Synthesis of 11-Deoxy-18-hydroxycorticosterone and 18-Hydroxycorticosterone 21-Acetates

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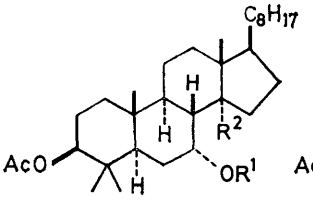
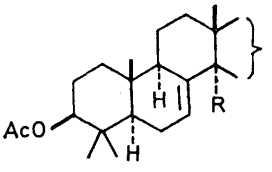
Functionalisation of the steroid 13-methyl group by nitrite photolysis in the presence of oxygen affords 18-nitrates. The 18-nitrate system provides convenient protection for the 18-hydroxy-group and generates the latter on reduction with zinc under neutral conditions. In this way, convenient syntheses of 11-deoxy-18-hydroxycorticosterone (Xi) and of 18-hydroxycorticosterone (XIIIg) have been completed.

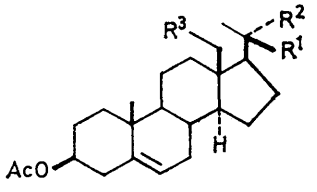
11-DEOXY-18-HYDROXYCORTICOSTERONE (Xi) and 18-hydroxycorticosterone (XIII g) are considered important



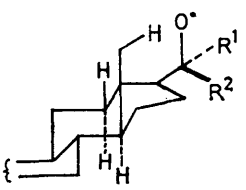
(I) a R^1 = NO, R^2 = Me,
b R^1 = H, R^2 = $CH_2 \cdot ONO_2$



(II) a; R = $CH_2 \cdot ONO_2$
b; R = $CH_2 \cdot OH$



(III) a; R^1R^2 = O, R^3 = H
b; R^1 = OH, R^2 = R^3 = H
c; R^2 = OH, R^1 = R^3 = H
d; R^1 = ONO, R^2 = R^3 = H
e; R^2 = ONO, R^1 = R^3 = H
f; R^1R^2 = O, R^3 = ONO_2
g; R^1 = OH, R^2 = H, R^3 = ONO_2
h; R^1 = H, R^2 = OH, R^3 = ONO_2

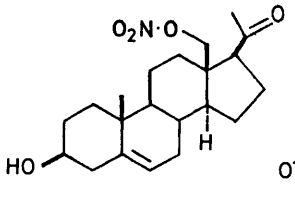


(IV) a; R^1 = Me, R^2 = H
b; R^1 = H, R^2 = Me

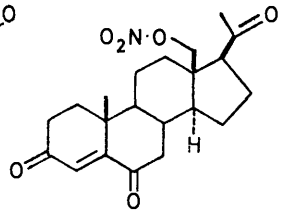
in hypertension.[1] Both steroids are produced by the adrenal cortex and have been proposed as intermediates in aldosterone biosynthesis.[2] We envisaged synthesis of 18-hydroxy-steroids *via* the 18-nitrates, the nitrate providing a convenient protecting group for OH. It was known[3] that irradiation of the nitrite (Ia) under oxygen gave the nitrate (Ib), which on dehydration gave the nitrate (IIa). Reduction with zinc gave smoothly the corresponding alcohol (IIb). We now describe the synthesis of 11-deoxy-18-hydroxycorticosterone 21-acetate (Xd) and 18-hydroxycorticosterone 21-acetate (XIIIf) by this approach.

Reduction of pregnenolone acetate (IIIa) with sodium borohydride gave the 20β-alcohol (IIIb) (80%) and the 20α-alcohol (IIIc) (13%). Irradiation[4] of the nitrite (IIId) prepared from the 20β-alcohol (IIIb) under oxygen gave the alcohol (IIIb), pregnenolone acetate (IIIa), the 20β-hydroxy-18-nitrate (IIIg), and the 20-oxo-18-nitrate (IIIf). The formation of the latter has analogy.[3] Jones oxidation of the nitrate (IIIg) gave the nitrate (IIIf). The nitrite (IIIe), prepared from the 20α-alcohol (IIIc), on irradiation under oxygen gave the 20α-hydroxy-18-nitrate (IIIh). That the 20α-alkoxyl radical (IVb) is superior to the 20β-radical (IVa) in C-18 functionalisation has ample precedent.[5] Jones oxidation of the nitrate (IIIg) gave the 20-oxo-18-nitrate (IIIf).

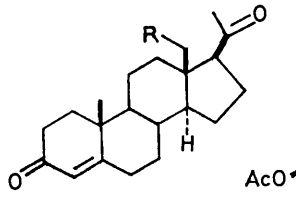
Although pregnenolone acetate (IIIa) is readily hydrolysed under basic conditions its 18-nitrate (IIIf) was inert to sodium hydrogen carbonate–methanol. Use of sodium carbonate–methanol resulted in epimerisation at C-17. Hydrolysis of (IIIf) with perchloric acid–methanol followed by oxidation with Jones reagent gave the enedione (VI) *via* (V). However, Oppenauer oxidation, with 1-methyl-4-piperidone as hydrogen acceptor,[6] gave the 18-nitrate (VIIa). Reduction of (VIIa) with zinc–ammonium acetate gave 18-hydroxyprogesterone (VIIb). Spectral data and the m.p. of the product

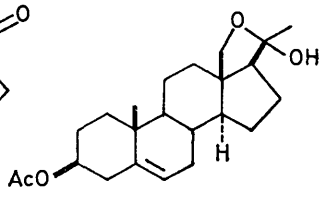


(V)



(VI)





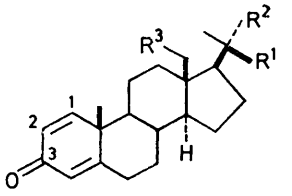
(VII) a; R = ONO_2
b; R = OH, hemiacetal

(VIII)

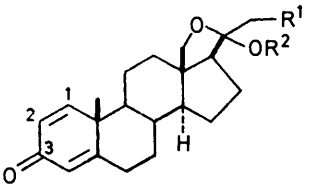
indicated that partial epimerisation at C-20 had occurred. The variation of literature m.p. and rotation data is in

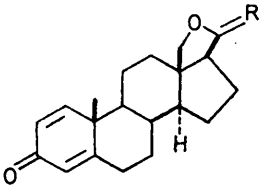
[1] C. E. Hall, S. Ayachi, and O. Hall, *Endocrinology*, 1973, **92**, 1175.
[2] P. Vecsei, D. OLoumer, and H. P. Wolff, *Experientia*, 1968, **24**, 1199.
[3] J. Allen, R. B. Boar, J. F. McGhie, and D. H. R. Barton, *J.C.S. Perkin I*, 1973, 2402; *cf.* Y. L. Chow, T. Hayasaka, and J. N. S. Tam, *Canad. J. Chem.*, 1970, **48**, 508.
[4] D. H. R. Barton, N. J. Basu, M. J. Day, R. H. Hesse, M. M. Pechet, and A. N. Starratt, preceding paper.
[5] A. L. Nussbaum and C. H. Robinson, *Tetrahedron*, 1962, **17**, 35; L. Velluz, G. Muller, R. Bardoneschi, and A. Poittevin, *Compt. rend.*, 1960, **250**, 725.
[6] R. Reich and J. F. W. Keana, *Synth. Comm.*, 1972, **2**, 323.

agreement with epimerisation occurring readily. 18-Nitroso-oxypregnenolone acetate (IIIf) was also converted into the 18-hydroxy-compound (VIII). Again, as in all 18-hydroxy-20-ketones prepared, spectral data were consistent with partial epimerisation at C-20. The conversion of 18-hydroxyprogesterone (VIIb) into 11-deoxy-18-hydroxycorticosterone (Xi) has been reported.[7]



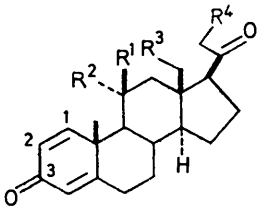
(IX) a; $R^1R^2=O$, $R^3=H$, 1,2-dihydro
b; $R^1R^2=O$, $R^3=H$
c; $R^1=OH$, $R^2=R^3=H$
d; $R^2=OH$, $R^1=R^3=H$
e; $R^1=ONO$, $R^2=R^3=H$
f; $R^2=ONO$, $R^1=R^3=H$
g; $R^1=OH$, $R^2=H$, $R^3=ONO_2$
h; $R^1=H$, $R^2=OH$, $R^3=ONO_2$
i; $R^1R^2=O$, $R^3=ONO_2$





(X) a; $R^1=R^2=H$
b; $R^1=OAc$, $R^2=H$
c; $R^1=R^2=H$, 1,2-dihydro
d; $R^1=OAc$, $R^2=H$, 1,2-dihydro
e; $R^1=H$, $R^2=SO_2\cdot C_6H_4Me$-*p*
f; $R^1=H$, $R^2=SO_2\cdot C_6H_4Me$-*p*, 1,2-dihydro
g; $R^1=OH$, $R^2=H$
h; $R^1=H$, $R^2=Et$, 1,2-dihydro
i; $R^1=OH$, $R^2=H$, 1,2-dihydro

(XI) a; $R=CH_2$
b; $R=O$



(XII) a; $R^1=OH$, $R^2=R^3=R^4=H$
b; $R^1=ONO$, $R^2=R^3=R^4=H$
c; $R^1=OH$, $R^2=R^4=H$, $R^3=ONO_2$
d; $R^1R^2=O$, $R^3=ONO_2$, $R^4=H$
e; $R^1=OH$, $R^2=R^3=H$, $R^4=OH$, 1,2-dihydro
f; $R^1=OH$, $R^2=R^3=H$, $R^4=OAc$, 1,2-dihydro
g; $R^1=OH$, $R^2=R^3=H$, $R^4=OAc$
h; $R^1=ONO$, $R^2=R^3=H$, $R^4=OAc$
i; $R^1=OH$, $R^2=H$, $R^3=ONO_2$, $R^4=OAc$
j; $R^1R^2=O$, $R^3=ONO_2$, $R^4=OAc$
k; $R^1R^2=O$, $R^3=R^4=H$

Since tritium-labelled 11-deoxy-18-hydroxycorticosterone (Xi) was required for clinical investigations its synthesis from 1,2-didehydroprogesterone (IXb) was undertaken. 2,3-Dichloro-5,6-dicyanobenzoquinone (DDQ) oxidised progesterone (IXa) to 1,2-didehydroprogesterone[4] (IXb). Selective reduction of the 20-ketone[8] with lithium tri-t-butoxyaluminium hydride gave the 20β-alcohol (IXc) as the major and the 20α-alcohol (IXd) as the minor product. The alcohols (IXc and d) gave the nitrites (IXe and f) with nitrosyl chloride in pyridine. Although the epimers were separable, preparative photolysis under oxygen was carried out on the mixture. The nitrates (IXg and h) formed were not isolated but oxidised with Jones reagent to the oxo-nitrate (IXi) isolated in 33% yield. Reduction with zinc–ammonium acetate gave 1,2-didehydro-18-hydroxyprogesterone (Xa). The absence of C-20 carbonyl absorption in the i.r. spectrum indicated the product existed exclusively as the hemiacetal.

In order to introduce the oxygen at C-21 the dehydration of (Xa) to the vinyl ether (XIa) by elimination of the toluene-*p*-sulphonate (Xe) [reported for the toluene-*p*-sulphonate (IXf)][9] or by dehydration of (Xa) with phosphoryl chloride [reported for (Xc)] was investigated, but the results were not promising. However, the method of Kirk and Rajagopalan[10] worked well. 1,2-Didehydro-18-hydroxyprogesterone (Xa), treated with lead tetra-acetate at 20 °C, gave the 21-acetate (Xb) in good yield. A similar reaction at 75 °C afforded the lactone (XIb), presumably by α-cleavage of the 20-alkoxyl radical derived from the acetate (Xb).

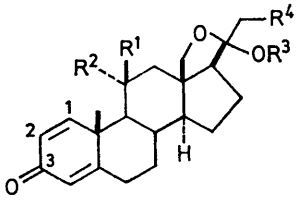
Hydrogenation of 1,2-didehydro-18-hydroxyprogesterone (Xa) over tristriphenylphosphinerhodium(I) chloride in ethanol–benzene gave the 20-ethoxy-compound (Xh). Acidic hydrolysis followed by oxidation with lead tetra-acetate gave 11-deoxy-18-hydroxycorticosterone 21-acetate (Xd).

18-Hydroxycorticosterone 21-acetate (XIIIf) was synthesised from corticosterone 21-acetate (XIIf). Photolysis of 1,2-didehydro-11β-nitroso-oxyprogesterone (XIIb) under oxygen was investigated first as a model synthesis. The incorporation of a 1,2-double bond ensured exclusive C-18 functionalisation[4] and permitted preparation of tritium-labelled (XIIIf). Irradiation of the nitrite (XIIb)[4] under oxygen gave 1,2-dihydro-11-oxoprogesterone (XIIk), 1,2-didehydro-11β-hydroxyprogesterone (XIIa), and the 11β-hydroxy-18-nitrate (XIIc). Reduction with zinc–ammonium acetate gave 11β,18-dihydroxypregna-1,4-diene-3,20-dione

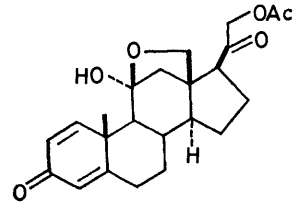
[7] M. P. Li, C. P. Lavitos, H. Traikov, M. K. Birmingham, and T. H. Chan, *J. Steroid Biochem.*, 1970, **1**, 259.
[8] J. A. Zoderic and J. Iriarte, *J. Org. Chem.*, 1962, **27**, 1756.
[9] Ciba Ltd., Brit. Pat. 957,432 (*Chem. Abs.*, 1964, **61**, 8374).
[10] D. N. Kirk and M. S. Rajagopalan, *J.C.S. Chem. Comm.*, 1974, 145.

(XIIIa). Jones oxidation of (XIIc) gave the 11-oxo-18-nitrate (XIId), which on reduction with zinc–ammonium acetate gave 18-hydroxypregna-1,4-diene-3,11,20-trione (XIIIb).

1,2-Didehydrocorticosterone 21-acetate (XIIg) was prepared by the oxidation of corticosterone 21-acetate (XIIf) with DDQ. Irradiation of the derived nitrite (XIIh) under oxygen gave the 11β-hydroxy-18-nitrate (XIIi). Reduction with zinc–ammonium acetate gave the required 1,2-didehydro-18-hydroxycorticosterone 21-acetate (XIIId). 18-Hydroxycorticosterone 21-acetate



(XIII) a ; R^1 = OH, R^2 = R^3 = R^4 = H
b ; R^1 R^2 = O, R^3 = R^4 = H
c ; R^1 = OH, R^2 = R^4 = H, R^3 = Me
d ; R^1 = OH, R^2 = R^3 = H, R^4 = OAc
e ; R^1 R^2 = O, R^3 = H, R^4 = OAc
f ; R^1 = OH, R^2 = R^3 = H, R^4 = OAc, 1,2-dihydro
g ; R^1 = R^4 = OH, R^2 = R^3 = H, 1,2-dihydro



(XIV)

(XIIIf) was obtained by tristriphenylphosphinerhodium-(I) chloride-catalysed hydrogenation. Benzene alone was used as solvent to prevent formation of the 20-ethoxy-derivative, acidic hydrolysis of which would have resulted in the 11β,18-epoxide.[11]

Analogous compounds in the 11-oxo-series were also prepared. Jones oxidation of the nitrate (XIIi) gave the 11-oxo-18-nitrate (XIIj). Reduction of the latter with zinc–ammonium acetate gave the 21-acetate (XIIIe). The n.m.r. and i.r. spectra of the product were consistent with an equilibrium mixture of hemiacetals (XIIIe) and (XIV).

In conclusion, the biologically important 11-deoxy-18-hydroxycorticosterone acetate (XIIIe) has been synthesised from 1,2-didehydro-11β-hydroxyprogesterone (XIIa), and 18-hydroxycorticosterone acetate (XIV) from corticosterone (XIIe). Clinical studies of these compounds have been hampered by lack of synthetic materials. However, both have now been prepared from readily available materials in short reaction sequences. By our syntheses, they are equally readily available in labelled form.

EXPERIMENTAL

For general experimental conditions see the preceding paper.[4] The 20α- (IIIc) and 20β- (IIIb) alcohols were prepared by a standard method.[12]

Preparation and Irradiation of Pregn-5-ene-3β,20β-diol 3-Acetate 20-Nitrite (IIId).—The *nitrite* (IIId) (2.4 g, 91%), prepared from the alcohol (IIIb) (2.5 g.) and nitrosyl chloride, had m.p. (from CH_2Cl_2–MeOH) 153—154.5° (decomp.), $[\alpha]_D^{21}$ −87° (*c* 1.05), $\nu_{max.}$ 1 735s, 1 635s, 1 600m, 1 250s, and 780s cm^{-1} (Found: C, 70.65; H, 8.9; N, 3.55. $C_{23}H_{35}NO_4$ requires C, 70.9; H, 9.05; N, 3.6%). Oxygen was bubbled through the nitrite (IIId) (2.0 g) in acetonitrile (500 ml) at −20 °C prior to and during irradiation (Pyrex filter) with a 200W medium pressure mercury arc for 1 h. Evaporation and chromatography on Fluorisil (eluant benzene–EtOAc, 1 : 0—19 : 1) gave (*a*) pregnenolone acetate (IIIa) (505 mg, 27%), (*b*) the alcohol (IIIb) (400 mg, 22%), (*c*) 20β-*alcohol* 18-*nitrate* (IIIg) (295 mg, 14%), m.p. (from hexane) 140—141°, $[\alpha]_D^{21}$ −51° (*c* 0.9), $\nu_{max.}$ 3 650w, 1 725s, 1 620s, and 1 280m cm^{-1}, τ 4.65 (1 H, m, 6-H), 5.40 (1 H, m, 3α-H), 5.50 (2 H, ABq, *J* 10 Hz, 18-H), 6.30 (1 H, m, 20-H), 8.00 (3 H, s, OAc), 8.85 (3 H, d, *J* 6.5 Hz, 21-H_3), and 8.97 (3 H, s, 19-H_3) (Found: C, 65.6; H, 8.3; N, 3.3. $C_{23}H_{35}NO_6$ requires C, 65.55; H, 8.35; N, 3.3%), and (*d*) the 20-*ketone* 18-*nitrate* (IIIf) (160 mg, 8%), m.p. (from hexane) 156—157°, $[\alpha]_D^{21}$ +24° (*c* 0.95), $\nu_{max.}$ 1 725s, 1 705s, 1 635s, 1 275s, and 1 240s cm^{-1}, τ 4.65 (1 H, m, 6-H), 5.50 (1 H, m, 3α-H), 5.66br (2 H, s, 18-H), 7.75 (3 H, s, 21-H_3), 8.00 (3 H, s, OAc), and 8.97 (3 H, s, 19-H_3) (Found: C, 65.9; H, 7.95; N, 3.25. $C_{23}H_{33}NO_6$ requires C, 65.85; H, 7.95; N, 3.35%). Jones oxidation of the alcohol (IIIg) gave the ketone (IIIf), identical with the photoproduct.

Preparation and Irradiation of Pregn-5-ene-3β20α-diol 3-Acetate 20-Nitrite (IIIe).—The *nitrite* (IIIe) (1.08 g, 91%) was prepared from the alcohol (IIIc) (1.1 g); m.p. (from CH_2Cl_2–MeOH) 110—111°, $[\alpha]_D^{21}$ −31° (*c* 0.8), $\nu_{max.}$ 1 735s, 1 630s, 1 245s, and 800s cm^{-1} (Found: C, 70.85; H, 8.85; N, 3.5. $C_{23}H_{35}NO_4$ requires C, 70.9; H, 9.05; N, 3.6%). Photolysis of the nitrite (1.0 g) as above and chromatography on Fluorisil gave (*a*) the nitrate (IIIh) (506 mg, 47%) as a wax (from hexane), $[\alpha]_D^{21}$ −44° (*c* 0.7), $\nu_{max.}$ 3 450m, 1 735s, 1 630s, 1 280s, and 1 240s cm^{-1}, τ 4.70 (1 H, m, 6-H), 5.40 (1 H, m, 3α-H), 5.61br (2 H, s, 18-H), 6.17 (1 H, m, 20-H), 8.00 (3 H, s, OAc), 8.80 (3 H, d, *J* 6 Hz, 21-H_3), and 9.00 (3 H, s, 19-H_3), and (*b*) the starting 20α-alcohol (IIIc) (180 mg, 20%). Jones oxidation of the 20α-alcohol 18-nitrate (IIIh) gave the 20-oxo-nitrate (IIIf), identical with that previously described.

18-*Nitro-oxyprogesterone* (VIIa).—The nitrate (IIIf) (395 mg) in methanol (15 ml)–perchloric acid (0.7 ml) was left for 8 h at 20 °C. Partition between water and dichloromethane and evaporation gave the crude 5,6-didehydro-3β-alcohol (V). The solid in toluene (35 ml) and 1-methyl-4-piperidone (3 ml) was heated to reflux under nitrogen (Dean–Stark apparatus). The first 5 ml of distillate were discarded, aluminium isopropoxide (490 mg) in toluene (3 ml) was added dropwise, and refluxing was continued (6 h). The toluene solution was washed with aqueous 1% sulphuric acid and water, and evaporated. P.l.c. gave *compound* (VIIa) (126 mg, 47%), m.p. (from EtOAc–hexane) 145—146°, $[\alpha]_D^{25}$ +190° (*c* 0.87), $\nu_{max.}$ 1 700m, 1 665s, 1 620s, and 1 280s cm^{-1}, $\lambda_{max.}$ 239—240 nm (ε 17 200), *m/e* 375 (M^+)

[11] R. H. Hesse and M. M. Pechet, *J. Org. Chem.*, 1965, **30**, 1723.
[12] P. Wieland and K. Miescher, *Helv. Chim. Acta*, 1949, **32**, 1922.

(Found: C, 67.15; H, 7.6; N, 3.55. $C_{21}H_{29}NO_5$ requires C, 67.15; H, 7.8; N, 3.75%).

Attempted Jones oxidation of the 3β-alcohol (V) gave the 4-*ene*-3,6-*dione* (VI), m.p. 178—179° (decomp.), $[\alpha]_D^{29}$ +45° (*c* 0.51), $\nu_{max.}$ 1 700s, 1 685s, 1 630s, 1 275s, and 870s cm^{-1}, $\lambda_{max.}$ 250 nm (ε 11 600), *m/e* 389 (M^+) (Found: C, 64.75; H, 7.0; N, 3.7. $C_{21}H_{27}NO_6$ requires C, 64.75; H, 7.0; N, 3.6%).

18-*Hydroxyprogesterone* (VIIb).—Ammonium acetate (0.5 g), followed by zinc dust (0.75 g) was added to the 18-nitrate (VIIa) (50 mg) in methanol (10 ml) at 0 °C. After 1 h at 0 °C water (100 ml) and dichloromethane (50 ml) were added. Filtration, evaporation, and p.l.c. of the organic phase gave 18-hydroxyprogesterone (VIIb) (31 mg, 71%), m.p. (from Me_2CO) 159—161° (bulk) (lit.,[13] 154.5°; lit.,[14] 178—180°), $[\alpha]_D^{22}$ +124° (*c* 0.79 in CH_2Cl_2) (lit.,[15] +112°; lit.,[16] +159°), $\nu_{max.}$ 3 500m, 1 660s, and 1 620w cm^{-1}, $\lambda_{max.}$ 240 nm (ε 16 900), *m/e* 330 (M^+) (Found: C, 76.65; H, 9.05. Calc. for $C_{21}H_{30}O_3$: C, 76.35; H, 9.15%).

18-*Hydroxypregnenolone* 3β-*Acetate* (VIII).—Zinc dust–ammonium acetate and pregnenolone acetate 18-nitrate (IIIf) (100 mg) gave compound (VIII) (69 mg, 78%), m.p. 171—173° (from Me_2CO) (lit.,[17] 171—174°), $[\alpha]_D^{25}$ −2° (*c* 0.6) (lit.,[17] +6°), $\nu_{max.}$ 3 500m, 1 735s, and 1 240s cm^{-1}, *m/e* 374 (M^+) (Found: C, 73.85; H, 8.95. Calc. for $C_{23}H_{34}O_4$: C, 73.75; H, 9.15%).

20β-*Hydroxypregna*-1,4-*dien*-3-*one* (IXc).—Lithium tri-t-butoxyaluminium hydride (35 g) was added to 1,2-didehydroprogesterone[16] (IXb) (17.0 g) in dry tetrahydrofuran (THF) (1 l). After 4 h at room temperature the solution was poured into aqueous 5% acetic acid (4 l) and extracted with ethyl acetate. The extract was washed with aqueous sodium carbonate and water. Evaporation gave compound (IXc) (11.3 g, 66%) contaminated by 10% 20α-alcohol (IXd) (from ethyl acetate). A repeated crystallisation (from EtOAc) gave pure 20β-alcohol (IXc), m.p. 187—191° (lit.,[18] 188—189°), $[\alpha]_D^{26}$ +18° (*c* 0.69) (lit.,[19] +16°), $\nu_{max.}$ 3 600m, 1 660s, 1 620m, and 1 600w cm^{-1}, $\lambda_{max.}$ 244 nm (ε 15 200) (Found: C, 80.05; H, 9.45. Calc. for $C_{21}H_{30}O_2$: C, 80.2; H, 9.6%).

20β-*Nitroso-oxypregna*-1,4-*dien*-3-*one* (IXe).—*Compound* (IXe) (112 mg, 93%), prepared from the 20β-alcohol (IXc) (110 mg) and nitrosyl chloride in pyridine, had m.p. (from EtOAc–hexane with a trace of pyridine) 145—147°), $[\alpha]_D^{26}$ +52° (*c* 0.51 in CH_2Cl_2) $\nu_{max.}$ 1 665s, 1 615s, 1 600w, and 880s cm^{-1}, $\lambda_{max.}$ 244 nm (ε 17 200) (Found: C, 73.45; H, 8.35; N, 3.9. $C_{21}H_{29}NO_3$ requires C, 73.45; H, 8.5; N, 4.05%).

1,2-*Didehydro*-18-*nitro-oxyprogesterone* (IXi) *and* 1,2-*Didehydro*-18-*hydroxyprogesterone* (Xa).—The 20-nitrite mixture (IXe and f) (8.0 g) and triethylamine (2 ml) in chlorobenzene (2.2 l) (in 4 batches) under oxygen were irradiated with a 200 W medium-pressure mercury arc for 150 min. The residue obtained by evaporation was dissolved in acetone (100 ml) and treated with Jones reagent (15 ml; dropwise over 5 min) at 0 °C. After 10 min water (300 ml) was added, the mixture was extracted with ethyl acetate, and the extract was washed with aqueous sodium hydrogen carbonate and water and evaporated. P.l.c. of the residue (1 g) gave the 18-*nitrate* (IXi) (380 mg, 33%), m.p. 148—150° (decomp.), $[\alpha]_D^{25}$ +128° (*c* 1.7 in CH_2Cl_2), $\nu_{max.}$ 1 700m, 1 660s, 1 635s, 1 620m, 1 600w, and 1 275s cm^{-1}, $\lambda_{max.}$ 243 nm (ε 16 900), τ 3.00 (1 H, d, *J* 10 Hz, 1-H), 3.80 (1 H, dd, *J* 10 and 2 Hz, 2-H), 3.95br (1 H, s, 4-H), 5.62 (2 H, ABq, *J* 10 Hz, 18-H), 7.80 (3 H, s, 21-H_3), and 8.73 (3 H, s, 19-H_3), *m/e* 373 (M^+) (Found: C, 67.65; H, 7.55; N, 3.7. $C_{21}H_{28}NO_5$ requires C, 67.55; H, 7.3; N, 3.75%). Treatment of the residue (1 g) with zinc dust–ammonium acetate chromatography on Fluorisil (eluant EtOAc–benzene, 3 : 47), and p.l.c. gave 1,2-*didehydro*-18-*hydroxyprogesterone* (Xa) (220 mg, 23%), m.p. (from EtOAc–hexane) 170—173°, $[\alpha]_D^{24}$ +74° (*c* 0.68), $\nu_{max.}$ 3 550m, 1 660s, 1 620m, and 1 600w cm^{-1}, $\lambda_{max.}$ 245 nm (ε 15 800), τ 3.00 (1 H, d, *J* 10 Hz, 1-H), 3.83 (1 H, dd, *J* 10 and 2 Hz, 2-H), 3.97br (1 H, s, 4-H), 6.27 (2 H, s, 18-H), 8.50 (3 H, s, 21-H_3), and 8.82 (3 H, s, 19-H_3), *m/e* 328 (M^+) (Found: C, 76.45; H, 8.3. $C_{21}H_{28}O_3$ requires C, 76.8; H, 8.6%).

1,2-*Didehydro*-11-*deoxy*-18-*hydroxycorticosterone* 21-*Acetate* (Xb).—Lead tetra-acetate (150 mg), glacial acetic acid (5 ml), and 1,2-didehydro-18-hydroxyprogesterone (100 mg) were kept at 20 °C under argon for 1 h. More lead tetra-acetate (150 mg) was added and after 1 h at 75 °C t.l.c. indicated complete reaction. Water and dichloromethane were added and the organic phase was washed with aqueous sodium hydrogen carbonate and water. Evaporation gave the 20,18-*lactone* (XIb) (61 mg, 65%), m.p. (from Me_2CO) 243—245°, $[\alpha]_D^{20}$ +36° (*c* 0.7), $\nu_{max.}$ 1 760s, 1 655s, 1 625m, and 1 605w cm^{-1}, $\lambda_{max.}$ 242—243 nm (ε 15 900), τ 3.08 (1 H, d, *J* 10 Hz, 1-H), 3.90 (1 H, dd, *J* 10 and 2 Hz, 2-H), 4.03br (1 H, s, 4-H), 6.00 (2 H, ABq, *J* 10 Hz., 18-H_2), and 8.80 (3 H, s, 19-H_3) (Found: C, 76.85; H, 7.95. $C_{20}H_{24}O_3$ requires C, 76.9; H, 7.75%). Oxidation with lead tetra-acetate of 1,2-didehydro-18-hydroxyprogesterone (100 mg) at 20 °C for 30 min with or without hydrochloric acid (concentrated; 1 drop) present gave *compound* (Xb) (91 mg, 79%), m.p. (from Me_2CO) 168—171° (bulk), $[\alpha]_D^{18}$ +81° (*c* 0.93 in CH_2Cl_2), $\nu_{max.}$ 3 550m, 1 735s, 1 660s, 1 620m, 1 600w, and 1 250s cm^{-1}, $\lambda_{max.}$ 240—241 nm (ε 16 800), τ 3.08 (1 H, d, *J* 10 Hz, 1-H), 3.90 (1 H, dd, *J* 10 and 2 Hz, 2-H), 4.03br (1 H, s, 4-H), 5.86 and 6.00 (2 H, s and q, respectively,* 21-H), 6.28 and 6.38 (2 H, 2s*, 18-H_2), 7.98 (3 H, s, OAc), and 8.86 (3 H, s, 19-H_3), *m/e* 386 (M^+) (Found: C, 71.75; H, 8.0. $C_{23}H_{30}O_5$ requires C, 71.45; H, 7.8%).

Hydrogenation of 1,2-*Didehydro*-18-*hydroxyprogesterone* (Xa) *and its Conversion into* 11-*Deoxy*-18-*hydroxycorticosterone* 21-*Acetate* (Xd).—1,2-Didehydro-18-hydroxyprogesterone (100 mg) and tristriphenylphosphinerhodium(I) chloride in benzene (15 ml)–ethanol (15 ml) were stirred under hydrogen at 1 atm and 20 °C for 16 h. Chromatography on Fluorisil (eluant Me_2CO–CH_2Cl_2, 1 : 9) and p.l.c. gave a single major product, probably the ethoxy-derivative (Xh). Hydrolysis for 1 h with acetic acid–water (19 : 1) and a trace of hydrochloric acid gave 18-hydroxyprogesterone (Xc), identical with that previously described. The reaction was repeated except that after hydrolysis the hemiacetal (Xc) was treated with lead tetra-acetate for 30

* Here and later the signals designated with an asterisk indicate the presence of 20-epimers in the solution used for the n.m.r. measurements.

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min at 20 °C. Work up gave 11-*deoxy*-18-*hydroxycorticosterone* 21-*acetate* (Xd) (39 mg, 34%), m.p. (from Me_2CO–hexane) 151—154° (bulk), $[\alpha]_D^{17}$ +132° (*c* 0.76), $\nu_{max.}$ 3 450m, 1 750s, 1 655s, and 1 240s cm^{-1}, $\lambda_{max.}$ 242 nm (ε 16 300), τ 4.34br (1 H, s, 4-H), 5.80 and 5.95 (2 H, s and q respectively,* 21-H_2), 6.24 and 6.34 (2 H, 2s,* 18-H_2), 7.00 (1 H, m, exch. D_2O,OH), 7.94 (3 H, s, OAc), and 8.90 (3 H, s, 19-H_3) (Found: C, 71.2; H, 8.55. $C_{23}H_{32}O_5$ requires C, 71.1; H, 8.3%).

11β, 18-*Dihydroxypregna*-1,4-*diene*-3,20-*dione* (XIIIa) *and the* 11-*Oxo-analogue* (XIIIb).—Irradiation of the nitrite (XIIb) (700 mg) in acetonitrile (160 ml)–triethylamine (0.5 ml) under oxygen and p.l.c. gave (*a*) 1,2-didehydro-11-oxoprogesterone (XIIk) (190 mg), (*b*) 1,2-didehydro-11β-hydroxyprogesterone (XIIa) (122 mg), and (*c*) the 18-*nitrate* (XIIc) (259 mg, 34%), m.p. (from CH_2Cl_2–MeOH) 162—164°, $[\alpha]_D^{22}$ +159° (*c* 0.9), $\nu_{max.}$ 3 450m, 1 700m, 1 650s, 1 620s, 1 610s, and 1 270s cm^{-1}, $\lambda_{max.}$ 243 nm (ε 14 900) (Found: C, 64.9; H, 6.95; N, 3.45. $C_{21}H_{27}NO_6$ requires C, 64.75; H, 7.0; N, 3.6%). Oxidation by Jones reagent (0.2 ml) of the nitrate (XIIc) (100 mg) in acetone (10 ml) for 10 min at 20 °C, work-up, and p.l.c. gave the *oxo-nitrate* (XIId) (89 mg, 89%), m.p. (from EtOAc–hexane) 146—147°, $[\alpha]_D^{24}$ +205° (*c* 0.8), $\nu_{max.}$ 1 705s, 1 660s, 1 630s, 1 605m, and 1 275s cm^{-1}, $\lambda_{max.}$ 240 nm (ε 16 000), *m/e* 387 (M^+) (Found: C, 64.95; H, 6.45; N, 3.4. $C_{21}H_{25}NO_6$ requires C, 65.1; H, 6.5; N, 3.6%). Reduction by ammonium acetate–zinc dust of the oxo-nitrate (XIId) (100 mg) gave 18-*hydroxypregna*-1,4-*diene*-3,11,20-*trione* (XIIIb) (54 mg, 61%), m.p. (from CH_2Cl_2–MeOH, then Me_2CO) 200—203° (bulk), $[\alpha]_D^{24}$ +153° (*c* 0.3), $\nu_{max.}$ 3 450m, 1 700m, 1 660s, 1 620m, and 1 600w cm^{-1}, $\lambda_{max.}$ 241 nm (ε 15 600), *m/e* 342 (M^+) (Found: C, 73.4; H, 7.7. $C_{21}H_{26}O_4$ requires C, 73.65; H, 7.65%). Likewise, reduction with ammonium acetate–zinc dust of the nitrate (XIIc) (100 mg) and p.l.c. gave the 11β,18-*diol* (XIIIa) (58 mg, 66%), m.p. (from acetone) 157—161° (bulk), $[\alpha]_D^{22}$ +128° (*c* 0.51 in CH_2Cl_2), $\nu_{max.}$ 3 550m, 3 400m, 1 660s, 1 620m, and 1 600w cm^{-1}, $\lambda_{max.}$ 241—242 nm (ε 15 900) (Found: C, 73.15; H, 8.2. $C_{21}H_{28}O_4$ requires C, 73.2; H, 8.2%).

1,2-*Didehydrocorticosterone* 21-*Acetate* (XIIg).—Oxidation of corticosterone 21-acetate (XIIf) (10.0 g) with DDQ and chromatography on Fluorisil (eluant MeOH–CH_2Cl_2, 3 : 97) gave crude compound (XIIg). This in dichloromethane was washed with aqueous sodium hydrogen carbonate and water. Evaporation gave *compound* (XIIg) (7.65 g, 77%), m.p. (from Me_2CO–hexane) 174—175.5°, $[\alpha]_D^{24}$ +161° (*c* 1.0), $\nu_{max.}$ 3 500m, 1 750s, 1 715m, 1 655s, 1 615m, and 1 235s cm^{-1}, $\lambda_{max.}$ 242 nm (ε 15 600) (Found: C, 71.3; H, 7.6. $C_{23}H_{30}O_5$ requires C, 71.5; H, 7.8%).

Preparation and Irradiation of 1,2-*Didehydrocorticosterone* 21-*Acetate* 11-*Nitrite* (XIIh).—The *nitrite* (XIIh) (2.5 g, 96%), prepared from 1,2-didehydrocorticosterone 21-acetate (XIIg) (2.4 g) and nitrosyl chloride in pyridine, had m.p. (from EtOAc–hexane) 165—167° (decomp.), $[\alpha]_D^{20}$ +218° (*c* 0.98), $\nu_{max.}$ 1 755s, 1 720s, 1 660s, 1 625m, 1 610w, and 1 240s cm^{-1}, $\lambda_{max.}$ 241 nm (ε 16 600) (Found: C, 66.4; H, 6.85; N, 3.55. $C_{23}H_{29}NO_6$ requires C, 66.5; H, 7.05; N, 3.35%). Irradiation of the nitrite (XIIh) (2.4 g) in acetonitrile (550 ml)–triethylamine (0.5 ml) under oxygen at 0—10 °C with a 200 W medium-pressure mercury arc for 70 min and p.l.c. gave the 18-nitrate (XIIi) (875 mg), m.p. (from EtOAc–hexane) 113° (decomp.; sealed tube), $[\alpha]_D^{21}$ +162° (*c* 0.4), $\nu_{max.}$ 3 550m, 1 755s, 1 730s, 1 660s, 1 630s, 1 280s, and 1 230s cm^{-1}, $\lambda_{max.}$ 240 nm (ε 15 800), *m/e* 447 (M^+) (Found: C, 61.65; H, 6.5; N, 2.9. $C_{23}H_{29}NO_8$ requires C, 61.75; H, 6.55; N, 3.15%).

Oxidation of 1,2-*Didehydro*-18-*nitro-oxycorticosterone* 21-*Acetate* (XIIi).—Oxidation with Jones reagent (0.3 ml) of the 11β-alcohol (XIIi) (250 mg) in acetone (30 ml) for 5 min at 20 °C, work-up, and p.l.c. gave the 11-*oxo-nitrate* (XIIj) (219 mg, 88%), m.p. (from propan-2-ol) 130—132°, $[\alpha]_D^{20}$ +298° (*c* 0.5), $\nu_{max.}$ 1 760s, 1 730s, 1 710s, 1 660s, 1 620s, 1 290s, and 1 220s cm^{-1}, $\lambda_{max.}$ 239—240 nm (ε 16 200), *m/e* 445 (M^+) (Found: C, 62.2; H, 6.15; N, 3.15. $C_{23}H_{27}NO_8$ requires C, 62.0; H, 6.1; N, 3.15%).

21-*Acetoxy*-18-*hydroxypregna*-1,4-*diene*-3,11-20-*trione* (XIIIe).—Reduction by zinc dust–ammonium acetate of the 11-oxo-nitrate (XIIj) (100 mg) and p.l.c. gave *compound* (XIIIe) (67 mg, 75%) as a foam, $[\alpha]_D^{21}$ +138° (*c* 0.72 in CH_2Cl_2), $\nu_{max.}$ 3 500m, 1 740m, 1 705m, 1 660s, 1 620m, 1 600w, and 1 225m cm^{-1}, $\lambda_{max.}$ 240—241 nm (ε 16 000), τ 2.44 (0.25 H, d, *J* 10 Hz, 1-H), 2.50 (0.75 H, s, *J* 10 Hz, 1-H), 3.88 (1 H, dd, *J* 10 and 2 Hz, 2-H), 4.00br (1 H, s, 4-H), 5.83 (1.5 H, ABq, *J* 12 Hz, 21-H), 6.02 (0.5 H, s, 21-H), 6.34 (2 H, s, 18-H_2), 7.94 (3 H, s, OAc), and 8.60 (3 H, s, 19-H_3), *m/e* 400 (M^+) (Found: C, 68.75; H, 7.3. $C_{23}H_{28}O_6$ requires C, 69.0; H, 7.05%).

1,2-*Didehydro*-18-*hydroxycorticosterone* 21-*Acetate* (XIIId).—Reduction by zinc dust–ammonium acetate of the 11β-alcohol nitrate (XIIi) (75 mg) and p.l.c. gave *compound* (XIIId) (50 mg, 73%), m.p. (from CH_2Cl_2–EtOAc) 194—197°, $[\alpha]_D^{22}$ +159° (*c* 0.73), $\nu_{max.}$ 3 500s, 1 740s, 1 660s, 1 620m, 1 600w, and 1 255s cm^{-1}, $\lambda_{max.}$ 240 nm (ε 16 000), τ 2.84 (1 H, d, *J* 10 Hz, 1-H), 3.84 (1 H, dd, *J* 10 and 2 Hz, 2-H), 5.67 (2 H, ABq, *J* 10 Hz, 18-H_2), 5.80 and 6.15 (2 H, s and q respectively, 21-H_2), 6.84br (1 H, s, exch. D_2O, OH), 7.90 (3 H, s, OAc), and 8.60 (3 H, s, 19-H_3) (Found: C, 68.55; H, 7.45. $C_{23}H_{30}O_6$ requires C, 68.65; H, 7.5%).

18-*Hydroxycorticosterone* 21-*Acetate* (XIIIf).—The dienone (XIIId) (80 mg) and tristriphenylphosphinerhodium(I) chloride (200 mg) in benzene (120 ml) were stirred at ambient pressure and temperature under hydrogen for 48 h. P.l.c., trituration with acetone, and repeated p.l.c. gave 18-*hydroxycorticosterone* 21-*acetate* (XIIIf) (32 mg, 40%), m.p. (from Me_2CO–hexane) 170—173°, $[\alpha]_D^{20}$ +177° (*c* 0.4 in CH_2Cl_2), $\nu_{max.}$ 3 550m, 1 745s, 1 655s, and 1 240s cm^{-1}, $\lambda_{max.}$ 244 nm (ε 16 500), τ 4.34 (1 H, s, 4-H), 5.65 and 6.25 (2 H, s and q respectively, 21-H_2), 5.77br (2 H, s, 18-H_2), 5.80 (1 H, m, 11-H), 7.05br (1 H, s, exch. D_2O, OH), 7.90 (3 H, s, OAc), and 8.59 (3 H, s, 19-H_3) (Found: C, 66.6; H, 8.06. $C_{23}H_{32}O_6$,0.5H_2O requires C, 66.8; H, 8.05%).

[5/723 *Received*, 16*th April*, 1975]

* See footnote on p. 2255.