5β-Pregn-6-ene-3α,17,20-triols

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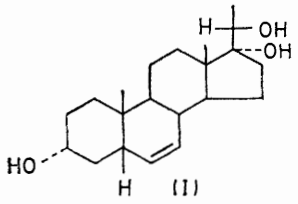
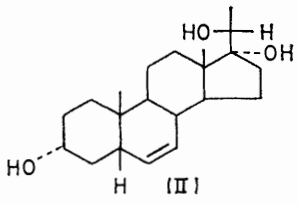
5β-Pregn-6-ene-3α,17,20α-triol (I) and its 20β-isomer (II), have been prepared and reduced with hydrogen to the corresponding pregnanes.

THE preparation of some Δ^6-5β-steroids by syntheses involving, as the first stage, hydroboration–oxidation of 3,3-ethylenedioxy-Δ^5-derivatives has been reported.[1] We envisaged 17α-acetoxy-3,3-ethylenedioxypregn-5-en-20-one (III) as a suitable starting material for the preparation of 5β-pregn-6-enetriols, required for labelling studies. Preliminary work showed that prolonged hydroboration followed by oxidation gave the corresponding 6β,17,20-triols and these, as the 17,20-acetonides, on dehydration gave the 6-enes. Removal of the protective grouping and partition chromatography of the product gave a poor yield of a compound identified by subsequent work as 17,20β-dihydroxy-5β-pregn-6-en-3-one. An attempt to carry out the



(I)



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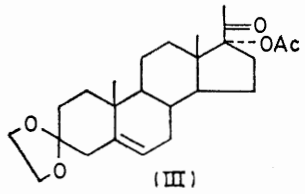
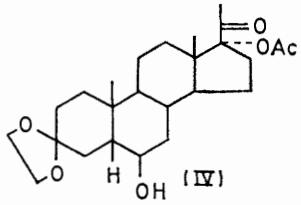
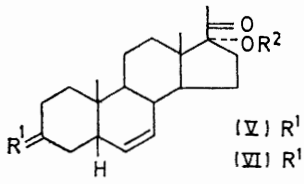


(III)



(IV)



(V) R^1 = O·CH_2·CH_2·O, R^2 = Ac
(VI) R^1 = O, R^2 = H

hydroboration with 1 mol. equiv. of the reagent was unsuccessful, starting material being recovered quantitatively. With larger amounts of reagent and intermediate reaction times, the 6β-hydroxy-group was introduced and the 17α-acetoxy- and 20-oxo-groups were substantially unaffected. Dehydration of 17α-acetoxy-3,3-ethylenedioxy-6β-hydroxy-5β-pregnan-20-one (IV) with phosphoryl chloride–pyridine gave the required 17α-acetoxy-3,3-ethylenedioxypregn-6-en-20-one (V), together with a little 3,3-ethylenedioxy-5β-pregna-6,16-dien-20-one.

Hydrolysis of the acetal (V) to give (VI) followed by reduction with lithium aluminium hydride gave a mixture of triols, of which 5β-pregn-6-ene-3α,17,20β-triol (II) was shown by paper chromatography to be the major constituent. This compound was partially separated from the 20α-isomer (I) by partition chromatography on Celite, but the yields were poor and alternative routes were studied. Reduction of the acetal (V) with lithium aluminium hydride gave a mixture of acetal diols, of which the 17,20α-diol was the major constituent. Hydrolysis of these acetals followed by reduction with sodium borohydride gave the mixed triols, which could be separated almost quantitatively by gradient elution from a neutral deactivated alumina column.[2] This proved to be the method of choice for separation in all subsequent work in the series. However, some separation of the precursor acetal diols could be achieved by fractional crystallisation, and this permitted the characterisation of some intermediates. Hydrolysis of the acetal diols followed by reduction with borohydride gave the respective 6-enetriols (I) and (II).

The 6-enetriols were smoothly hydrogenated over palladium–charcoal to furnish 5β-pregnane-3α,17,20α- and -3α,17,20β-triols, respectively, identical with reference samples.

EXPERIMENTAL

N.m.r. spectra were obtained for solutions in C_5D_5N (unless stated otherwise) at 100 MHz. Specific rotations are recorded for dioxan solutions and were determined with the ETL-NPL Automatic Polarimeter type 143A (Bendix Electronics Ltd.). I.r. spectra were recorded for KBr discs. Microanalyses were carried out by Dr. F. B. Strauss, Oxford. Reactions were followed by t.l.c. and products examined by paper chromatography in Bush systems A, B_2, and B_3.[3] As expected, in all cases the 20α-ols were slightly more polar than the 20β-epimers.

17α-Acetoxy-3,3-ethylenedioxy-6β-hydroxy-5β-pregnan-20-one.—17α-Acetoxy-3,3-ethylenedioxypregn-5-en-20-one (9 g) in anhydrous tetrahydrofuran (350 ml) was treated at 0 °C with an excess of diborane gas in a stream of nitrogen. After 2 h at room temperature the solution was treated with crushed ice followed by sodium hydroxide (12 g) in water (100 ml). Hydrogen peroxide (30%; 48 ml) was then

[1] D. N. Kirk and D. R. A. Leonard *J.C.S. Perkin I*, 1973, 1836.
[2] A. E. Kellie and A. P. Wade, *Biochem. J.*, 1957, **66**, 199.
[3] I. E. Bush, *Biochem. J.*, 1952, 370.

added slowly. The mixture was stirred (1.5 h) and then diluted with water (2 l). The product, isolated in ethyl acetate, was obtained as a glass. Crystallisation from methanol gave starting material (3.25 g). The major part of the partially crystalline residue was dehydrated without further purification. The 6β-*hydroxyacetal* was obtained by crystallisation from methanol containing a trace of pyridine as rods, m.p. 193—197°; $\nu_{max.}$ 3 440, 1 735, 1 720, 1 255, 1 115, 1 080, and 1 060 cm^{-1} (Found: C, 69.1; H, 8.9. $C_{25}H_{38}O_6$ requires C, 69.1; H, 8.8%).

17α-*Acetoxy*-3,3-*ethylenedioxy*-5β-*pregn*-6-*en*-20-*one*.—The crude 6β-hydroxy-acetal (6 g) in anhydrous pyridine (60 ml) was treated dropwise at 0 °C with phosphoryl chloride (8 ml) with stirring, and left at room temperature overnight. The mixture was chilled thoroughly in ice–salt and, with stirring, was treated with ice and then iced water. The crystalline product was collected and the aqueous filtrate retained (see below). The crystalline product (2.9 g) in benzene was filtered through a column of basic alumina (Brockmann grade 1; 100 g) to remove coloured impurities. Recrystallisation from benzene–petroleum gave 17α-acetoxy-3,3-ethylenedioxypregn-5-en-20-one (0.25 g) in the first crop. The filtrate gave the *pregn*-6-*en*-20-*one* (1.2 g). Purification from methanol gave plates, m.p. 170—172°; $[\alpha]_D$ −1.3°; $\nu_{max.}$ 3 020, 1 735, 1 715, 1 645, 1 258, 1 245, 1 100, 1 053, 850, 840, and 670 cm^{-1}; τ ($CDCl_3$) 9.35 (18-H_3), 9.12 (19-H_3), 7.97 and 7.87 (each s, OAc and 21-H_3), 6.06 (ethylenedioxy), and 4.53 (6,7-H_2) (Found: C, 71.75; H, 8.8. $C_{25}H_{35}O_5$ requires C, 72.1; H, 8.7%).

3,3-*Ethylenedioxy*-5β-*pregna*-6,16-*dien*-20-*one*.— The aqueous filtrate from the above preparation deposited a further crystalline product (0.128 g). Purification from aqueous methanol gave the 6,16-*dien*-20-*one* 3-*acetal*, as blades, m.p. 194—198°; $[\alpha]_D$ +7.7°; $\nu_{max.}$ 3 020, 1 665, 1 645sh, 1 588, 1 095, 1 045, and 748 cm^{-1}; τ ($CDCl_3$–C_5D_5N) 9.10 (18- and 19-H_3), 7.75 (21-H_3), 6.09 (ethylenedioxy), 4.51 (6,7-H_2), and 3.30 (16-H) (Found: C, 77.45; H, 9.05. $C_{23}H_{32}O_3$ requires C, 77.5; H, 9.05%).

17α-*Acetoxy*-5β-*pregn*-6-*ene*-3,20-*dione*.—17α-Acetoxy-3,3-ethylenedioxy-5β-pregn-6-en-20-one (590 mg) in acetic acid (12 ml) and water (1.2 ml) was stored overnight at room temperature. Dilution with water gave the crude 3-one (242 mg). Purification from ethanol gave *prisms*, m.p. 206—209°; $\nu_{max.}$ 3 020, 1 735, 1 720, 1 705, 1 650sh, 1 264, 1 250, 1 122, and 1 021 cm^{-1}; τ ($CDCl_3$) 9.39 (18-H_3), 9.02 (19-H_3), 7.94 and 7.88 (each s, OAc and 21-H_3), and 4.42 (6,7-H_2) (Found: C, 73.9; H, 8.6. $C_{23}H_{32}O_4$ requires C, 74.2; H, 8.7%).

5β-*Pregn*-6-*ene*-3α,17,20α- *and* -3α,17,20β-*triols*.—The above crude 3,20-dione (188 mg) in dry ether (50 ml) was added to a suspension of lithium aluminium hydride (203 mg) in dry ether (5 ml). After stirring for 5 h at room temperature water was added to destroy the excess of hydride and the product was isolated *via* ether. Paper chromatography in the Bush B_2 system [3] showed two compounds of similar polarity, the slightly more polar of which was assumed to be the 3α,17,20α-triol. Partition chromatography on Celite in a related solvent system led to separation of the pure components, albeit with considerable overlap. The less polar component was crystallised from acetone–hexane to give 5β-*pregn*-6-*ene*-3α,17,20β-*triol* as rods (16.1 mg), m.p. 205—207°; $[\alpha]_D$ +3.1°; $\nu_{max.}$ 3 360, 3 020, 1 645, 1 060, and 740 cm^{-1}; τ 9.07 (18-H_3), 9.04 (19-H_3), 5.81 (20-H), and 4.44 (6,7-H_2) (Found: C, 75.55; H, 9.9. $C_{21}H_{34}O_3$ requires C, 75.4; H, 10.25%). The more polar compound, purified from acetone–hexane, was the 3α,17,20α-*triol*, blades (6.6 mg), m.p. 211—213°; $[\alpha]_D$ −2.7°; $\nu_{max.}$ 3 575, 3 380, 3 020, 1 640, 1 065, 1 017, and 745 cm^{-1}; τ 9.22 (18-H_3), 9.10 (19-H_3), 5.88 (20-H, q, *J* 6 Hz; collapsed to s on irradiation at 8.49), and 4.49 (6,7-H_2) (Found: C, 75.2; H, 9.9. $C_{21}H_{34}O_3$ requires C, 75.4; H, 10.25%).

Preparation of Further Quantities of the 6-*Enetriols by Chromatography employing the Gradient Elution Technique*.[2] —Treatment of the filtrate rich in 6-ene remaining after the isolation of crystalline 3,3-ethylenedioxy-6-en-20-one (residues of three experiments carried on a similar scale were combined) with lithium aluminium hydride followed by hydrolysis with aqueous acetic acid and reduction with sodium borohydride gave a gum (2.95 g). Chromatography on Woelm neutral alumina (50 cm × 3 cm int. diam. column; gradient elution with 2—8% ethanol in benzene) gave 5β-pregn-6-ene-3α,17,20α-triol (1.5 g; m.p. 186—200°) and the 3α,17,20β-triol (0.7 g; m.p.185—196°). Recrystallisation of each epimer from acetone–hexane gave the 20α-triol (0.53 g), m.p. 205—209°, and the 20β-triol (0.25 g), m.p. 196—203°.

3,3-*Ethylenedioxy*-5β-*pregn*-6-*ene*-17,20α- *and* -17,20β-*diols* —17α-Acetoxy-3,3-ethylenedioxy-5β-pregn-6-ene-3,20-dione (3.09 g) in dry ether (400 ml) was added to a stirred suspension of lithium aluminium hydride (3.09 g) in ether (75 ml). After 3.25 h stirring at room temperature, the mixture was chilled and the excess of hydride was decomposed by cautious addition of water. The product was isolated *via* ether. Crystallisation from acetone–hexane and then from acetone gave 3,3-*ethylenedioxy*-5β-*pregn*-6-*ene*-17,20α-*diol* as blades (716 mg), m.p. 186—190°; $\nu_{max.}$ 3 560, 3 472, 3 030, 1 092, 898, and 753 cm^{-1}; τ 9.26 (18-H_3), 9.09 (19-H_3), 6.17 (ethylenedioxy), and 4.47 (6,7-H_2) (Found: C, 73.4; H, 9.6. $C_{23}H_{36}O_4$ requires C, 73.4; H, 9.6%). The acetone–hexane filtrate gave a crystalline product (493 6 mg) which after two further recrystallisations from acetone–hexane gave the 17,20β-*diol* as rods (70.7 mg), m.p. 165—166° (the 17,20β-diol was sometimes obtained as crystals of m.p. 106—109°; the identity of the two forms was beyond doubt); $\nu_{max.}$ 3 470, 3 020, 1 645, 1 100, 1 030, 998, and 742 cm^{-1}; τ 90.9 and 9.08 (18- and 19-H_3), 6.16 (ethylenedioxy), and 4.44 (6,7-H_2) (Found: C, 73.2; H, 9.7. $C_{23}H_{36}O_4$ requires C, 73.4; H, 9.6%). The filtrates from the two acetal diols were not examined further at this stage in view of the work described above.

17,20α-*Dihydroxy*-5β-*pregn*-6-*en*-3-*one*.—The above 3,3-ethylenedioxy-5β-pregn-6-ene-17,20α-diol (716 mg) in acetic acid (20 ml) and water (2 ml) was stored at room temperature overnight. Water (80 ml) was added to give the 3-*one* as blades (589 mg), m.p. 190—193°. Crystallisation from acetone–hexane gave needles, m.p. 206—211°; $[\alpha]_D$ −11.2°; $\nu_{max.}$ 3 560, 3 420, 3 020, 1 705, 1 650, 1 285, 1 018, and 1 010 cm^{-1}; τ 9.17 (18-H_3), 9.09 (19-H_3), 5.85 (q, 20-H), and 4.42 (6,7-H_2) (Found: C, 76.1; H, 9.6. $C_{21}H_{32}O_3$ requires C, 75.85; H, 9.7%).

17,20β-*Dihydroxy*-5β-*pregn*-6-*en*-3-*one*.—The 3,3-ethylenedioxy-5β-pregn-6-ene-17,20β-diol (197 mg) in acetic acid (5 ml) and water (0.5 ml) was stored overnight. Water (20 ml) was added and the product crystallised from acetone–hexane to give the 3-*one* as prisms, m.p. 185—190°; $[\alpha]_D$ −8 4°; $\nu_{max.}$ 3 542, 3 500sh, 3 020, 1 705, 1 650sh, 1 080, 1 028, 994, and 962 cm^{-1}; τ 9.12 (18-H_3), 9.03 (19-H_3), 5.80 (q, 20-H), and 4.47 (6,7-H_2) (Found: C, 75.4; H, 9.6. $C_{21}H_{32}O_3$ requires C, 75.85; H, 9.7%),

identical with the dihydroxy-6-en-3-one obtained by prolonged hydroboration–oxidation of (III), formation of the mixed acetonides, dehydration of the 6β-hydroxy-grouping, removal of the protective groupings, and partition chromatography on Celite.

The 6-enetriols were readily obtained from the corresponding 17,20-dihydroxy-3-ones as follows.

5β-*Pregn*-6-*ene*-3α,17,20α-*triol*. 17,20α-Dihydroxy-5β-pregn-6-en-3-one (589 mg) in redistilled methanol (120 ml) with sodium borohydride (600 mg) was stored overnight at room temperature. Dilution with water (300 ml) gave the crude triol (473 mg). Extraction of the filtrate with ether gave a further 123 mg. Purification from acetone–hexane gave the triol (511 mg), identical with the compound described above.

5β-*Pregn*-6-*ene*-3α,17,20β-*triol* 17,20β-Dihydroxy-5β-pregn-6-en-3-one (133 mg) in redistilled methanol (30 ml) with sodium borohydride (150 mg) was stored overnight at room temperature. Dilution with water (75 ml) gave the crude triol (113 mg). Recrystallisation from acetone–hexane gave the triol (75 mg), identical with the compound described above.

5β-*Pregnane*-3α,17,20α-*triol*.—The unsaturated triol (19.7 mg) in pure dioxan (5 ml) was hydrogenated over 5% Pd–C (19 5 mg) for 2.25 h. Crystallisation of the product from acetone–hexane gave 5β-pregnane-3α,17,20α-triol (15 mg), m.p. and mixed m.p. 236—239°, identical (i.r. spectra, paper chromatography, and t.l.c.) with authentic material.

5β-*Pregnane*-3α,17,20β-*triol*.—The unsaturated triol (20 mg) in pure dioxan (5 ml), hydrogenated over 5% Pd–C (20 mg) for 1.75 h gave 5β-pregnane-3α,17,20β-triol (19 mg), m.p. and mixed m.p. 209—211°, identical (i.r. spectra and chromatographic behaviour) with authentic material.

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