18-Substituted Steroids. Part 8.† An Improved Synthesis of 11β,18,21-Trihydroxypregn-4-ene-3,20-dione (' 18-Hydroxycorticosterone ')

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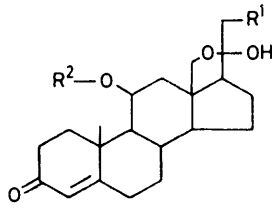
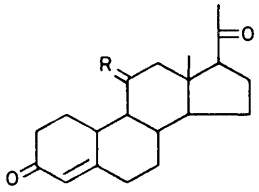
' 18-Hydroxycorticosterone ' (1) has been prepared from 11β-formyloxy-20-hydroxypregn-4-en-3-one (6) by application of the ' hypoiodite ' series of reactions [$Pb(OAc)_4$–I_2–$h\nu$; oxidation; solvolysis], followed by acetoxylation at C-21 by lead tetra-acetate in acetic acid. Alkaline hydrolysis then gave 18-hydroxycorticosterone.

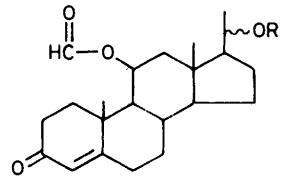
Our two previous syntheses of the biologically important 18-hydroxycorticosterone (1) started from 3β-acetoxypregn-5-ene-11,20-dione [1] and 6β,11α-dihydroxy-3α,5-cyclo-5α-pregnan-20-one,[2] respectively. Neither of these materials is continuously available, however, so we turned our attention to 11α-hydroxyprogesterone as a commercially available material from which to commence a synthesis. We also hoped to improve on previous yields. This has been achieved.



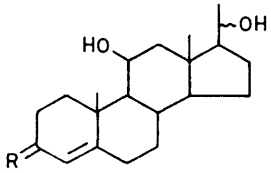
(1) R^1 = OH, R^2 = H
(2) R^1 = H, R^2 = CHO
(3) R = OAc, R = CHO



(4) R = O
(5) R = <OCHO H



(6) R = H
(7) R = CHO



(8) R = <OH H
(9) R = O

In preliminary experiments (by Dr. M. Hossain), we had employed conventional methods to proceed from 11α-hydroxyprogesterone in several steps to 3,3-ethylenedioxy-20β-hydroxypregn-5-en-11-one. Application of the ' hypoiodite ' reaction [$Pb(OAc)_4$–I_2–$h\nu$, followed by oxidation and solvolysis] to functionalise C-18 resulted at best in yields of 10—12% of the required 18,20-hemiacetal. The 11-oxo function appears to be responsible for the exceptional inefficiency at this stage. Further difficulties were encountered in the steps needed to reduce the 11-oxo to the 11β-hydroxy group, where protection and subsequent deprotection at C-3 and C-20 were necessary. This approach was therefore not carried to completion, and does not warrant a detailed description.

† Part 7, D. N. Kirk and B. W. Miller, *J. Chem. Soc., Perkin Trans. 1*, 1981, 2818.

We then examined the possibility of proceeding through a suitably protected 11β-hydroxyprogesterone derivative, although having previously rejected this approach, fearing that the proximity of the 11β-hydroxy group (or its ester) to C-18 would interfere with the generation or subsequent reaction of a radical at C-18. This fear proved unfounded. The 11β-formate was found to provide satisfactory protection, and could readily be hydrolysed by alkali. We also established that the 11β-acetate could be used, and although resistant to ordinary alkaline hydrolysis, could be cleaved by the procedure of Gassman and Schenk [Bu^tOK (4 mmol) + H_2O (1 mmol) in dry ether + steroid (1 mmol), stirred for 24 h].[3] The 11β-formate was more convenient to handle, however, so all development work was carried out on this ester.

Pregn-4-ene-3,11,20-trione (4), obtained by Jones' oxidation of 11α-hydroxyprogesterone, was reduced with sodium borohydride or preferably by lithium aluminium hydride to give pregn-4-ene-3,11β,20-triol (8) which was not purified but was oxidised selectively (Oppenauer or activated MnO_2) at C-3 to give 11β,20-dihydroxypregn-4-en-3-one (9) (mainly the 20β-isomer). When sodium borohydride was used in the reduction, this product was contaminated with 5α-pregnane-3β,11β,20-triol which proved difficult to separate, and was carried through subsequent steps until a separation could be achieved after the hypoiodite reaction (see Experimental section).

Smooth formylation of the two hydroxy-groups in the 11β,20-diol (9) was achieved under basic conditions by the method of Höfle and co-workers,[4] using 4-dimethylaminopyridine as catalyst. This method is far superior to that of Oliveto and co-workers [5] (formic acid–acetic anhydride, catalysed by toluene-*p*-sulphonic acid), which in our hands gave products heavily contaminated with a troublesome yellow gum, removed only with difficulty. The diformate (7) was selectively hydrolysed to 11β-formyloxy-20-hydroxypregn-4-en-3-one (6) by ethanolic toluene-*p*-sulphonic acid at room temperature. Application of the ' hypoiodite ' series of reactions then led to 18,20-epoxy-11β-formyloxy-20-hydroxypregn-4-en-3-one (2) isolated chromatographically in *ca.* 20% yield. The other major product was 11β-formyloxypregn-4-ene-3,20-dione (5) (33%), which could be recycled. Acetoxylation at the C-21 position by the method of Kirk and Rajagopalan [6] (lead tetra-acetate in acetic

acid) converted the 11β-formyloxy-hemiacetal (2) into 21-acetoxy-18,20-epoxy-11β-formyloxy-20-hydroxypregn-4-en-3-one (18-hydroxycorticosterone 21-acetate 11-formate) (3). Hydrolysis of both ester groups in alcoholic potassium hydroxide gave 18-hydroxycorticosterone, in an overall yield of 14% from the easily accessible 11β-formate (6).

EXPERIMENTAL

I.r. spectra refer to KBr discs unless otherwise stated. N.m.r. spectra were recorded at 100 MHz in $CDCl_3$ with Me_4Si as internal standard. Melting points were determined with a Reichert microscope and are uncorrected. Preparative high-pressure liquid chomatography (h.p.l.c.) was performed on a Waters Prep LC/System 500 with μ Porasil columns. Solvents were purified before use as described previously.[6]

11β,20-*Dihydroxypregn*-4-*en*-3-*one* (*a*); *Reduction of Pregn*-4-*ene*-3,11,20-*trione* (4) *by Lithium Aluminium Hydride*.—The trione (4) (6.0 g) in freshly distilled tetrahydrofuran (THF) (150 ml) with lithium aluminium hydride (2.4 g) was heated under reflux for 2 h. Aqueous magnesium sulphate was then added, followed by solid magnesium sulphate. The solution was filtered, dried (K_2CO_3), and then taken to dryness on a rotary evaporator. The resulting crude pregn-4-ene-3,11β,20-triol (8), $\nu_{max.}$ 3 400 and 1 030 cm^{-1}, in dry chloroform (100 ml) was added to activated manganese dioxide[7] (50 g) and stirred at room temperature for 16 h. After filtration the solvent was removed under reduced pressure to give 11β,20-*dihydroxypregn*-4-*en*-3-*one* (9) (5.0 g) m.p. 206—210 °C (from acetone); $\nu_{max.}$ ($CHCl_3$) 3 590, 1 660, and 1 615 cm^{-1}; δ 1.02 (s, 13β-Me), 1.13 (d, *J* 6 Hz, 21-H_3), 1.44 (s, 10β-Me), *ca.* 3.7 (m, 20-H), *ca.* 4.35 (m, 11α-H), and 5.68 (s, 4-H) (Found: C, 75.7; H, 9.8. $C_{21}H_{32}O_3$ requires C, 75.9; H, 9.7%). No attempt was made to separate isomers at C-20.

11β,20-*Di*(*formyloxy*)*pregn*-4-*en*-3-*one* (7).—The 11β,20-diol (5.0 g) in dry dichloromethane (100 ml) was cooled to −30 °C. Triethylamine (50 ml), formic acid (10 ml), and 4-dimethylaminopyridine (2.0 g) were added, followed by acetic anhydride (30 ml) over 30 min. The solution was stirred for a further 30 min then allowed to warm to room temperature. Water (200 ml) was added and the organic layer was washed with sodium hydrogen carbonate solution until neutral and dried (K_2CO_3). Removal of the solvent under reduced pressure gave crude 11β,20-*di*(*formyloxy*)-*pregn*-4-*en*-3-*one* (7) (5.8 g) which was purified by preparative h.p.l.c. (25% ethyl acetate in hexane as mobile phase) to give 5.13 g, m.p. 166—169 °C (from ether), $\nu_{max.}$ 1 710, 1 670, 1 615, 1 190, and 1 170 cm^{-1}; δ 0.84 (s, 13β-Me), 1.21 (d, *J* 6 Hz, 21-H_3), 1.28 (s, 10β-Me), *ca.* 4.9 (m, 20-H), *ca.* 5.5 (m, 11α-H), 5.7 (s, 4-H), 8.0 (s, –OCHO), and 8.05 (s, –OCHO) (Found: C, 71.2; H, 8.4. $C_{23}H_{32}O_5$ requires C, 71.1; H, 8.3%).

11β-*Formyloxy*-20-*hydroxypregn*-4-*en*-3-*one* (6).—The 11,20-diformate (7) (5.0 g) in absolute ethanol (200 ml) containing toluene-*p*-sulphonic acid (0.6 g) was left at room temperature for 16 h. The solution was poured into water (300 ml) and the steroid was extracted into ethyl acetate (3 × 100 ml) which was dried (K_2CO_3). The solution was taken to dryness on a rotary evaporator and the resulting solid was purified by preparative h.p.l.c. (EtOAc–hexane, 1 : 1) to give 11β-*formyloxy*-20-*hydroxypregn*-4-*en*-3-*one* (6) (4.0 g), m.p. 224—227 °C (from acetone–hexane), $\nu_{max.}$ 3 400, 1 710, 1 650, 1 615, 1 200, and 1 175 cm^{-1}; δ 0.82 (s, 13β-Me), 1.16 (d, *J* 6 Hz, 21-H_3), 1.28 (s, 10β-Me), *ca.* 3.62 (m, 20-H), *ca.* 5.5 (m, 11α-H), 5.65 (s, 4-H), and 8.04 (s, 11β-OCHO) (Found: C, 72.7; H, 9.1. $C_{22}H_{32}O_4$ requires C, 73.1; H, 9.0%).

18,20-*Epoxy*-11β-*formyloxy*-20-*hydroxypregn*-4-*en*-3-*one* (2).—11β-Formyloxy-20-hydroxypregn-4-en-3-one (6) (5.0 g) in dry cyclohexane (800 ml) with lead tetra-acetate (15.0 g) and iodine (2.7 g) was heated to reflux temperature and irradiated with two 500 W photoflood lamps until the colour of iodine had disappeared (30—50 min). The cooled solution was filtered, washed with sodium thiosulphate solution (200 ml; 5%), and dried (K_2CO_3), and the solvent was removed under reduced pressure. The residual gum, in acetone (200 ml), was cooled to 0 °C and Jones' chromic acid reagent was slowly added until a persistent orange colour resulted. Sodium acetate (100 g) in water (200 ml) was added and the steroid was extracted into benzene (3 × 200 ml). The combined benzene fractions were washed with saturated sodium chloride solution, dried (K_2CO_3), and taken to dryness on a rotary evaporator. The resulting gum in 70% aqueous dioxan (500 ml) containing silver acetate (5.0 g) was heated under reflux for 2 h. The cooled solution was filtered and concentrated on a rotary evaporator, water (200 ml) was added, and the steroid was extracted into ethyl acetate (3 × 200 ml) which was washed and dried (K_2CO_3). Removal of the solvent under reduced pressure gave a semi-solid product which contained two main components. Separation by preparative h.p.l.c. (EtOAc–hexane, 1 : 1) gave 11β-*formyloxypregn*-4-*ene*-3,20-*dione* (5) (1.65 g), m.p. 156—160 °C (from acetone), $\nu_{max.}$ 1 705, 1 670, 1 610, 1 180, and 1 145 cm^{-1}; δ 0.8 (s, 13β-Me), 1.32 (s, 10β-Me), 2.1 (s, 21-H_3), *ca.* 5.59 (m, 11α-H), 5.64 (s, 4-H), and 8.04 (s, 11β-OCHO) (Found: C, 73.4; H, 8.3. $C_{22}H_{30}O_4$ requires C, 73.7; H, 8.4%); followed by 18,20-*epoxy*-11β-*formyloxy*-20-*hydroxypregn*-4-*en*-3-*one* (2) (1.08 g), m.p. 158—161 °C (from EtOAc–hexane), $\nu_{max.}$ 3 400, 1 720, 1 670, 1 615, and 1 170 cm^{-1}; δ 1.22 (s, 10β-Me), 1.48 (s, 21-H_3), 3.74 and 3.91 (d, d, *J* 9 Hz, 18-H_2), *ca.* 5.64 (m, 11α-H), 5.68 (s, 4-H), and 8.07 (s, 11β-OCHO) (Found: C, 70.3; H, 8.2. $C_{22}H_{30}O_5$ requires C, 70.6; H, 8.1%).

21-*Acetoxy*-18,20-*epoxy*-11β-*formyloxy*-20-*hydroxypregn*-4-*en*-3-*one* (3).—18,20-Epoxy-11β-formyloxy-20-hydroxypregn-4-en-3-one (2) (1.0 g) in acetic acid was stirred with lead tetra-acetate (1.2 g) for 10 min then poured into water (250 ml). The steroid was extracted into ethyl acetate (3 × 100 ml) which was washed with sodium hydrogen carbonate solution until neutral and then dried (K_2CO_3). Preparative h.p.l.c. (EtOAc–hexane, 1 : 1) gave 21-*acetoxy*-18,20-*epoxy*-11β-*formyloxy*-20-*hydroxypregn*-4-*en*-3-*one* (3) (900 mg) as a gum, $\nu_{max.}$ 3 420, 1 720, 1 665, 1 615, and 1 200 cm^{-1}; δ 1.24 (s, 10β-Me), 2.12 (s, 21-OAc), 3.81 and 3.97 (d, d, *J* 10 Hz, 18-H_2), 4.17 and 4.27 (d, d, *J* 11 Hz, 21-H_2), *ca.* 5.6 (m, 11α-H), 5.68 (s, 4-H), and 8.06 (s, 11β-OCHO).

18-*Hydroxycorticosterone* (1).—The above 21-acetate, 11-formate (3) (900 mg) in methanol (60 ml) with methanolic potassium hydroxide (7.5 ml; 6% w/v) was heated under reflux for 45 min and allowed to cool. Water (200 ml) was then added and the steroid was extracted into ethyl acetate (3 × 200 ml) which was washed and dried (K_2CO_3). A drop of triethylamine was added and the solvent was removed under reduced pressure to give 18-hydroxycorticosterone (1) (750 mg), m.p. 152—155 °C (from ethyl acetate) [lit. 148—150 °C[1] or 163—164 °C (racemate)[8]]; $\nu_{max.}$ 3 400, 1 670, 1 620, and 1 028 cm^{-1}; δ 1.44 (s, 10β-Me), 3.7 and 3.8 (d,

d, J 12 Hz, 21-H_2), 3.84 and 4.38 (d, d, J 10 Hz, 18-H_2), *ca.* 4.4 (m, 11α-H), and 5.65 (s, 4-H).

Reduction of Pregn-4-ene-3,11-20-trione (4) *by Sodium Borohydride*.—The trione (4) (9.5 g) in ethanol–tetrahydrofuran (1 : 1; 500 ml, plus 2 ml of 1M sodium hydroxide) was stirred with sodium borohydride (5.0 g) for 1 h at room temperature. Further sodium borohydride (5.0 g) was added and the mixture was heated under reflux for 8 h. The cooled solution was poured into water (500 ml) and the steroid was extracted into ethyl acetate (3 × 200 ml) which was then dried (K_2CO_3) and taken to dryness. The residue was treated with aluminium isopropoxide (10.0 g) and acetone (20 ml) in benzene (300 ml) under reflux for 1 h, cooled, and poured into dilute sulphuric acid (200 ml; 2.5M). The organic layer was washed with saturated sodium chloride solution (2 × 100 ml), dried (K_2CO_3), and taken to dryness to give crude 11β,20-*dihydroxypregn*-4-*en*-3-*one* (9) (8.3 g).

The diol prepared above was later found to be contaminated with 5α-pregnane-3β,11β,20-triol, which emerged after the hypoiodite sequence of reactions, including the oxidation step. Two 5α-saturated products were isolated by preparative h.p.l.c. (EtOAc–hexane, 1 : 1) during the purification of the corresponding 4-en-3-ones (2) and (5). The first was 11β-*formyloxy*-5α-*pregnane*-3,20-*dione* (0.63 g), m.p. 188—190 °C (from acetone), $\nu_{max.}$ 1 715, 1 705, 1 190, and 1 165 cm^{-1}; δ 0.77 (s, 13β-Me), 1.13 (s, 10β-Me), 2.08 (s, 21-H_3), *ca.* 5.6 (m, 11α-H), and 8.07 (s, 11β-OCHO). The 5α-configuration was indicated by the strongly positive c.d. curve,[9] Δε (dioxan) +4.43 (293 nm) (Found: C, 73.3; H, 8.9. $C_{22}H_{32}O_4$ requires C, 73.4; H, 8.9%).

The second was 18,20-*epoxy*-11β-*formyloxy*-20-*hydroxy*-5α-*pregnan*-3-*one* (0.2 g), m.p. 137—140 °C (from acetone), $\nu_{max.}$ 3 450, 1 720, 1 710, 1 185, and 1 165 cm^{-1}; Δε (dioxan) +1.02 (293 nm);[9] δ 1.06 (s, 10β-Me), 1.46 (s, 21-H_3), 3.71 and 3.87 (d, d, J 10 Hz, 18-H_2), *ca.* 5.6 (m, 11α-H), and 8.07 (s, 11β-OCHO) (Found: C, 70.6; H, 8.5. $C_{22}H_{32}O_5$ requires C, 70.3; H, 8.5%).

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