dry benzene (20 ml.) was heated under reflux for 25 hr. After filtration, the benzene solution was washed with 4% aqueous sodium hydroxide, then with water, and dried, and the solvent was removed. Crystallisation of the residue from aqueous methanol gave the 1,4-*diene* (0·5 g.), needles, m. p. 153°, $[\alpha]_D^{24\cdot5}$ +145° (*c* 0·8), $\lambda_{max.}$ 244 mμ (log ε 4·2) (Found: C, 81·2; H, 8·7. $C_{22}H_{28}O_2$ requires C, 81·4; H, 8·7%).

16α,17α-*Methylenepregna*-4,6-*diene*-3,20-*dione*.—A mixture of 3β-hydroxy-16α,17α-methylenepregn-5-en-20-one [3] (3 g.), aluminium t-butoxide (3 g.), and *p*-benzoquinone (4 g.) in dry benzene (350 ml.) was left for 60 hr. at room temperature. The mixture was washed with aqueous alkali, then with water, dried, and evaporated. A solution of the gummy residue in benzene was percolated through a column of alumina (80 g.), and the eluted material was purified from aqueous methanol. The 4,6-*diene* separated in needles (1 g.), m. p. 159—160°, $[\alpha]_D^{25}$ +177° (*c* 1·0), $\lambda_{max.}$ 283·5 mμ (log ε 4·4) (Found: C, 81·0; H, 8·4. $C_{22}H_{28}O_2$ requires C, 81·4; H, 8·4%).

4-*Chloro*-16α,17α-*methylenepregn*-4-*ene*-3,20-*dione* (I; $R^1 = R^3 = H$, $R^2 = Cl$).—16α,17α-Methylenepregn-4-ene-3,20-dione (3 g.) in ether (150 ml.) was treated with a 0·84M-solution of chlorine in propionic acid (13 ml.) at −30°, and the mixture kept at this temperature in the dark for 18 hr. More ether was then added, and the solution washed repeatedly to remove acid. The residue of crude 4ξ,5ξ-dichloride obtained on removal of the solvent at <30° was treated with pyridine (2 ml.) in benzene (10 ml.), and the mixture was kept for 4 hr. at room

[15] Plattner, Heusser, and Herzig, *Helv. Chim. Acta*, 194 9, **32**, 270.

temperature. The product was isolated with ether and crystallised from methanol, to give the 4-*chloro-derivative* (2·2 g.), needles, m. p. 196—197°, $[\alpha]_D^{24}$ +220° (*c* 1·0), $\lambda_{max.}$ 255 mμ (log ε 4·13) (Found: C, 72·8; H, 8·3; Cl, 11·0. $C_{22}H_{29}ClO_2$ requires C, 73·3; H, 8·1; Cl, 9·8%).

3β,5α,6β-*Trihydroxy*-16α,17α-*methylenepregnan*-20-*one*.—3β-Hydroxy-16α,17α-methylenepregn-5-en-20-one (5 g.) in chloroform (50 ml.) was treated for 18 hr. at room temperature with monoperphthalic acid (3·8 g.) in ether (30 ml.). The product, a mixture of 5,6-epoxides (3·5 g.), was isolated in the usual way, dissolved in acetone (100 ml.) and water (15 ml.) containing periodic aid (1·5 g.), and refluxed for 5 min. The solid obtained on the addition of water crystallised from methanol, to give the *triol* (2·8 g.), prisms, m. p. 230—232°, $[\alpha]_D^{25}$ +46° (*c* 0·6) (Found: C, 69·5; H, 9·5. $C_{22}H_{34}O_4,H_2O$ requires C, 69·4; H, 9·5%).

5α-*Hydroxy*-16α,17α-*methylenepregnane*-3,6,20-*trione*.—A stirred solution of the foregoing compound (1 g.) in acetone (100 ml.) was treated with the Jones reagent [14] (1·5 ml.) dropwise during 5 min. The mixture was poured into water, and the precipitate was purified from methanol–methylene dichloride. The *trione* (0·7 g.) formed needles, m. p. 285—287°, $[\alpha]_D^{22}$ +59° (*c* 0·7) (Found: C, 73·9; H, 8·3. $C_{22}H_{30}O_4$ requires C, 73·7; H, 8·4%).

16α,17α-*Methylenepregn*-4-*ene*-3,6,17-*trione*, prepared by refluxing a solution of the foregoing compound (0·8 g.) in 1% methanolic potassium hydroxide (20 ml.) for 20 min., separated from acetone in plates (0·3 g.), m. p. 235—237°, $[\alpha]_D^{25}$ +58° (*c* 0·9), $\lambda_{max.}$ 250·5 mμ (log ε 4·04) (Found: C, 77·1; H, 8·3. $C_{22}H_{28}O_3$ requires C, 77·6; H, 8·3%).

20β-*Hydroxy*-16α,17α-*methylenepregn*-4-*en*-3-*one* (II; R = H).—Lithium aluminium hydride (22 g.) in dry ether (1 l.) was added slowly to 16α,17α-methylenepregn-4-ene-3,20-dione (15 g.) in dry tetrahydrofuran (350 ml.). The mixture was stirred and refluxed for 2 hr., then cooled, and the excess of reducing agent was removed by the addition of acetone. Sufficient saturated aqueous Rochelle salt was added to give a clear supernatant liquid, which was decanted from inorganic salts, dried, and evaporated. Crystallisation of the residue from aqueous acetone gave crude 16α,17α-methylenepregn-4-ene-3ξ,20β-diol (11·0 g.), m. p. 177—178°, $[\alpha]_D^{25}$ +54°, with an infrared spectrum indicating the absence of oxo-functions. This product (10·5 g.) in dry dioxan (400 ml.) was treated with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (10·5 g.) and set aside for 18 hr. at room temperature. Ether (2 l.) was then added, and the whole washed with dilute aqueous sodium hydroxide, then with water, dried, and evaporated. Crystallisation of the residue from aqueous acetone gave 20β-*hydroxy*-16α,17α-*methylenepregn*-4-*en*-3-*one* (8·0 g.), needles, m. p. 176—177°, $[\alpha]_D^{25}$ +105° (*c* 1·0), $\lambda_{max.}$ 240·5 mμ (log ε 4·2) (Found: C, 80·0; H, 9·4. $C_{22}H_{32}O_2$ requires C, 80·4; H, 9·8%). The 20β-*acetate* crystallised from acetone–hexane in needles, m. p. 123—125°, $[\alpha]_D^{23}$ +139° (*c* 0·8), $\lambda_{max.}$ 240·5 mμ (log ε 4·23) (Found: C, 77·5; H, 8·9. $C_{24}H_{34}O_3$ requires C, 77·8; H, 9·25%).

2α-*Methyl*-16α,17α-*methylenepregn*-4-*ene*-3,20-*dione* (I; R^1 = Me, R^2 = R^3 = H).—A mixture of 20β-hydroxy-16α,17α-methylenepregn-4-en-3-one (2·5 g.), ethyl formate (5 ml.), and sodium hydride (2·5 g.) in dry benzene (75 ml.) was stirred for 40 hr. under oxygen-free nitrogen. The yellow sodio-derivative was collected by filtration, washed with ether, and air-dried. Its solution in acetone (250 ml.) was heated with methyl iodide (20 ml.) and potassium carbonate under reflux for 23 hr. After removal of carbonate by filtration, and of solvent by evaporation *in vacuo*, the residue was dissolved in methanol (100 ml.) to which sodium methoxide (1 g.) had been added, and the mixture was refluxed for 3 hr. under dry oxygen-free nitrogen. The product (1·8 g.) was isolated with ether, and its stirred solution in acetone (20 ml.) treated with the Jones reagent (1·5 ml.) dropwise during 5 min. The crystalline product (1·2 g.) obtained on addition of water was purified from acetone, to give 2α-*methyl*-16α,17α-*methylenepregn*-4-*ene*-3,20-*dione*, needles, m. p. 221—223°, $[\alpha]_D^{24}$ +211° (*c* 1·0), $\lambda_{max.}$ 239·5 mμ (log ε 4·17) (Found: C, 81·6; H, 9·7. $C_{23}H_{32}O_3$ requires C, 81·1; H, 9·5%). The infrared spectrum revealed the presence of two ketone groups and the absence of a hydroxyl group.

20β-*Hydroxy*-16α,17α-*methylene*-5β-*pregnan*-3-*one*, prepared by hydrogenation of 20β-hydroxy-16α,17α-methylenepregn-4-en-3-one (3 g.) over 5% palladium–charcoal (0·5 g.) in pyridine (50 ml.), crystallised from acetone–hexane in needles (1·7 g.), m. p. 130—132°, $[\alpha]_D^{25}$ +29° (*c* 0·4) (Found: C, 80·2; H, 10·35. $C_{22}H_{34}O_2$ requires C, 79·95; H, 10·4%).

16α,17α-*Methylene*-5β-*pregnane*-3,20-*dione*.—The foregoing compound (1·7 g.) in pyridine (10 ml.) was added to chromium trioxide (2 g.) in pyridine (20 ml.) and kept for 18 hr. at room temperature. The product was isolated in the usual way and purified from aqueous methanol. The *dione* (0·8 g.) formed prisms, m. p. 132°, $[\alpha]_D^{22}$ +127° (*c* 1·1), $\nu_{max.}$ (in CCl_4) 1717 (3-oxo) and 1686 cm.$^{-1}$ (20-oxo-16α,17α-methylene) (Found: C, 80·95; H, 9·95. $C_{22}H_{32}O_2$ requires C,

80·4; H, 9·8%). The optical rotatory dispersion curve confirmed the 5β-pregnane configuration.

16α,17α-*Pyrazoline Derivative of* 6α-*Methylpregna*-4,16-*diene*-3,20-*dione*.—6α-Methylpregna-4,16-diene-3,20-dione [9] (3 g.) was treated for 24 hr. at room temperature with ethereal diazomethane prepared from *N*-methyl-*N*-nitrosotoluene-*p*-sulphonamide (6 g.). The solvent was removed and the residue crystallised from methanol, to give the *pyrazoline derivative* (3 g.), needles, m. p. 153—154°, $[\alpha]_D^{22}$ +112° (*c* 0·5), $\lambda_{max.}$ 238—239 mμ (log ε 4·22) (Found: C, 74·7; H, 8·9; N, 8·1. $C_{23}H_{32}N_2O_2$ requires C, 75·0; H, 8·7; N, 7·6%).

6α-*Methyl*-16α,17α-*methylenepregn*-4-*ene*-3,20-*dione* (I; $R^1 = R^2 = H$, $R^3 = Me$).—The foregoing compound (5 g.) in acetone (100 ml.) was treated with boron trifluoride–ether complex (6 ml.). After 30 min. at room temperature, the product was isolated with ether, and its solution in benzene percolated through a column of alumina (60 g.). Removal of solvent from the eluate and crystallisation of the residue from hexane gave 6α-*methyl*-16α,17α-*methylene-pregn*-4-*ene*-3,20-*dione* (2·2 g.), needles, m. p. 126—128°, $[\alpha]_D^{24}$ +178° (*c* 1·0), $\lambda_{max.}$ 240 mμ (log ε 4·19) (Found: C, 80·8; H, 9·3. $C_{23}H_{32}O_2$ requires C, 81·2; H, 9·4%).

6α-*Methyl*-16α,17α-*methylenepregna*-1,4-*diene*-3,20-*dione*.—A solution of the foregoing compound (1·5 g.) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (1·5 g.) in dry benzene (100 ml.) was heated under reflux for 20 hr. The cooled mixture was washed with aqueous sodium hydroxide until almost colourless, then with water, dried, and evaporated. The residue was chromatographed on alumina, elution with benzene–ether (2 : 1) giving material which crystallised from aqueous methanol. The 1,4-*diene*-3,20-*dione* (400 mg.) formed rods, m. p. 163—165°, $[\alpha]_D^{25}$ +115·5° (*c* 1·0), $\lambda_{max.}$ 244 mμ (log ε 4·2), $\nu_{max.}$ (in CCl_4) 1686, 1666, 1629, and 1608 cm.$^{-1}$ (Found: C, 81·3; H, 8·7. $C_{23}H_{30}O_2$ requires C, 81·6; H, 8·9%).

6-*Methyl*-16α,17α-*methylenepregna*-4,6-*diene*-3,20-*dione*.—A solution of 6α-methyl-16α,17α-methylenepregn-4-ene-3,20-dione (10 g.), chloranil (10 g.), and *p*-nitrophenol (1 g.) in redistilled butan-2-ol (100 ml.) was refluxed for 7 hr. The cooled mixture was diluted with ether, washed with alkali, water, and dried, and the solvents were removed. A benzene solution of the residue was passed through alumina (100 g.), to give material which was crystallised from aqueous methanol. The 4,6-*diene*-3,20-*dione* (1·5 g.) formed needles, m. p. 138—140°, $[\alpha]_D^{22}$ +177° (*c* 1·1), $\lambda_{max.}$ 289·5 mμ (log ε 4·38), $\nu_{max.}$ (in CH_2Cl_2) 1676, 1656, 1625, and 1578 cm.$^{-1}$ (Found: C, 81·8; H, 8·8. $C_{23}H_{30}O_2$ requires C, 81·6; H, 8·9%).

6-*Methylpregna*-4,6,16-*triene*-3,20-*dione*.—A mixture of 3β-hydroxy-6-methylpregna-5,16-dien-20-one [9] (16 g.), aluminium t-butoxide (15 g.), and *p*-benzoquinone (23 g.) in dry benzene (1 l.) was left for 40 hr. at room temperature. The product was isolated in the usual way and crystallised from acetone–hexane to give the *triene* (4·25 g.) as needles, m. p. 169—171°, $[\alpha]_D^{25}$ +140° (*c* 1·0), $\lambda_{max.}$ 239 (log ε 4·08) and 288·5 mμ (log ε 4·37) (Found: C, 81·2; H, 8·5. $C_{22}H_{28}O_2$ requires C, 81·4; H, 8·7%).

The 16α,17α-*pyrazoline derivative of* 6-*methylpregna*-4,6,16-*triene*-3,20-*dione*, prepared by treating the foregoing compound (4·5 g.) with diazomethane [prepared from *N*-methyl-*N*-nitrosotoluene-*p*-sulphonamide (10 g.)] in ether (150 ml.) for 18 hr. at room temperature, crystallised from aqueous acetone in prisms (2·05 g.), m. p. 165—166°, $[\alpha]_D^{23}$ +81° (*c* 1·0), $\lambda_{max.}$ 287·5 mμ (log ε 4·36), $\nu_{max.}$ (in CH_2Cl_2) 1706, 1656, 1625, 1579, and 1548 cm.$^{-1}$ (Found: C, 74·9; H, 8·3. $C_{23}H_{30}N_2O_2$ requires C, 75·4; H, 8·25%). Treatment with boron trifluoride–ether complex in acetone gave 6-methyl-16α,17α-methylenepregna-4,6-diene-3,20-dione, identical with a sample prepared as described above.

6-*Methyl*-16α,17α-*methylenepregna*-1,4,6-*triene*-3,20-*dione*, prepared by heating a mixture of 6-methyl-16α,17α-methylenepregna-4,6-diene-3,20-dione (4 g.) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (4 g.) in dry benzene (150 ml.) under reflux for 24 hr., formed needles (from aqueous methanol), m. p. 143—144°, $[\alpha]_D^{21}$ +122° (*c* 1·0), $\lambda_{max.}$ 227·5 (log ε 4·14), 253—254 (log ε 3·97), and 303 mμ (log ε 4·08), $\nu_{max.}$ (in CH_2Cl_2) 1680, 1655, 1612, and 1581 cm.$^{-1}$ (Found: C, 81·9; H, 8·35. $C_{23}H_{28}O_2$ requires C, 82·1; H, 8·4%).

16α,17α-*Pyrazoline Derivative of* 21-*Acetoxypregna*-4,16-*diene*-3,11,20-*trione*.—21-Acetoxypregna-4,16-diene-3,11,20-trione (8 g.) in tetrahydrofuran (200 ml.) was added to diazomethane [prepared from *N*-methyl-*N*-nitrosotoluene-*p*-sulphonamide (17 g.)] in ether (100 ml.) and the mixture set aside overnight. The crystals [3·9 g.; m. p. 178—179° (effervescence)] which had separated were removed, and the mother-liquor was washed with water, a further quantity of crystals [2·2 g., m. p. 172—174° (effervescence)] separating from the organic phase. The combined products were purified from aqueous acetone, to give the *pyrazoline derivative*, needles,

m. p. 188° (effervescence), $[\alpha]_D^{25}$ +183° (*c* 0·9) (Found: C, 67·5; H, 6·8; N, 6·9. $C_{24}H_{30}N_2O_5$ requires C, 67·6; H, 7·1; N, 6·6%).

21-*Acetoxy*-16α,17α-*methylenepregn*-4-*ene*-3,11,20-*trione*.—The foregoing compound (2·3 g.), suspended in acetone (15 ml.), was treated with freshly redistilled boron trifluoride–ether complex (2 ml.). After 1 hr. at room temperature, water was added, and the product isolated with methylene dichloride. Crystallisation from methanol gave 21-acetoxy-16α,17α-methylenepregn-4-ene-3,11,20-trione (300 mg.), needles, m. p. 192—193·5°, $[\alpha]_D^{20}$ +268° (*c* 1·1), $\lambda_{max.}$ 237·5 mμ (log ε 4·2) (Found: C, 71·7; H, 7·7. Calc. for $C_{24}H_{30}O_5$: C, 72·3; H, 7·6%) {lit.,[12] gives m. p. 190°, $[\alpha]_D$ +276°, $\lambda_{max.}$ 238 mμ (ε 15,700)}.

The 16α,17α-*pyrazoline derivative of* 3-*methoxy*-19-*norpregna*-1,3,5(10),16-*tetraene*-20-*one*, prepared by treating the pregnatetraene-20-one [13] (1 g.) in tetrahydrofuran (25 ml.) with an excess of diazomethane in ether (20 ml.) for 18 hr. at room temperature, crystallised from methylene dichloride–methanol in prisms (700 mg.), m. p. 180—182° (effervescence), $[\alpha]_D^{24}$ +160° (*c* 0·9), $\lambda_{max.}$ 221 (ε 9450), 278 (ε 2200), and 287 mμ (ε 2115) (Found: C, 74·6; H, 8·25; N, 7·95. $C_{22}H_{28}N_2O_2$ requires C, 74·95; H, 8·0; N, 7·95%).

3-*Methoxy*-16α,17α-*methylene*-19-*norpregna*-1,3,5(10)-*triene*-20-*one* (III), prepared by treating the foregoing compound (2 g.) in acetone (40 ml.) with boron trifluoride–ether complex (2 ml.) for 30 min. at room temperature, crystallised from methanol as needles (1·1 g.), m. p. 137—139°, $[\alpha]_D^{24}$ +167°, $\lambda_{max.}$ 229 (ε 9115), 278 (ε 2066), and 287 mμ (ε 1950) (Found: C, 81·15; H, 8·75. $C_{22}H_{28}O_2$ requires C, 81·45; H, 8·7%).

17α-*Methyl*-19-*norpregn*-4-*ene*-3,20-*dione* (IV).—The foregoing compound (9 g.) in ether (450 ml.) was added to lithium (5 g.) in liquid ammonia (500 ml.), and the mixture was stirred for 15 min. After the addition of methanol (175 ml.) dropwise during a further 15 min., the mixture was stirred for a further 10 min., and the ammonia allowed to evaporate overnight. The product, isolated with ether, was obtained as a gum showing infrared bands (Perkin-Elmer Infracord) at 3400 (OH) and 1690, 1660 cm.$^{-1}$ [3-methoxy-2,5(10)-diene]. Its solution in methanol (150 ml.) was treated with 2N-hydrochloric acid (50 ml.) and refluxed for 1 hr. Removal of the solvents under reduced pressure gave a gummy residue showing infrared bands at 3450 (OH), 1675, and 1615 cm.$^{-1}$ (4-en-3-one). This material, in acetone (140 ml.), was treated with the Jones reagent [14] (4 ml.) dropwise during 5 min., and the product was isolated with ether. The gum so obtained, having no infrared hydroxyl absorption, was chromatographed on alumina (120 g.), elution with benzene–light petroleum (b. p. 40—60°) (1 : 4) giving a solid which was crystallised from methanol. 17α-*Methyl*-19-*norpregn*-4-*ene*-3,20-*dione* (3·3 g.) formed prisms, m. p. 124—126°, $[\alpha]_D^{22}$ +117° (*c* 1·0), $\lambda_{max.}$ 240 mμ (log ε 4·23), $\nu_{max.}$ (in CCl_4) 1706 (20-one), 1679, and 1621 cm.$^{-1}$ (4-en-3-one) (Found: C, 79·8; H, 9·2. $C_{21}H_{30}O_2$ requires C, 80·2; H, 9·6%).

3β-*Acetoxy*-17α-*methylpregn*-5-*en*-20-*one*.—3β-Hydroxy-16α,17α-methylenepregn-5-en-20-one (10 g.) and toluene-*p*-sulphonic acid (0·1 g.) in dry benzene (100 ml.) and dihydropyran (5 ml.) were stirred for 2½ hr. at room temperature. The solution was washed with dilute aqueous sodium hydrogen carbonate, and the solvent removed. Crystallisation of the residue from aqueous methanol containing a drop of pyridine gave the crude 3β-tetrahydropyranyl ether (10 g.), needles, m. p. 110—114°, showing no infrared hydroxyl absorption. This compound (2 g.) in tetrahydrofuran (50 ml.) was added to lithium (1 g.) in liquid ammonia (100 ml.), and the mixture was stirred under reflux for 10 min. Methanol (35 ml.) was added, the ammonia allowed to evaporate, and the product isolated with ether. A crude solid (1·6 g.) was obtained showing hydroxyl but no carbonyl infrared absorption. Its solution in pyridine (15 ml.) was added to chromium trioxide (1·5 g.) in pyridine (15 ml.) and set aside overnight. The product, isolated with ether, was treated successively with acetic acid (10 ml.) for 2 hr. at 25°, and, after isolation, with acetic anhydride (5 ml.) and pyridine (5 ml.) for 18 hr. at room temperature. Purification from acetone gave 3β-acetoxy-17α-methylpregn-5-en-20-one (0·9 g.), plates, m. p. 182—184°, $[\alpha]_D^{23}$ −30°, $\nu_{max.}$ (in CCl_4) 1733, 1240 (OAc), 1703 cm.$^{-1}$ (20-one) (Found: C, 77·2; H, 9·4. Calc. for $C_{24}H_{36}O_3$: C, 77·4; H, 9·7%) {lit.,[15] m. p. 185—187°, $[\alpha]_D$ −31·6°}.

16α,17α - *Methylene* - 19 - *norprogesterone*. — 3 - Methoxy - 16α,17α - methylene - 19 - norpregna-1,3,5(10)-trien-20-one (III) (5 g.) in dry tetrahydrofuran (150 ml.) was refluxed for 2 hr. with lithium aluminium hydride (2 g.) in dry ether (100 ml.). The excess of reagent was decomposed with acetone, and the product isolated with ether. It was obtained as a gum (5 g.) having no infrared carbonyl absorption. This gum was reduced with lithium in liquid ammonia, and the product was treated with dilute hydrochloric acid in acetone and then oxidised with the Jones

reagent as described above for compound (IV). The resulting product was chromatographed on alumina (150 g.) in benzene–light petroleum (b. p. 40—60°). Elution with benzene afforded crystalline fractions which were combined and crystallised from aqueous methanol, to give 16α,17α-*methylene*-19-*norprogesterone* (0·75 g.) as needles, m. p. 169—169·5°, $[\alpha]_D^{25}$ +165° (*c* 1·0), $\lambda_{max.}$ 239—240 mμ (log ε 4·23), $\nu_{max.}$ (in CCl_4) 1686 (20-ketone), 1681, 1620 cm.$^{-1}$ (Δ^4-3-one) (CaF_2 prism) (Found: C, 80·4; H, 8·65. $C_{21}H_{28}O_2$ requires C, 80·7; H, 9·0%).

The *pyrazoline derivative* (V), prepared by treating 3β-acetoxypregna-5,16-dien-20-one (10 g.) with diazoethane [from *N*-ethyl-*N*-nitrosotoluene-*p*-sulphonamide (42 g.)] in ether (250 ml.) for 18 hr. at room temperature, crystallised from methanol as plates (8 g.), m. p. 172° (decomp.), $[\alpha]_D^{21}$ −84° (*c* 0·2) (Found: C, 72·9; H, 8·8; N, 7·2. $C_{25}H_{36}N_2O_3$ requires C, 73·0; H, 8·5. N, 6·8%).

16α,17α-*Ethylidene*-3β-*hydroxypregn*-5-*en*-20-*one*.—Boron trifluoride–ether complex (7 ml.) was added to the foregoing compound (10 g.) in acetone (100 ml.) and kept for 45 min. at room temperature. The product was isolated in the usual way and crystallised from methylene dichloride–methanol, giving needles (6 g.), m. p. 156—158°. A solution of this nitrogen-free product and potassium hydroxide (4 g.) in methanol (100 ml.) and water (30 ml.) was refluxed for 1 hr., and the deposited solid (5 g.) purified from aqueous methanol. 16α,17α-*Ethylidene*-3β-*hydroxypregn*-5-*en*-20-*one* crystallised in needles, m. p. 229—230°, $[\alpha]_D^{25}$ +33·5° (*c* 0·9), $\nu_{max.}$ (in CCl_4) 1692 (20-one), 3605 cm.$^{-1}$ (OH) (Found: C, 80·7; H, 10·0. $C_{23}H_{34}O_2$ requires C, 80·65; H, 10·0%).

16α,17α-*Ethylidenepregn*-4-*ene*-3,20-*dione* (VI).—A mixture of the foregoing compound (3 g.) and aluminium t-butoxide (5 g.) in toluene (200 ml.) and cyclohexanone (60 ml.) was refluxed for 1 hr. After addition of Rochelle salt (25 g.) in water (150 ml.), solvents were removed by steam-distillation, and the product was collected by filtration. Purified from acetone–hexane, 16α,17α-*ethylidenepregn*-4-*ene*-3,20-*dione* formed prisms (1·7 g.), m. p. 170—171°, $[\alpha]_D^{26}$ +190° (*c* 0·8), $\lambda_{max.}$ 239—240 mμ (log ε 4·22) (Found: C, 80·9; H, 9·2. $C_{23}H_{32}O_2$ requires C, 81·1; H, 9·5%).

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