New Syntheses of 19,21-Dihydroxypregn-4-ene-3,20-dione, 21-Hydroxy-19-norpregn-4-ene-3,20-dione, and 11β,19,21-Trihydroxypregn-4-ene-3,20-dione

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19,21-Dihydroxypregn-4-ene-3,20-dione has been synthesized from 3β-acetoxypregn-5-en-20-one *via* the 'hypoiodite reaction' [treatment of the 5α-bromo-6β-hydroxy derivative with $Pb(OAc)_4$ and I_2, with irradiation], and Henbest acetoxylation at C-21; oxidation of the intermediate 21-monoacetate to the 19-oxo derivative and alkaline cleavage gave 21-hydroxy-19-norpregn-4-ene-3,20-dione. A similar synthesis of 11β,19,21-trihydroxypregn-4-ene-3,20-dione from 3β-acetoxypregn-5-ene-11,20-dione proceeded through intermediates with the 11β-hydroxy function protected as its acetate. Unusual features mainly of conformational origin were observed in the presence of the 11β-acetoxy substituent; some were helpful to the synthesis, while others led to undesirable side reactions.

19,21-Dihydroxypregn-4-ene-3,20-dione (19-hydroxy-deoxycorticosterone; '19-OH-DOC') (9) and 11β,19,21-trihydroxypregn-4-ene-3,20-dione (19-hydroxycorticosterone; '19-OH-B') (27) are steroids with at most very weak sodium-retaining properties, sometimes found among the minor constituents of corticosteroid extracts.[1-3] Samples were obtained during the period 1955—1963 by incubation of DOC [4,5] or 19-OH-DOC,[6] respectively, with adrenal homogenates. Chemical syntheses were also reported at about the same time: 19-OH-DOC from strophanthidin [7] *via* 19-acetoxy-3-oxoandrost-4-ene-17β-carboxylic acid,[8] or from 3β,21-diacetoxypregn-5-en-20-one *via* a 'hypoiodite reaction',[9] and 19-OH-B from the 3,20-bis(ethylene acetal) of corticosterone acetate *via* a Barton reaction,[10] which afforded products of intramolecular attack at C-18 as well as at C-19.

21-Hydroxy-19-norpregn-4-ene-3,20-dione ('19-nor-DOC'), a more potent sodium-retaining steroid than DOC itself,[11-13] has been found in the urine of rats with adrenal regeneration hypertension [14] and has kaliuretic activity. Recently it has been identified in human urine,[15] but any role in human hypertension remains to be established. 19-Nor-DOC has been synthesized by a variety of methods.[12,16,17]

As samples of 19-OH-DOC, 19-nor-DOC, and 19-OH-B were required for the Steroid Reference Collection, we undertook their syntheses from available starting materials, 3β-acetoxypregn-5-en-20-one (pregnenolone acetate) for the DOC derivatives, and 3β-acetoxypregn-5-ene-11,20-dione for 19-OH-B. Although our routes to 19-OH-DOC and 19-nor-DOC have features in common with earlier syntheses, we report them briefly as convenient alternatives. Some unexpected observations of chemical interest were made during the synthesis of 19-OH-B.[18]

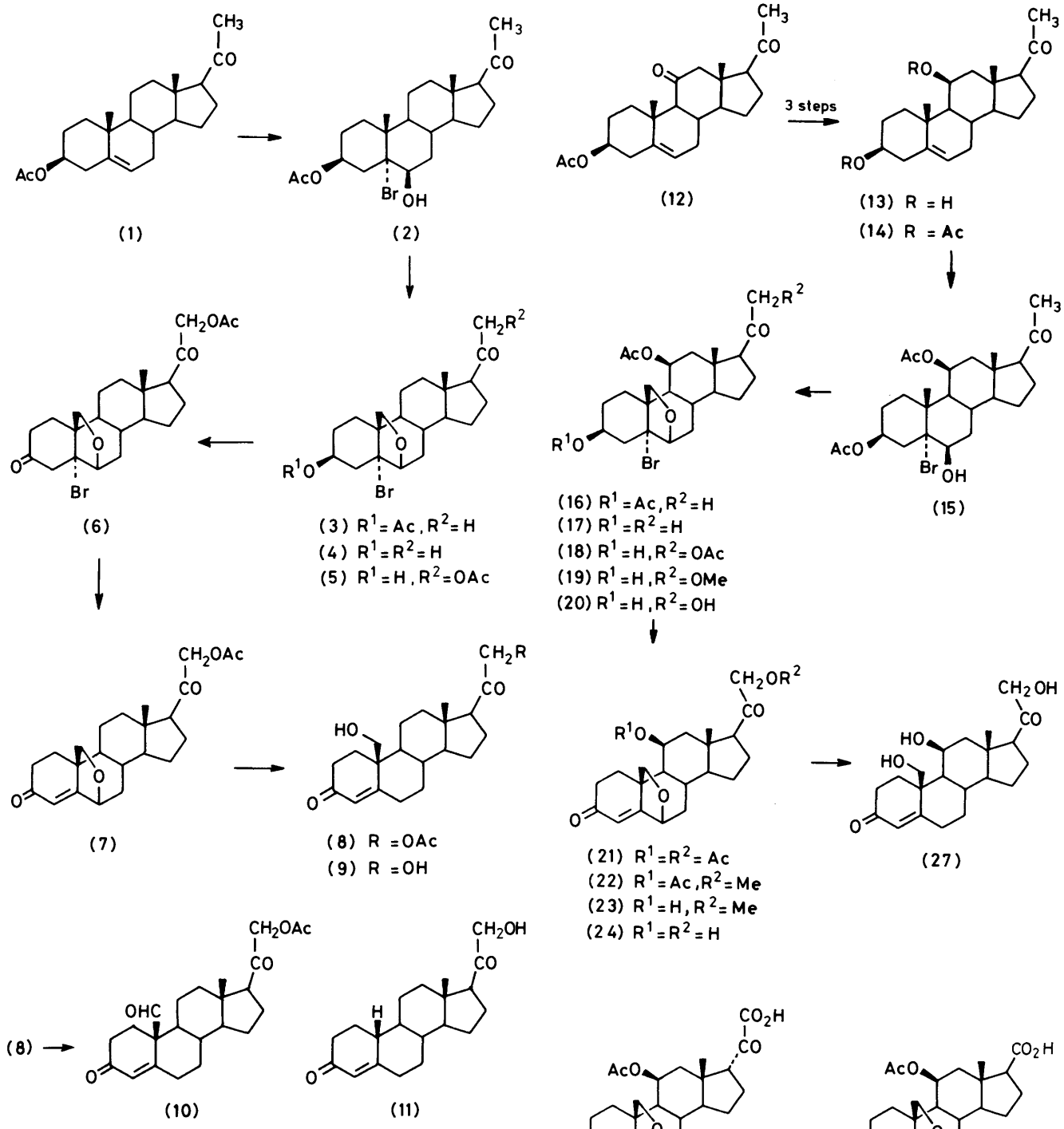
19-Hydroxydeoxycorticosterone ('19-OH-DOC') *and* *19-Nordeoxycorticosterone* ('19-Nor-DOC') (*Scheme* 1).—Pregnenolone acetate (1) was converted into its 5α-bromo-6β-hydroxy derivative (2) by the addition of hypobromous acid. By-products included the 6β-bromo-5α-hydroxy isomer, the 5α,6α-epoxide, and the 5α,6β-diol, in accordance with earlier reports.[19,20] Application of the 'hypoiodite reaction' [$Pb(OAc)_4$, I_2; *hν*] [21] converted the bromohydrin (2) into the known 5α-bromo-6β,19-epoxide (3),[22] which after hydrolysis of the 3-acetate was acetoxylated at C-21 by the Henbest procedure [$Pb(OAc)_4$–BF_3 in benzene–methanol].[23] Jones oxidation then gave the unstable 5α-bromo-3-ketone (6) which was immediately dehydrobrominated by sodium acetate in methanol to the 6β,19-epoxy-4-en-3-one (7). Reductive cleavage of the epoxide by zinc dust to give 19-OH-DOC 21-acetate was accompanied by partial acetylation at C-19 when acetic acid [9,24,25] was used as solvent; acetylation was avoided by using propan-2-ol containing 10% of acetic acid, when 19-OH-DOC 21-acetate (8) was obtained in excellent yield. Very mild alkaline hydrolysis afforded 19-OH-DOC (9). 19-Nor-DOC (11) was obtained by oxidising the 21-acetate (8) to obtain 19-oxo-DOC 21-acetate (10),[26] which readily underwent decarbonylation to lose C-19 during alkaline hydrolysis.

19-Hydroxycorticosterone (19-OH-B) (*Scheme* 2).—The Barton reaction applied to an 11β-nitrite led to reaction at C-18 as well as at C-19.[10] To avoid competition from functionalization at C-18, we chose instead the hypoidite route from the 5α-bromo-6β-hydroxy compound (15). Previous work in our laboratory [27] had established the feasibility of using an 11β-acetoxy intermediate as a convenient means of protection of 11β-OH during a hypoiodite reaction, the subsequent hydrolysis of this very hindered ester now presenting no problems.[28]

3β-Acetoxypregn-5-ene-11,20-dione (12) was converted *via* its ethylene acetal and reduction (with $LiAlH_4$) into the 11β-hydroxypregnenolone (13). Acetylation of both hydroxy groups with acetic anhydride–pyridine, catalysed by 4-dimethylaminopyridine,[29] was quantitative.

In contrast to the rather inefficient hypobromous acid addition to pregnenolone acetate (above), formation of the required bromohydrin (15) from 3β,11β-diacetoxypregn-5-en-20-one (14) was virtually quantitative. This unexpected advantage was attributed in retrospect to the overcrowded nature of the β-face of the molecule. The undesired 6β-bromo-5α-hydroxy by-product in the case of pregnenolone acetate results from β-face attack of the reagent,[30] and was probably the source of other by-products in the 11-deoxy series, the 5α,6α-epoxide and 5α,6β-diol. A molecular model indicates that the buttressing effect of the axial 11β-acetoxy substituent would force the C-19 methyl group closer than usual to the β-face of the Δ^5-olefinic bond, leading to preferential α-attack.

The critical step of functionalization at C-19 to give the 6β,19-epoxide was also found to be assisted by the presence of the 11β-acetoxy substituent, the yield of 6β,19-epoxide (16) also being quite exceptionally almost quantitative after the proportions of reagents used in the hypoiodite reaction had been optimised. The β-face compression inferred above would bring the C-19 methyl and 6β-hydroxy groups into even



Scheme 1.

Scheme 2.

closer proximity than usual, a situation apparently advantageous for hydrogen abstraction from the methyl group.[31,32]

In contrast to the favourable features of reactions leading to the 6β,19-epoxide, the subsequent 21-acetoxylation at C-21 was rendered unusually difficult by the presence of the 11β-acetoxy substituent. The reason is not clear. After a careful selective hydrolysis of the 3β-acetoxy group, to permit later oxidation at C-3, the Henbest method of 21-acetoxylation was employed as in the preparation of 19-OH-DOC. H.p.l.c. monitoring of the progress of the reaction showed 40—50% conversion into the 21-acetoxy derivative (18) after 5 h, but longer times led to the appearance of by-products which were

difficult to separate cleanly. Optimum yields were obtained by stopping the reaction after 7 h, and separating the 21-acetoxy compound (18) from unchanged 20-ketone (17) and small amounts of by-products by preparative h.p.l.c., rather than attempting the separation of the more complex product mixture after longer times.

Two major by-products from the 21-acetoxylation were identified as the 21-methoxy (19) and 21-hydroxy derivative (20), respectively. The 21-methoxylated material (19) could amount to 20—30% of the total products, although the yields were not reproducible and varied with the scale of reaction. The 21-acetoxy (18) and 21-methoxy (19) compounds were incompletely separated by h.p.l.c., but could be separated readily after Jones oxidation of the mixture and dehydrobromination to afford the corresponding 6β,19-epoxy-Δ^4-3-oxo compounds (21) and (22), respectively. The 21-methoxylated products were characterised by their spectral characteristics, including their mass spectra (see Experimental section).

Products from relatively prolonged reactions (>7 h) also afforded a more polar fraction (h.p.l.c.), in up to 18% yield, which was identified as the 21-hydroxy derivative (20) from its n.m.r. spectrum (Experimental section). The reason for the formation of this product is unknown, since the conditions of the Henbest acetoxylation are not hydrolytic, and hydrolysis during work-up could not account for the dependence of the yield on long acetoxylation times. We had previously observed the unexpected formation of a hydroxylated product during the conversion of the enolic acetate 3-acetoxycholesta-3,5-diene (28) into 6β-acetoxycholest-4-en-3-one (29) by lead tetra-acetate in acetic acid, when 6β-hydroxycholest-4-en-3-one (30) was invariably obtained as a minor product.[33] This observation has not been explained, but could possibly be attributable to the formation and subsequent hydrolysis (during work-up) of a steroidal alkoxylead intermediate of undetermined structure.

Very long reaction times (2 days) for the 21-acetoxylation resulted in a fourth product (*ca.* 17% yield), which was notably less polar than any of the first three. The n.m.r. spectrum showed the characteristics expected of a 21-substituted derivative of the pregnan-20-one (17), but the structure of this product remains unknown.

Jones oxidation of 11,21-diacetoxy-5-bromo-6β,19-epoxy-3β-hydroxypregnan-20-one (18), followed immediately by dehydrobromination (sodium acetate–methanol), gave the required 4-en-3-one (21). The contaminating 21-methoxy derivative (22) was normally removed at this stage by preparative h.p.l.c. The maximum overall yield of 11β,21-diacetoxy-6β-19-epoxypregn-4-ene-3,20-dione (21) from the 21-deoxy precursor (17) was *ca.* 30%.

To complete the synthesis of 19-OH-B it was necessary to reduce the 6β,19-epoxy-4-en-3-one system with zinc dust and to hydrolyse the 11β- and 21-acetoxy groups. Since the 19-hydroxy-4-en-3-one would be expected to suffer a retro-Aldol cleavage with loss of C-19 under strongly alkaline conditions, the hydrolysis was carried out before cleavage of the 6β,19-epoxide. Hydrolysis experiments using the 21-methoxylated product (22) as a model compound showed that the 11β-acetoxy group in this series is unusually susceptible to hydrolysis, probably because steric hindrance around the 11β-position is reduced by the distortion resulting from the presence of the 6β,19-epoxy bridge, which pulls C-19 away from the 11β-oxygen substituent. Whereas normal 11β-acetoxy steroids are stable to ordinary alkaline systems, and require 'naked hydroxide'[28] for their hydrolysis, the present compound was 40% hydrolysed in 4 h by potassium hydrogen carbonate in refluxing aqueous methanol, and fully hydrolysed overnight.

Under similar conditions the 11β,21-diacetate (21) was completely hydrolysed at C-21 in 45 min (t.l.c.), and rather less than 50% hydrolysed at C-11 after 4 h. By this time a small proportion of the 17α-isomer (25) of the 11β-monoacetate (22) had also appeared (t.l.c.). Overnight reaction completed the hydrolysis at C-11, and the 11β,21-diol (24) was isolated by preparative t.l.c.

Some oxidative degradation of the side-chain was invariably observed to accompany the hydrolysis, even though the reaction was normally performed under nitrogen.[34–36] The degradation product isolated was the 11β-acetoxyandrostene-17β-carboxylic acid (26). When air was not excluded during the hydrolysis the acid (26) became the major product. Hydrolysis with 'naked hydroxide'[28] at room temperature under nitrogen gave similar results.

Control experiments, in which the 11-deoxy analogue, 21-acetoxy-6β,19-epoxypregn-4-ene-3,20-dione (7) was subjected to hydrolysis with potassium hydrogen carbonate in aqueous methanol, under conditions matching those used for the 11β-acetoxy derivative, gave no appreciable evidence of oxidative degradation of the side-chain, irrespective of whether oxygen was excluded. This is a further illustration of the significant and not always predictable effect of the 11β-oxygen substituent on the chemistry of the side-chain. No explanation is apparent.

The final reductive cleavage of the 6β,19-epoxide ring was achieved by treating the diol (24) with zinc dust in refluxing propan-2-ol containing acetic acid (9 : 1). These conditions had no serious detrimental effect on the product, 19-OH-B (27), and caused no acetylation of hydroxy functions. The structure of the product (27) was confirmed from its spectral characteristics (Experimental section), and from the mass spectrum of its 19,21-bis(trimethylsilyl) derivative.

Experimental

M.p.s were determined on a Reichert melting point microscope. N.m.r. spectra were recorded at 100 MHz for solutions in deuteriochloroform, with tetramethylsilane as internal standard. I.r. spectra were determined for potassium bromide discs. Mass spectra were determined at Queen Elizabeth College on the University of London Intercollegiate Research Service Kratos MS-25 double-focusing mass spectrometer integrated with a Perkin-Elmer Sigma 3 gas chromatograph with DS 50 data processing systems. G.l.c. was carried out on a column of 1% OV1 at 250 °C following conversion into trimethylsilyl ethers by *N,O*-bis(trimethylsilyl)trifluoroacetamide. Mass spectrometer conditions: source temp. 200 °C, ionising voltage 70 eV, ionising current 100 μA, accelerating voltage 1.5 kV, scan speed 1 s per decade. Thin-layer chromatography (t.l.c.) was carried out on 4 cm × 20 cm glass plates coated with Merck silica gel G and 60 PF_{254} in the ratio 1 : 1, and visualised with sulphuric acid–ethanol (1 : 1) by ultraviolet light. Analytical high pressure liquid chromatography (h.p.l.c.) was carried out using Waters Associates 30 cm × 3.9 mm i.d. μ-Bondapak C-18 and μ-Porasil columns, with detection by differential refractometer. All solvents were purified before use.[37] Boron trifluoride–diethyl ether was freshly distilled from calcium hydride. Light petroleum refers to the fraction of boiling range 60—80 °C.

5-Bromo-6β,19-epoxy-3β-hydroxy-5α-pregnan-20-one (4).—Preparation of this compound followed essentially the procedure described by Akhtar and Barton[22] (see text).

Acetoxylation at C-21.—5-Bromo-6β,19-epoxy-3β-hydroxy-5α-pregnan-20-one (4) (1 g) in 5% methanolic benzene (30 ml) was stirred with boron trifluoride–diethyl ether (5 ml) for 20 min at room temperature. Lead tetra-acetate (2.13 g) was then added and the stirring was continued for 5 h. The mixture

was diluted with benzene then washed with water, sodium hydrogen carbonate solution, and water to neutrality. The gummy product (1.4 g) which remained after evaporation of the solvent crystallised from acetone–light petroleum to give 21-*acetoxy*-5-*bromo*-6β,19-*epoxy*-3β-*hydroxy*-5α-*pregnan*-20-*one* (5) as needles (480 mg), m.p. 153—155 °C, $\nu_{max.}$ 3 600 and 3 480 (OH), 1 750 (21-OAc), 1 722 (20-ketone), 1 495, and 860 cm^{-1} (6β,19-epoxide [38]); δ 0.7 (s, 18-H_3), 2.18 (s, 21-OAc), 3.8 (AB-q, δ_A 3.68, δ_B 3.92, *J* 8 Hz, 19-H_2), 4.06, 4.08 (m, d, overlapping 3- and 6-H), and 4.61 (AB-q, δ_A 4.50, δ_B 4.72, *J* 16 Hz, 21-H) (Found: C, 58.6; H, 7.1; Br, 16.55. $C_{23}H_{33}BrO_5$ requires C, 58.8; H, 7.0; Br, 16.85%).

21-*Acetoxy*-6β,19-*epoxypregn*-4-*ene*-3,20-*dione* (7).—The 21-acetate (5) in acetone (5 ml) at 5 °C was treated dropwise with Jones reagent until there was a permanent orange colour; then the excess of reagent was destroyed by adding propan-2-ol dropwise. After filtration the solution was diluted with dichloromethane, which was washed with water and dried ($MgSO_4$). Evaporation of solvent without heating gave the unstable 21-*acetoxy*-5-*bromo*-6β,19-*epoxy*-5α-*pregnane*-3,20-*dione* (6), needles, m.p. 103—104 °C, $\nu_{max.}$ 1 730—1 740, and 1 250 cm^{-1}; δ 0.74 (s, 18-H_3), 2.20 (s, 21-OAc), 4.01—4.06 (overlapping AB-q and d, 19-H_2 and 6-H), 4.63 (AB-q, δ_A 4.5, δ_B 4.76, *J* 16 Hz, 21-H_2).

Without further purification, the bromo-ketone (6) was treated with sodium acetate (1.3 g) and methanol (15 ml), and the mixture was heated under reflux for 1 h, when t.l.c. showed the reaction to be complete. Water was added and the product was extracted into dichloromethane which was washed, dried ($MgSO_4$), and evaporated to give 21-acetoxy-6β,19-epoxypregn-4-ene-3,20-dione (7) as needles (463 mg). Crystallisation from acetone–light petroleum gave the pure product (310 mg), m.p. 193—194 °C (lit.,[9] m.p. 193—196 °C), $[\alpha]_D$ +3.3° (*c*, 1.6% in $CHCl_3$) (lit.,[9] $[\alpha]_D^{23}$ +4.3°); $\nu_{max.}$ 1 750 (21-OAc), 1 730 (20-CO), and 1 670 cm^{-1} (4-en-3-one); δ 0.8 (s, 18-H_3), 2.2 (s, 21-OAc), 3.86 (AB-q, δ_A 3.52, δ_B 4.20, *J* 8 Hz, 19-H_2), 4.65 (overlapping d, q, 6-H and 21-H_2), and 5.85 (s, 4-H).

21-*Acetoxy*-19-*hydroxypregn*-4-*ene*-3,20-*dione* (8).—(*a*) *Acetic acid as solvent.* 21-Acetoxy-6β,19-epoxypregn-4-ene-3,20-dione (7) (50 mg) in glacial acetic acid (5 ml) was stirred with zinc dust (1.3 g) over a steam bath for 15 min, after which time the reaction appeared to be complete (t.l.c.). The mixture was filtered and the zinc was washed several times with acetic acid. The filtrate was evaporated under reduced pressure leaving an oily product which was extracted into dichloromethane. The solution was washed with water and saturated sodium hydrogen carbonate solution, dried ($MgSO_4$) and evaporated to give a mixture of products (78 mg) which were separated by h.p.l.c. Fraction 1 (29.4 mg) crystallised from acetone–light petroleum to give the required 19-hydroxy compound (8), m.p. 192—196 °C (lit.,[7] m.p. 197—199 °C), $\nu_{max.}$ 3 400 (19-OH), 1 750 (21-OAc), 1 730 (20-CO), 1 680 (3-CO), and 1 620 cm^{-1} (4-ene); δ 0.66 (s, 18-H_3), 2.18 (s, 21-OAc), 3.99 (AB-q, δ_A 3.92, δ_B 4.06, *J* 6 Hz, 19-H_2), 4.60 (AB-q, δ_A 4.48, δ_B 4.72, *J* 16 Hz, 21-H_2), and 5.94 (s, 4-H).

Fraction 2 (7 mg) was unchanged 6β,19-epoxide (7). The final, minor and least polar fraction was 19,21-diacetoxypregn-4-ene-3,20-dione, identical with a sample obtained by acetylation of the 21-acetate (Ac_2O–pyridine), m.p. 120—121 °C (lit.,[7] m.p. 127 °C), $\nu_{max.}$ 1 750 (OAc), 1 730 (20-CO), 1 680 and 1 620 cm^{-1} (4-en-3-one); δ 0.72 (s, 18-H_3), 2.0 (s, 19-OAc), 2.18 (s, 21-OAc), 4.41 (AB-q, δ_A 4.14, δ_B 4.68, *J* 12 Hz, 19-H_2), 4.60 (AB-q, δ_A 4.48, δ_B 4.72, *J* 16 Hz, 21-H_2), and 5.9 (s, 4.4).

(*b*) *Using propan-2-ol–acetic acid.* The 6β,19-epoxide (7) (200 mg) in propan-2-ol (20 ml) and acetic acid (2 ml) was stirred and heated under reflux with zinc dust (2.7 g; previously activated by brief washing with dilute hydrochloric acid). The reaction was monitored by t.l.c. and was essentially complete after 3 h. The filtered solution was evaporated under reduced pressure and the product was extracted into ethyl acetate, which was washed with saturated sodium hydrogen carbonate and water, and dried ($MgSO_4$). Evaporation of the solvent afforded a crystalline product (290 mg) which was recrystallised from acetone–light petroleum to give the pure 19-hydroxy compound (8) (111 mg).

19,21-*Dihydroxypregn*-4-*ene*-3,20-*dione* (19-OH-DOC) (9).—The 21-acetate (8) (130 mg) in methanol (35 ml) flushed with nitrogen was treated with potassium hydroxide (130 mg; in the minimum volume of water). The mixture was stirred at room temperature for 5½ h when t.l.c. indicated the hydrolysis was complete. A few drops of acetic acid were added, followed by water, and the product was extracted into dichloromethane which was washed and dried ($MgSO_4$). The product after evaporation of the solvent was 19-OH-DOC (118 mg) of 95% purity (g.l.c.), which crystallised from acetone–light petroleum, m.p. 158—160 °C (lit.,[17] m.p. 163—165 °C); $[\alpha]_D$ +176° (*c*, 5% in $CHCl_3$) (lit.,[17] +180°). $\nu_{max.}$ 3 400 (O–H), 1 710 (20-CO), and 1 660 cm^{-1}; δ 0.7 (s, 18-H_3), 3.26 (t, *J* 4 Hz, 21-OH), 3.98 (AB-q, δ_A 4.05, δ_B 3.90, *J* 10 Hz, 19-H_2), 4.18 (d, *J* 4 Hz, 21-H_2), and 5.92 (s, 4-H).

19-*Oxodeoxycorticosterone Acetate* (21-*Acetoxy*-19-*oxopregn*-4-*ene*-3,20-*dione*) (10).—21-Acetoxy-19,21-dihydroxypregn-4-ene-3,20-dione (8) (90 mg) in dichloromethane (2 ml) was stirred at room temperature while pyridinium chlorochromate (74.8 mg) was added. After 30 min the mixture was poured onto a column of Florisil, and the steroid was eluted with diethyl ether. Evaporation of the solvent left an oil which crystallised on adding light petroleum to give 19-oxo-deoxycorticosterone acetate (10) (55 mg), m.p. 114—117 °C (lit.,[26] m.p. 122 °C), $\nu_{max.}$ 1 750 (21-OAc), 1 735 (20-CO), 1710 (19-CHO), 1 680 (3-CO), and 1 620 (4-ene); δ 0.69 (s, 18-H_3), 2.18 (s, 21-OAc), 4.58 (AB-q, δ_A 4.50, δ_B 4.76, *J* 16 Hz, 21-H_2), 5.96 (s, 4-H), and 9.9 (s, 19-H).

19-*Nordeoxycorticosterone* (11).—19-Oxodeoxycorticosterone acetate (10) (46 mg) in methanol (10 ml) containing potassium hydroxide (10 mg, dissolved in the minimum volume of water) was heated under reflux for 1 h, after which time t.l.c. showed the reaction was complete. After evaporation of most of the methanol, water was added to precipitate the product, which was purified by preparative t.l.c. to give 21-hydroxy-19-norpregn-4-ene-3,20-dione (20 mg), m.p. 124—125 °C (acetone–light petroleum) (lit.,[14] m.p. 131 °C), $\nu_{max.}$ 3 400 (O–H), 1 735 (20-CO), and 1 670 cm^{-1} (4-ene); δ 0.71 (s, 18-H_3), 3.20 (t, *J* 4 Hz, 21-OH), 4.18 (d, *J* 4 Hz, 21-H_2), and 5.82 (4-H).

3β,11β-*Dihydroxypregn*-5-*en*-20-*one* (13).—This was obtained from 3β-hydroxypregn-5-ene-11,20-dione (12) essentially as described.[39]

3β,11β-*Diacetoxypregn*-5-*en*-20-*one* (14).—3β,11β-Dihydroxypregn-5-en-20-one (1.5 g) in pyridine (30 ml) was treated with *N*,*N*-dimethylaminopyridine (90 mg) and acetic anhydride (14 ml) and left overnight at room temperature before being poured into ice–water. The precipitated *diacetate* (1.8 g) was essentially a single product (h.p.l.c.), m.p. 155—158 °C (acetone–light petroleum), $\nu_{max.}$ 1 750 (OAc) and 1 710 cm^{-1} (20-ketone); δ 0.76 (s, 18-H_3), 1.10 (s, 19-H_3), 2.04, 2.06 (s, s, 3- and 11-OAc), 2.10 (s, 21-H_3), 4.6 (m, *W* 30 Hz, 3α-H),

5.3 (d, 11α-H), and 5.5 (d, *J* 4 Hz, 6-H) (Found: C, 71.2; H, 8.7. $C_{25}H_{36}O_5$ requires C, 72.1; H, 8.7%).

3β,11β-*Diacetoxy-5-bromo-6β-hydroxy-5α-pregnan-20-one* (15).—The diacetate (14) (1.1 g) in dioxane (10 ml) was treated with perchloric acid (1.8 ml of 60% $HClO_4$ in 10 ml of water) then cooled and stirred in an ice-bath. Water (2 ml) was added, followed by *N*-bromoacetamide (546 mg) in portions during 30 min. The mixture was further stirred for 30 min while being allowed to warm to room temperature, then aqueous 15% sodium thiosulphate (30 ml) was added, followed by more water to precipitate the product. The resulting solid (1.4 g) was essentially a single compound (h.p.l.c.). Crystallisation from acetone–light petroleum gave the *bromohydrin* (15), m.p. 149—151 °C, $\nu_{max.}$ 3 500 (6β-OH), 1 740 and 1 250 (3- and 11-OAc), and 1 700 cm^{-1} (20-ketone); δ 0.76 (s, 18-H_3), 1.36 (s, 19-H_3), 2.00 (s, 3-OAc), 2.04 (s, 11-OAc), 4.16 (d, *J* 4 Hz, 6-H), 5.3 (d, *J* 4 Hz, 11α-H), and 5.4 (m, *W* 28 Hz, 3α-H) (Found: C, 58.1; H, 7.5; Br, 14.85. $C_{25}H_{37}BrO_6$ requires C, 58.6; H, 7.0; Br, 15.6%).

3β,11β-*Diacetoxy-5-bromo-6,19-epoxy-5α-pregnan-20-one* (16).—A mixture of the bromohydrin (5) (2.5 g) and calcium carbonate (10 g) in cyclohexane (500 ml) was stirred and heated under reflux for 20 min, then lead tetra-acetate (15 g; dried by vacuum under nitrogen) and iodine (3.75 g; resublimed) were added simultaneously. The reaction was carried out under nitrogen with irradiation by two 500-W photo-flood lamps. The colour of the iodine disappeared after 1.1 h. The mixture was then filtered through a bed of Celite, which was washed with more hot cyclohexane. The filtrate was shaken with aqueous 15% sodium thiosulphate (100 ml) and dried ($MgSO_4$). Evaporation of the solvent left a gum (2.95 g) (h.p.l.c. single peak) which crystallised from acetone–light petroleum to give the 6β,19-*epoxide* (16), m.p. 175—176 °C; $\nu_{max.}$ 1 450 and 860 cm^{-1} (16β,19-epoxide); δ 0.74 (s, 18-H_3), 2.04 (s, 3-OAc), 2.06 (s, 11-OAc), 2.1 (s, 21-H_3), 4.06 (AB-q, δ_A 3.90, δ_B 4.22, *J* 8 Hz, 19-H_2), 4.1 (d, *J* 4 Hz, 6-H), 5.18 (d, *J* 4 Hz, 11α-H), and 5.2 (m, 3α-H) (Found: C, 58.6; H, 6.9; Br, 14.9. $C_{25}H_{35}BrO_6$ requires C, 58.7; H, 6.9; Br, 15.6%).

11β-*Acetoxy-5-bromo-6β,19-epoxy-3β-hydroxy-5α-pregnan-20-one* (17).—The diacetate (16) (1.28 g) in methanol (50 ml) was heated under reflux with saturated aqueous sodium carbonate (300 mg) and sufficient water to redissolve the initial precipitate. Hydrolysis was complete after 1 h (t.l.c.), and the solution was then cooled, the solvent was partially evaporated, and the product was precipitated in ice–water. Crystallisation from acetone–light petroleum gave the 11-*acetate* (17) (1.08 g), m.p. 147—148 °C; $\nu_{max.}$ 3 500 (3-OH), 1 740 and 1 250 cm^{-1} (11β-OAc); δ 0.76 (s, 18-H_3), 2.01 (s, 11-OAc), 2.08 (s, 21-H_3), 4.05 * (AB-q, δ_A 3.90, δ_B 4.20, *J* 8 Hz, 19-H_2), 4.06 * (d, *J* 4 Hz, 6-H), 4.06 * (m, 3α-H), and 5.16 (d, *J* 4 Hz, 11α-H) (Found: C, 58.8; H, 7.0; Br, 16.6. $C_{23}H_{33}BrO_5$ requires C, 58.8; H, 7.0; Br, 17.0%).

Acetoxylation at C-21.—11β-Acetoxy-5-bromo-6β,19-epoxy-3β-hydroxy-5α-pregnan-20-one (17) (922 mg, 1.97 mmol) was added to a mixture of 5% methanolic benzene (30 ml) and boron trifluoride–diethyl ether (5 ml). After being stirred for 20 min at room temperature, lead tetra-acetate (1.7 g, 2 equiv., dried by vacuum under nitrogen) was added. After 7 h stirring, a white crystalline solid had appeared. Addition of water precipitated brown PbO_2. The product was extracted into diethyl ether, which was washed, dried ($MgSO_4$), and evaporated to give a gum (983 mg). The constituents were separated stepwise by h.p.l.c. with a solvent system containing ethyl acetate and light petroleum (3 : 7) with the addition of 1% (v/v) of methanol. The crude product was injected in ethyl acetate (1 ml) with a solvent flow-rate of 1.5 ml min^{-1}.

Four fractions were collected. Fraction 1 (200 mg) was identified as unchanged starting material (17). Fraction 2 (429.8 mg) was mainly the required 21-acetoxy derivative (18), but was contaminated with traces of impurities, including the 21-methoxy derivative (19). It was a gum, $\nu_{max.}$ 3 600 (3-OH), 1 740 and 1 240 cm^{-1} (11- and 21-OAc), δ 0.80 (s, 18-H_3), 2.02 (s, 11-OAc), 2.16 (s, 21-OAc), 4.1 * (d, *J* 4 Hz, 6-H), 4.04 * (AB-q, δ_A 3.90, δ_B 4.18, *J* 8 Hz, 19-H_2), 4.0 * (m, 3α-H), 4.56 (s, 21-H_2), and 5.16 (d, 11α-H). The 21-methoxy contaminant was removed at the following stage (see text).

Fraction 3 (100 mg) was 11β-*acetoxy-5-bromo-6β,19-epoxy-3β,21-dihydroxy-5α-pregnan-20-one* (20), crystals, m.p. 152—154 °C (from methanol), $\nu_{max.}$ 3 500 (3- and 21-OH), 1 730, 1 240 (11-OAc), and 1 720 cm^{-1} (20-ketone); δ 0.80 (s, 18-H_3), 2.02 (s, 11-OAc), 3.16 (t, *J* 6 Hz, 21-OH), 4.05 * (AB-q, δ_A 3.9, δ_B 4.2, *J* 8 Hz, 19-H_2), 4.1 * (m, 3α-H), 4.1 * (d, *J* 4 Hz, 6-H), and 4.16 (d, *J* 6 Hz, 21-H_2). On irradiation at the resonance frequency of the 21-OH proton, at δ 3.16, the 21-H_2 doublet (δ 4.16) collapsed to a singlet (Found: C, 57.2; H, 7.0; Br, 16.4. $C_{23}H_{33}BrO_6$ requires C, 56.9; H, 6.85; Br, 16.5%).

11β,21-*Diacetoxy-6β,19-epoxypregn-4-ene-3,20-dione* (21).—11β,21-Diacetoxy-5-bromo-6β,19-epoxy-3β-hydroxy-5α-pregnan-20-one (18) (429 mg) in acetone (15 ml) at ice-bath temperature was stirred during dropwise addition of Jones reagent until there was a permanent orange colour in the solution. After 30 min the excess of reagent was destroyed by adding propan-2-ol, the precipitated chromium salts were removed by filtration, and the solution was evaporated under reduced pressure. The residual gum was extracted into dichloromethane, which was washed with water, dried ($MgSO_4$), and evaporated under reduced pressure without heat. Anhydrous sodium acetate (1.1 g) and methanol (15 ml) were added, and the mixture was heated under reflux for 1.5 h. After evaporation of the methanol the residue was extracted into dichloromethane, which was washed with water and dried ($MgSO_4$). Evaporation of solvent gave an oil (336 mg), which was separated by h.p.l.c. (μ-Porasil column; ethyl acetate–light petroleum–methanol, 50 : 50 : 1) into three fractions. Fraction 1 (55 mg) was a complex mixture and was discarded. Fraction 2 (101 mg) contained the required 11β,21-diacetoxy-6β,19-epoxypregn-4-ene-3,20-dione (21) as well as the 21-methoxy analogue (22). Fraction 3 (147 mg) was essentially the 11β,21-diacetate (21). Repeated h.p.l.c. purification of fractions 2 and 3 in the same system afforded pure samples.

11β,21-*Diacetoxy-6β,19-epoxypregn-4-ene-3,20-dione* (21) was a gum, $\nu_{max.}$ 1 730, 1 250 (3- and 21-OAc), and 1 670 cm^{-1} (Δ^4-3-ketone); δ 0.87 (s, 18-H_3), 2.07 (s, 11β-OAc), 2.16 (s, 21-OAc), 4.05 (AB-q, δ_A 3.50, δ_B 4.60, *J* 8 Hz, 19-H_2), 4.56 (s, 21-H_2), 4.64 (d, *J* 7 Hz, 6-H), 5.3 (d, *J* 4 Hz, 11α-H), and 5.84 (s, 4-H); *m/z* 444 ($C_{25}H_{32}O_7$, M^+; 8%), 371 ($M^+ - CH_2OAc$; 12), 321 (8), 283 ($M^+ - COCH_2OAc - HOAc$; 8), 253 ($M^+ - COCH_2OAc - HOAc - CH_2O$; 28), 149 (45) and 43 (100).

11β-*Acetoxy-6β,19-epoxy-21-methoxypregn-4-ene-3,20-dione* (22) was also a gum, $\nu_{max.}$ 1 730, 1 250 (11-OAc), and 1 670 cm^{-1} (Δ^4-3-ketone); δ 0.84 (s, 18-H_3), 3.4 (s, 21-OMe), 3.95 (s, 21-H_2), 4.08 (AB-q, δ_A 3.50, δ_B 4.60, *J* 8 Hz, 19-H_2), 4.7 (d, *J* 6 Hz, 6-H), 5.3 (d, *J* 4 Hz, 11α-H), and 5.84 (s, 4-H); *m/z* 416 ($C_{24}H_{32}O_6$, M^+; 11%), 371 ($M^+ - CH_2OMe$; 45), 283 ($M^+ - COCH_2OMe - HOAc$; 14), and 253 ($M^+ - COCH_2OMe - HOAc - CH_2O$; 100).

* Overlapping peaks.

Trial Hydrolysis of 11β-*Acetoxy*-6β,19-*epoxy*-21-*methoxypregn*-4-*ene*-3,20-*dione* (22) *with Potassium Hydrogen Carbonate*.—The 21-methoxy compound (22) (16 mg) in methanol (1 ml) containing potassium hydrogen carbonate (10 mg; in the minimum amount of water) was heated under reflux for 2.5 h. The solvent was evaporated and the product was extracted into ethyl acetate which was washed, dried ($MgSO_4$) and evaporated to give a gum (10 mg). H.p.l.c. gave two fractions; one (4.5 mg) was the starting material, and the other was 6β,19-*epoxy*-11β-*hydroxy*-21-*methoxypregn*-4-*ene*-3,20-*dione* (23) (3.1 mg), m.p. 216—219 °C (methanol), $\nu_{max.}$ 3 400 (11-OH), 1 720 (20-ketone), and 1 660 cm^{-1} (Δ^4-3-ketone); δ 0.96 (s, 18-H_3), 3.40 (s, 21-OMe), 3.98 (s, 21-H_2), 4.20 (AB-q, δ_A 3.60, δ_B 4.80, *J* 8 Hz, 19-H_2), 4.30 (d, 11α-H), 4.67 (d, *J* 5 Hz, 6-H), and 6.8 (s, 4-H); *m/z* 374 ($C_{22}H_{30}O_5$, M^+; 21%), 329 (M^+ − CH_2OMe; 50), 301 (M^+ − CO·CH_2-OMe; 3), 283 (M^+ − CO·CH_2OMe − H_2O; 14), and 253 (M^+ − $COCH_2OMe$ − H_2O − CH_2O; 100).

Hydrolysis of 11β,21-*Diacetoxy*-6β,19-*epoxypregn*-4-*ene*-3,20-*dione* (21).—The diacetate (21) (100 mg) in methanol (10 ml; previously purged with nitrogen) was heated under reflux with potassium hydrogen carbonate (80 mg in 0.5 ml water) for 16 h. The methanol was then evaporated and the product was extracted into dichloromethane, which was washed with water and dried ($MgSO_4$).

The resulting 6β,19-*epoxy*-11β,21-*dihydroxypregn*-4-*ene*-3,20-*dione* (24) was purified by preparative t.l.c. to give an amorphous solid (41.6 mg), m.p. 130—135 °C, $\lambda_{max.}$ (methanol) 235 nm (ε 9 280); $\nu_{max.}$ 1 710 (20-ketone) and 1 670 cm^{-1} (Δ^4-3-ketone); δ 0.96 (s, 18-H_3), 3.20 (t, *J* 6 Hz, 21-OH), 4.12 (AB-q, δ_A 3.48, δ_B 4.80, *J* − 8 Hz, 19-H_2), 4.18 (d, *J* 4 Hz, 21-H_2), 4.36 (d, *J* 4 Hz, 11α-H), 4.68 (d, *J* 6 Hz, 6-H), and 5.8 (s, 4-H) (Found: C, 68.0; H, 7.9. $C_{21}H_{28}O_5$ requires C, 69.9; H, 7.9%). *m/z* (as 21-trimethylsilyl ether) 432 ($C_{24}H_{36}$-O_5Si, M^+; 7%), 329 (M^+ − CH_2OSiMe_3; 2), 283 (M^+ − CO·CH_2OSiMe_3 − H_2O; 8), 253 (M^+ − CO·CH_2OSiMe_3 − H_2O − CH_2O; 36), and 73 (100).

The aqueous washings were acidified and further extracted with dichloromethane, which was washed, dried, and evaporated. Preparative t.l.c. purification of the residue gave 11β-*acetoxy*-6β,19-*epoxy*-3-*oxoandrost*-4-*ene*-17β-*carboxylic acid* (26) (8.6 mg), m.p. 267—269 °C (from methanol); $\nu_{max.}$ 3 300—2 500 (CO_2H), 1 730, 1 250 (11-OAc), 1 680 (Δ^4-3-ketone), and 1 650 cm^{-1} (hydrogen-bonded CO_2H); δ 0.95 (s, 18-H_3), 2.08 (s, 11-OAc), 4.05 (AB-q, δ_A 3.50, δ_B 4.60, *J* 8 Hz, 19-H_2), 4.70 (d, *J* 6 Hz, 6-H), 5.30 (d, *J* 4 Hz, 11α-H), and 5.84 (s, 4-H); *m/z* 388 ($C_{22}H_{28}O_6$, M^+; 19%), 272 (25), 270 (38), 131 (56) and 43 (100) (Found: C, 67.8; H, 7.3. $C_{22}H_{28}O_6$ requires C, 68.0; H, 7.3%).

A similar hydrolysis without exclusion of air gave predominantly the androstenecarboxylic acid (26).

Hydrolysis of 21-*Acetoxy*-6β,19-*epoxypregn*-4-*ene*-3,20-*dione* (7) *as a Control Experiment*.—Two hydrolyses were carried out under identical conditions, except that one was under nitrogen and the other in air. 21-Acetoxy-6β,19-epoxypregn-4-ene-3,20-dione (20 mg) in methanol containing potassium hydrogen carbonate (6 mg in the minimum amount of water) was treated as in the foregoing experiment. The product in each case was the corresponding 21-*alcohol* (18.7 mg from reaction under N_2; 16.9 mg from reaction in air), m.p. 169—170 °C (acetone–light petroleum), $\nu_{max.}$ 3 450 (21-OH), 1 700 (20-ketone), and 1 680 cm^{-1} (Δ^4-3-ketone); δ 0.78 (s, 18-H_3), 3.14 (t, *J* 5 Hz, 21-OH), 3.87 (AB-q, δ_A 3.52, δ_B 4.22, *J* 8 Hz, 19-H_2), 4.18 (d, *J* 4 Hz, 21-H_2), 4.68 (d, *J* 5 Hz, 6-H), and 5.82 (s, 4-H) (Found: C, 72.55; H, 8.25. $C_{21}H_{28}O_4$ requires C, 73.2; H, 8.2%).

11β,19,21-*Trihydroxypregn*-4-*ene*-3,20-*dione* (19-*Hydroxycorticosterone*) (27).—The 6β,19-epoxy derivative (24) (8 mg) in propan-2-ol (4.5 ml) containing acetic acid (0.5 ml) was treated with zinc dust (600 mg, freshly activated by washing with 5% HCl several times followed by water, methanol, and diethyl ether and then dried under vacuum). The mixture was stirred and heated under reflux for 2 h, then the solvent was evaporated under reduced pressure and the product was extracted into dichloromethane, which was washed and dried ($MgSO_4$). The crude product (9 mg) after evaporation of the solvent was purified by preparative t.l.c. to give 19-hydroxycorticosterone (3 mg), $\nu_{max.}$ 3 500 (OH), 1 710 (20-ketone), 1 660 and 1 620 cm^{-1} (Δ^4-3-ketone); $\lambda_{max.}$ (methanol) 243 nm (ε 10 000) (lit.,[10] 243 nm); δ 0.96 (s, 18-H_3), 3.84 (AB-q, δ_A 3.58, δ_B 4.10, *J* 12 Hz, 19-H_2), 4.20 (s, 21-H_2), 4.40 (d, *J* 4 Hz, 11-H), and 5.8 (s, 4-H); *m/z* (as 19,21-bis-trimethylsilyl ether) 506 ($C_{27}H_{46}O_5Si_2$, M^+; 28%), 491 (M^+ − Me; 29), 476 (M^+ − Me_2; 57), 462 (40), 388 (M^+ − Me − CH_2OSiMe_3; 18), 254 (20), 225 (20), and 73 (100).

The t.l.c. plate also afforded unchanged 6β,19-epoxide (3 mg).

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