An Improved Route to 19-Hydroxypregn-4-ene-3,20-dione and Synthesis of its [19-$^2H_2$] Analogue

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3β-Acetoxy-5-bromo-6β,19-epoxy-5α-pregnan-20-one is more reliably converted into 19-hydroxyprogesterone *via* reductive opening of the epoxide to give 3β-acetoxy-19-hydroxypregn-5-en-20-one than by a previously published procedure. 19-Hydroxyprogesterone has been converted into its [19^2-H_2] analogue in good yield.

As part of a programme to synthesize deuterium-labelled pregnane derivatives, we required considerable quantities of 19-hydroxypregn-4-ene-3,20-dione (19-hydroxyprogesterone) (1) and its [19-$^2H_2$]-labelled form. Unfortunately, the published [1-4] syntheses of 19-hydroxyprogesterone from 3β-hydroxypregn-5-en-20-one (2) were unsatisfactory in our hands from the key intermediate 6β,19-epoxide (3). For example, alkaline hydrolysis of the epoxide (3) and oxidation (Jones) to the unstable bromo ketone (4), followed by zinc-promoted opening of the 6β,19-epoxide, has been reported [1] to give 19-hydroxyprogesterone in 50% yield. We found these steps erratic, giving compound (1) of variable purity in yields over the range 19—34%. An improved procedure for the conversion of the 6β,19-epoxide (3) into 19-hydroxyprogesterone (1) is now reported.

Treatment of the 6β,19-epoxide (3) with activated zinc in propan-2-ol containing a catalytic amount of acetic acid at reflux gave 3β-acetoxy-19-hydroxypregn-5-en-20-one (5) (98%). Protection of the 19-hydroxy group of compound (5) as the tetrahydropyranyl ether, followed by removal of the 3-acetate group in methanolic potassium hydroxide, led to the selectively protected diol (6) (74%). Oxidation of the alcohol (6) under the modified Oppenauer conditions of Keana and Reich [5] (aluminium isopropoxide in toluene, with *N*-methyl-4-piperidone as hydrogen acceptor) gave, after preparative high-performance liquid chromatography (h.p.l.c.), 19-hydroxyprogesterone tetrahydropyranyl ether (7) (76%). Finally, the tetrahydropyranyl group was removed by mild acidic hydrolysis to give pure 19-hydroxyprogesterone (1) (76%). The overall yield of 42% from the epoxide (3) was reproducible over several runs.

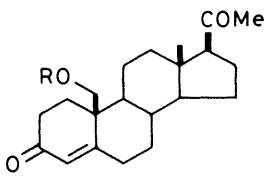
19-Hydroxyprogesterone was used as the starting material for the synthesis of the [19-$^2H_2$] analogue by a method similar to that reported [6] for the preparation of the corresponding labelled androstenedione. Oxidation of compound (1) with a large excess of Jones reagent in acetone (0 °C; 2.5 h) gave the carboxylic acid (8) which, without purification, was converted into the methyl ester (9) with diazomethane (overall yield 72%). Use of only a slight excess of Jones reagent or a shorter reaction time resulted in a mixture of the methyl ester (9) and the aldehyde (10) (identified from n.m.r. and i.r. spectra). The ester (9) was converted into the bisethylenedioxy derivative (11) which, without purification, was reduced with lithium aluminium deuteride in tetrahydrofuran (THF) to give 3,3:20,20-bisethylenedioxy[19-$^2H_2$]pregn-5-en-19-ol (12) (65%). Hydrolysis of the acetal (12) in aqueous acetone containing toluene-*p*-sulphonic acid then gave 19-hydroxy-[19-$^2H_2$]progesterone, 97% dideuteriated at C-19 [74% yield; 35% overall from (1)].

Experimental

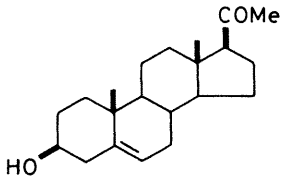
M.p.s were determined with a Reichert hot-stage apparatus. I.r. spectra refer to KBr discs. N.m.r. spectra were determined at 100 MHz for solutions in deuteriochloroform with tetramethylsilane as internal standard. Preparative h.p.l.c. was carried out on a Waters Associates Prep LC/System 500, using Preppak-500/silica cartridges. Deuterium analysis was by mass spectrometry, with direct insertion of the sample. All solvents were distilled before use. Light petroleum refers to the fraction, b.p. 60—80 °C. THF was dried by distillation from lithium aluminium hydride. Solutions of organic products were evaporated under reduced pressure at <40 °C.

3β-*Acetoxy*-19-*hydroxypregn*-5-*en*-20-*one* (5).—Activated zinc dust [7] (12.5 g) was added to a suspension of 3β-acetoxy-5-bromo-6β,19-epoxy-5α-pregnan-20-one [1] (3) (6.81 g, 15 mmol) in propan-2-ol (750 ml) and acetic acid (11 ml). The suspension was stirred and heated under reflux for 2 h, cooled, filtered, and the residue was washed with propan-2-ol. The combined filtrate and washings were evaporated and the organic residue was dissolved in ethyl acetate. The solution was washed in turn with saturated aqueous sodium hydrogen carbonate and water, dried (Na_2SO_4), and evaporated to give 3β-acetoxy-19-hydroxypregn-5-en-20-one (5) (5.51 g, 98%), m.p. 161—166 °C (from acetone–hexane) (lit.,[2] 165—176 °C); $\nu_{max.}$ 3 520, 1 725, and 1 705 cm^{-1}.

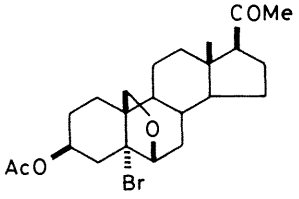
3β-*Hydroxy*-19-(*tetrahydropyran*-2-*yloxy*)*pregn*-5-*en*-20-*one* (6).—2,3-Dihydropyran (8 ml, 90 mmol, distilled from sodium) was added to a solution of the monoacetate (5) (5.61 g, 15 mmol) and toluene-*p*-sulphonic acid (250 mg) in dry THF (100 ml). After 24 h at room temperature the solution was diluted with diethyl ether (400 ml), washed in turn with saturated aqueous sodium hydrogen carbonate and water, dried (Na_2SO_4–K_2CO_3), and evaporated. The oily residue was dissolved in methanol (250 ml), and methanolic 5% potassium hydroxide (18.5 ml; 16.5 mmol KOH) was added. The solution was heated under reflux for 1 h, cooled, evaporated, and the organic residue was dissolved in diethyl ether (150 ml). The solution was washed with water, dried (Na_2SO_4–K_2CO_3), and evaporated. The residue was crystallised from acetone–hexane to give 3β-*hydroxy*-19-(*tetrahydropyran*-2-*yloxy*)*pregn*-5-*en*-20-*one* (6) (4.60 g, 74%), m.p. *155*—163 °C; $\nu_{max.}$ 3 480 and 1 695 cm^{-1}; δ 0.66 (s, 18-H_3), 2.12 (s, 21-H_3), 3.24 and 4.02 (ABq, J_{AB}, 10 Hz, 19-H_2), 3.9—3.3 (m, THP), 4.48 (1 H, br s, THP), and *ca.* 5.6 (m, 6-H) (Found: C, 75.4; H, 9.7. $C_{26}H_{40}O_4$ requires C, 75.0; H, 9.7%).



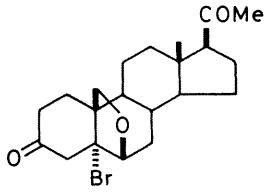
(1) R = H
(7) R = THP



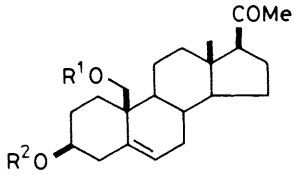
(2)



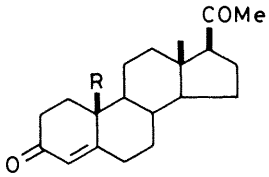
(3)



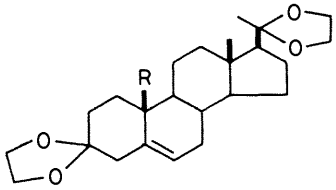
(4)



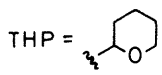
(5) R^1 = H, R^2 = Ac
(6) R^1 = THP, R^2 = H



(8) R = CO_2H
(9) R = CO_2Me
(10) R = CHO



(11) R = CO_2Me
(12) R = CD_2OH



19-(*Tetrahydropyran-2-yloxy*)*pregn*-4-*ene*-3,20-*dione* (7).—A solution of the alcohol (6) (4.58 g, 11 mmol) and *N*-methyl-4-piperidone (46 ml, freshly distilled) in toluene (250 ml, distilled from CaH_2) under dry nitrogen was heated until 50 ml of toluene had distilled, then a solution of aluminium isopropoxide (7.6 g, 33 mmol) in toluene (40 ml) was added. The mixture was stirred and heated under reflux under nitrogen for 5 h, cooled, diluted with diethyl ether (500 ml), washed quickly in turn with dilute sulphuric acid (5%; 2 × 400 ml) and water, dried (Na_2SO_4–K_2CO_3), and evaporated. The crystalline residue was purified by preparative h.p.l.c. [ethyl acetate–light petroleum (2 : 3) as mobile phase] to give 19-(*tetrahydropyran-2-yloxy*)*pregn*-4-*ene*-3,20-*dione* (7) (3.46 g, 76%), m.p. 129—139 °C (from acetone–hexane); $\nu_{max.}$ 1 705, 1 675, and 1 620 cm^{-1}; δ 0.66 (s, 18-H_3), 2.12 (s, 21-H_3), 3.62 (superimposed on THP multiplet at 3.4—3.7) and 4.04 (ABq, J_{AB} 10 Hz, 19-H_2), 4.5 (1 H, br s, THP), and 5.88 (s, 4-H) (Found: C, 75.5; H, 9.15. $C_{26}H_{38}O_4$ requires C, 75.3; H, 9.2%).

Hydrolysis of the Tetrahydropyranyl Ether (7).—(a) *With aqueous acetic acid.* A suspension of the tetrahydropyranyl ether (7) (3.31 g, 8 mmol) in acetic acid–water [30 ml (4 : 1)] was stirred at room temperature for 5 d. The solution was diluted with ethyl acetate (150 ml), washed in turn with saturated aqueous sodium hydrogen carbonate and water, dried (Na_2SO_4), and evaporated. Crystallisation of the residue from acetone–hexane gave 19-hydroxyprogesterone (1) (1.83 g), m.p. 166—168 °C (lit.,[1] 165—168 °C); $\nu_{max.}$ 3 330, 1 715, 1 665, and 1 615 cm^{-1}. Preparative h.p.l.c. [ethyl acetate–light petroleum (1 : 1) as mobile phase] of the material left in the mother-liquor gave a further crop of the alcohol (1) (174 mg); total yield 76%.

(b) *With hydrochloric acid.* Concentrated hydrochloric acid (0.2 ml) was added to a solution of the tetrahydropyranyl ether (7) (1.46 g, 3.53 mmol) in acetone–water [75 ml (4 : 1)]. After being kept at room temperature for 7 d the solution was evaporated to *ca.* 30 ml, diluted with water, and extracted with ethyl acetate. The extract was washed with water, dried (K_2CO_3), concentrated, and allowed to crystallise to give 19-hydroxyprogesterone (1) (0.90 g, 77%), m.p. 165—168 °C (lit.,[1] 165—168 °C).

Methyl 3,20-*Dioxopregn*-4-*en*-19-*oate* (9).—Jones chromic acid reagent (12 ml) was added during 5 min to a stirred solution of the alcohol (1) (3.30 g, 10 mmol) in acetone (120 ml, distilled from $KMnO_4$) at 0—5 °C. The brown mixture was stirred at 0—5 °C for 2.5 h, then excess of oxidant was destroyed with propan-2-ol and the solvents were evaporated. The residue was partitioned between ethyl acetate (100 ml) and water (50 ml). The aqueous phase was re-extracted with ethyl acetate and the combined extracts were washed with water, dried (Na_2SO_4), and evaporated. A solution of the residue in methanol (40 ml) and diethyl ether (160 ml) was treated with a solution of diazomethane in diethyl ether (50 ml, *ca.* 3%). After 1 h the solution was evaporated, and the residue was crystallised from acetone–hexane to give methyl 3,20-dioxopregn-4-en-19-oate (9) (2.15 g), m.p. 141—143 °C (lit.,[8] 143—144 °C). Preparative h.p.l.c. [ethyl acetate–light petroleum (1 : 3) as mobile phase] of the mother-liquor residue gave a further crop of the ester (9) (418 mg), m.p. 142—144 °C; total yield 72%.

3,3:20,20-*Bisethylenedioxy*[19-$^2H_2$]*pregn*-5-*en*-19-*ol* (12).—The methyl ester (9) (2.51 g, 7 mmol), ethane-1,2-diol (14 ml), and toluene-*p*-sulphonic acid (90 mg) were stirred and heated under reflux in benzene (100 ml) under a Dean–Stark trap for 7 h. The solution was cooled, washed in turn with saturated aqueous sodium hydrogen carbonate and water, dried (Na_2SO_4–K_2CO_3), and evaporated. The residue, taken up in dry THF (70 ml), was added during 15 min to a stirred suspension of lithium aluminium deuteride (760 mg, 18 mmol, 98% D) in dry THF (35 ml) at room temperature. The suspension was stirred and heated under reflux for 3 h, cooled to 0—5 °C, treated during 5 min with THF–water [20 ml (5 : 1)] and filtered. The filter residue was washed with THF and the combined filtrate and washings were evaporated. Crystallisation of the residue from methanol gave 3,3:20,20-bisethylenedioxy[19-$^2H_2$]pregn-5-en-19-ol (12) (1.91 g, 65%), m.p. 186—190 °C; $\nu_{max.}$ 2 190 and 2 080 cm^{-1} (C–D).

The corresponding non-deuteriated material had m.p. 190—192 °C; $\nu_{max.}$ 3 530 cm^{-1}; δ 0.84 (s, 18-H_3), 1.30 (s, 21-H_3), 3.94 (OCH_2CH_2O, s superimposed on the 19-H_2 ABq),

and *ca.* 5.7 (m, 6-H) (Found: C, 71.2; H, 9.1. $C_{25}H_{38}O_5$ requires C, 71.6; H, 9.15%).

19-*Hydroxy*[19-$^2H_2$]*pregn*-4-*ene*-3,20-*dione*.—The alcohol (12) (2.10 g, 5 mmol) and toluene-*p*-sulphonic acid (200 mg) were stirred and heated under reflux in acetone (100 ml) and water (50 ml) for 3 h. The solution was cooled, the solvent was evaporated, and the residue was dissolved in ethyl acetate (100 ml). The solution was washed in turn with saturated aqueous sodium hydrogen carbonate and water, dried (Na_2SO_4), and evaporated. Crystallisation of the residue from acetone–hexane gave 19-hydroxy[19-$^2H_2$]pregn-4-ene-3,20-dione (1.22 g, 74%), m.p. 167—169 °C (lit.,[1] 165—168 °C for non-deuteriated material); $\nu_{max.}$ 2 210 and 2 090 cm^{-1} (C–D); *m/z* 332 (M^+, 42), 331 (0.97), 330 (0.42), 300 (100), and 257 (19%) (97% $^2H_2$).

The corresponding non-deuteriated material had *m/z* 330 (M^+, 40), 329 (0.49), 328 (0.98), 300 (100), and 257 (20%).

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