1,4-Dioxene(2,3-Dihydro-1,4-dioxine) in Organic Synthesis. Part 9[1]. Preparation of Biologically Active Side-Chains From 17-Oxosteroids†

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Steroidal 17α-2,3-dihydro-1,4-dioxin-6-yl)-17β-ols of type (**2**), readily available from 17-oxo steroids and 2,3-dihydro-1,4-dioxine, are easily converted into 21-hydroxy-20-oxo steroids with or without a double bond at the 16(17) position as well as to the dihydroxyacetone side-chain.

Since 17-oxo steroids became readily available by microbiological degradation of abundant sterols,[2] the construction of pharmacologically useful side-chains at the 17-position[3] has been much studied.[4]

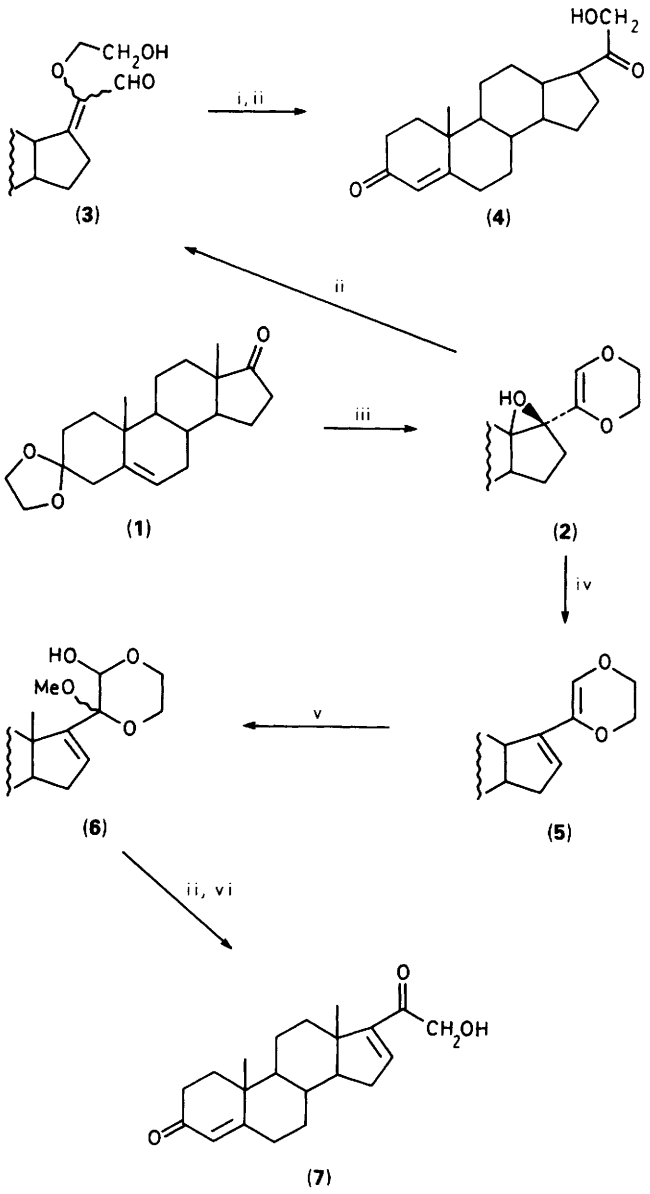
As part of our general interest in the synthetic applications of 2,3-dihydro-1,4-dioxine (1,4-dioxene), we have examined the use of this electron-rich olefin for carbon–carbon bond formation with simultaneous introduction of useful functional groups.[5] In complementary studies, we have developed novel procedures for the elaboration of highly oxygenated side-chains starting from 17-oxo steroids. We report here the synthesis of 21-hydroxy-20-oxo steroids with or without a double bond at the strategically important 16(17)-position as well as the preparation of the dihydroxyacetone side-chain with the natural (cortisone side-chain) and the unnatural stereochemistry (17-epicortisone).

Addition of 17-keto steroids to dioxenyl-lithium (2,3-dihydro-1,4-dioxin-2-yl-lithium), prepared by lithiation of 1,4-dioxene, smoothly occurred to afford 17α-dioxenyl-17β-hydroxy derivatives in good yields. These allylic alcohols have been found to be valuable intermediates for the construction of steroid side-chains.

First, we developed an efficient route to the known 21-hydroxyprogesterone (**4**). Thus the tertiary alcohol (**2**), obtained from the ketone (**1**),[6] underwent an allylic acid-promoted rearrangement under very mild conditions (silica gel–5% oxalic acid; room temperature) leading to the enol ether of the α-keto aldehyde (**3**) as a mixture of stereoisomers. Reduction of crude compound (**3**) with lithium aluminium hydride, followed by acid hydrolysis of the enol ether, afforded 21-hydroxyprogesterone (**4**) (40% overall yield) which was identical with an authentic sample (IR, NMR, m.p.). It is interesting to note that purification of the intermediates in this sequence is unnecessary and the transformation of (**2**) to (**4**) is essentially a 'one-pot' synthesis.

The same adduct (**2**) could also be easily converted into (**7**) containing an oxygenated side-chain along with a double bond at the 16(17) position. To this end, the allylic alcohol (**2**) was smoothly dehydrated with acetic anhydride in the presence of pyridinium toluene-*p*-sulphonate (PPTS) in refluxing dichloromethane to provide the diene (**5**) in 78% yield. Oxidation of this compound with *m*-chloroperbenzoic acid (MCPBA) in methanol occurred regioselectively on the electron-rich carbon–carbon double bond of the dioxene entity leading to the hemiacetal (**6**) as a mixture of diastereoisomers. Reduction of (**6**) with $NaBH_4$ followed by acid hydrolysis gave 21-hydroxypregna-4,16-diene-3,20-dione (**7**) in 68% overall yield (Scheme 1). It is worth noting that enones such as (**7**) have been a synthetic target since they are immediate precursors of the clinically important 16-substituted glucocorticoids.[3]

In a similar way, we were able to convert 17-oxo steroids into



Scheme 1. *Reagents:* i, $LiAlH_4$; ii, H_3O^+; iii, 2,3-dihydro-1,4-dioxin-6-yl-lithium; iv, Ac_2O–PPTS; v, MCPBA–MeOH; vi, $NaBH_4$.

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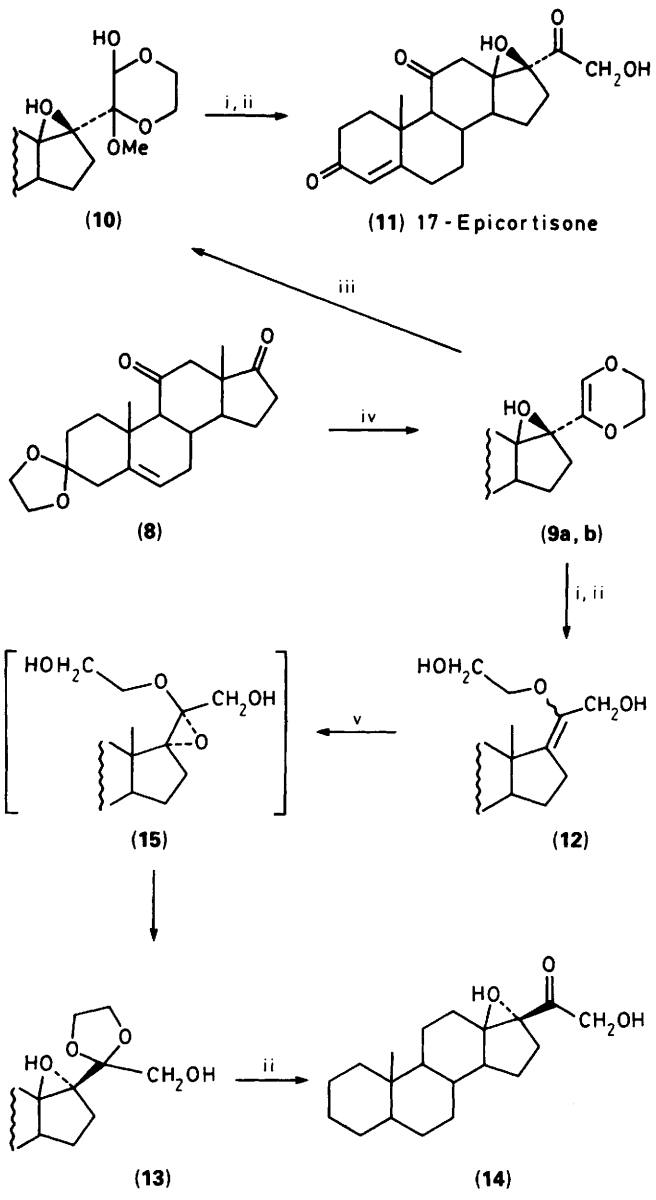

Scheme 2. *Reagents:* i, $NaBH_4$; ii, H_3O^+; iii, MCPBA, MeOH; iv, 2,3-dihydro-1,4-dioxin-6-yl-lithium; v, MCPBA.

corticosteroids possessing the dihydroxyacetone side-chain with 17α-(non-natural) or 17β-configurations depending on the reaction sequences. Thus, addition of dioxenyl-lithium to the diketone (**8**),[7] prepared from 5-androstene-3,11,17-trione by selective ketalization[8] (69%), afforded the allylic alcohol (**9a**). Oxidation of (**9a**) with *m*-chloroperbenzoic acid in methanol gave the hemiacetal (**10**) as a mixture of diastereoisomers. Reduction of crude (**10**) with $NaBH_4$ followed by acid hydrolysis led to the 17-epicortisone (**11**) in 38% overall yield from (**8**).

Inversion of the stereochemistry at C-17 and elaboration of the two-carbon side-chain was accomplished on (**9b**) obtained from 5α-androstan-17-one (70%). Although the dioxenyl group in (**9b**) has the unnatural α-orientation, this stereochemistry was corrected by the following transformations: acid-catalyzed allylic rearrangement and reduction with $NaBH_4$ afforded enol ether (**12**) as a mixture of stereoisomers. Epoxidation of this compound with MCPBA in dichloromethane cleanly gave masked dihydroxyacetone (**13**) in 90% yield. The formation of the ethylene ketal (**13**) can be easily understood in terms of an intramolecular cyclisation following the opening of the intermediate oxirane (**15**) (Scheme 2). Acid hydrolysis of (**13**) was readily effected with toluene-p-sulphonic acid (PTSA) in refluxing aqueous acetone affording 17α,21-dihydroxyandrostan-20-one (**14**) in 92% yield.

Thus starting from easily available raw materials, 17-oxo steroids and 1,4-dioxene, we have achieved an efficient and flexible route to several steroid with biologically active side-chains.

Experimental

Unless otherwise stated, m.p.s were determined on a Reichert apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer spectrometer 399 as solutions in CCl_4. NMR spectra were recorded on a Varian T60 or a Bruker W.P. 200 instruments as solutions in $CDCl_3$. Commercially available reagents and solvents were purified and dried when necessary by usual methods. All reactions were monitored by TLC carried out on 0.2 mm E. Merck silica gel plates ($60F_{254}$) using UV light and 5% ethanolic phosphomolybdic acid and heat as developing agent. Flash chromatography was performed on 40–63 μm (400–230 mesh) silica gel 60 with ethyl acetate (AcOEt)–light petroleum (b.p. 40–60 °C) (PE) as eluant. $[\alpha]_D$ Values were determined in $CHCl_3$.

Addition of 2,3-Dihydro-1,4-dioxine to 17-Oxo Steroids: General Procedure.—t-Butyl-lithium (1.7M/pentane; 12.9ml, 22 mmol) was added to stirred 1,4-dioxene[9] (neat; 1.9 g, 25 mmol) cooled at −40 °C to give a white suspension which was stirred for 2 h at −20 °C; a solution of the corresponding ketone (20 mmol) in THF (20 ml) was then added at −70 °C over a period of 15 min. The mixture was stirred at −10 °C for 2 h before addition of aqueous ammonium chloride. The mixture was extracted with ether, and the extract worked up to give crude material which was purified by flash chromatography.

17α-(2,3-Dihydro-1,4-dioxin-6-yl)-17β-hydroxyandrost-5-en-3-one ethylene ketal (**2**). From androst-5-ene-3,17-dione 3-ethylene ketal (**1**). Flash chromatography with AcOEt–PE (1:4) as eluant yielded (**2**) (75%), m.p. 151–153 °C (ether–light petroleum) (Found: C,71.9; H, 8.6. $C_{25}H_{36}O_5$ requires C, 72.11; H, 8.65%); ν_{max} 3 580, 1 670, and 1 100 cm^{-1}; δ_H(60 MHz) 0.87 (3 H, s, 19-Me), 1.00 (3 H, s, 19-Me), 1.98 (1 H, s), 3.90 (4 H, m), 4.0 (4 H, m), 5.30 (1 H, m), and 5.43 (1 H, s); δ_C 14.1 (q, C-18), 18.7 (q, C-19), 22.7 (t), 30.8 (t), 31.2 (t), 32.3 (d), 33.4 (t), 33.8 (t), 36.3 (t), 41.5 (t), 46.3 (s), 49.3 (d), 63.5 (t), 63.9 (t), 64.2 (t), 83.5 (s, C-17), 109.2 (s, C-3), 121.7 (d, C-6), 124.5 (d), 138.8 (s), and 139.9 (s).

17α-(1,4-Dioxin-6-yl)-17β-hydroxyandrost-5-ene-3,11-dione 3-ethylene ketal (**9a**). From androst-5-ene-3,11,17-trione 3-ethylene ketal (**8**). Flash chromatography with AcOEt–PE (3:4) yielded (**9a**) (64%), m.p. 186–188 °C (ether–light petroleum) (Found: C,69.8; H, 8.15. $C_{25}H_{34}O_6$ requires C, 69.76; H, 7.90%); ν_{max} 3 580, 1 710, 1 675, and 1 100 cm^{-1}; δ_H(200 MHz) 0.85 (18-Me, s), 1.24 (3 H, s, 19-Me), 3.95 (4 H, s), 4.04–4.08 (4 H, m), 5.35 (1 H, m), and 6.12 (1 H, s); δ_C 14.7 (q, C-18), 17.6 (q, C-19), 22.5, 30.5, 32.0, 33.8, 33.9, 34.7, 36.7, 41.3, 48.0, 49.0, 52.5, 59.8 (d), 63.5 (t), 64.0 (t), 64.1 (t), 82.2 (s, C-17), 108.8 (s, C-3), 120.3 (d, C-6), 124.7 (d), 138.1 (s), 140.8 (s, C-5), and 210.7 (s, C- 11).

17α-(2,3-Dihydro-1,4-dioxin-1-yl)-17β-hydroxy-5α-androstane (**9b**). From 5α-androstan-17-one. Flash chromatography with AcOEt–PE (1:6) as eluant yielded (**9b**) as white solid, m.p. 165–167 °C (ether) (Found: C, 76.9; H, 10.3. $C_{23}H_{36}O_3$ requires C, 76.66; H, 10.00%); ν_{max} 3 580 and 1 675 cm^{-1}; δ_H(200 MHz) 0.74 (3 H, s, 19-Me), 0.81 (3 H, s, 18-Me), 2.65 (1 H, br, s), 3.96–4.01 (4 H, m), and 5.93 (1 H, s); δ_C 12.2 (q, C-19), 14.4 (q, C-18), 20.6 (t), 22.1 (t), 26.8 (t), 29.0 (t, 2 C), 31.8 (t), 33.8 (t), 34.1 (t), 36.2

(t + s), 38.6 (t), 46.8 (t), 46.8 (s), 47.0 (d), 49.4 (d), 54.4 (d), 63.6 (t), 63.9 (t), 83.7 (s), 124.6 (d), and 139.3 (s).

21-*Hydroxypregn*-4-*ene*-3,20-*dione* (21-*Hydroxyprogesterone*) (**4**).—To a stirred suspension of silica gel (70–230 mesh; 2 g) in dichloromethane (5 ml) was added an 5% aqueous oxalic acid (7 drops). After 5 min, a solution of the adduct (**2**) (416 mg, 1 mmol) in dichloromethane (5 ml) was added and stirring was continued until disappearance of the starting material. Solid sodium hydrogen carbonate was added and the solid phase was separated by suction filtration. Evaporation of the solvent under reduced pressure gave crude (**3**) (440 mg) which was dissolved in THF (5 ml) and added to a stirred solution of $LiAlH_4$ (100 mg) in THF. Stirring was continued for 10 min after which a solution of 30% HCl was carefully added. The reaction mixture was then stirred at room temperature and extracted with ether. Flash chromatography of the crude product afforded pure (**4**) (132 mg, 40%) which showed analytical and spectral data identical with those of an authentic sample.

17,23-*Dihydro*-1,4-*dioxin*-6-*ylandrosta*-5,16-*dien*-3-*one*-*Ethylene Ketal* (**5**).—A mixture of the tertiary alcohol (**2**) (416 mg, 1 mmol), pyridinium toluene-*p*-sulphonate (20 mg), and acetic anhydride (10 drops) in anhydrous dichloromethane (20 ml) was refluxed for 2 h. Excess of anhydride was then destroyed with aqueous sodium hydrogen carbonate and the organic layer was separated, dried, and worked up. Flash chromatography of the crude product with AcOEt–PE(1:6) as eluant afforded (**5**) (318 mg, 78%), m.p. 167–169 °C (methanol–dichloromethane), $[\alpha]_D$ −16.7 (*c* 1.19); ν_{max} 1 650 and 1 095 cm^{-1}; δ_H(200 MHz) 0.91 (3 H, s, 19-Me), 1.03 (3 H, s, 18-Me), 3.90 (4 H, m), 4.2–4.0 (4 H, m), 5.77 (1 H, m), and 6.89 (1 H, s); δ_C 16.3 (q, C-18), 18.7 (q, C-19), 20.9 (t), 30.1 (t), 30.8 (t), 31.0 (t), 31.2 (t), 35.8 (t), 36.1 (t), 36.6 (s), 41.7 (d), 45.7 (s), 49.8 (d), 57.1 (d), 64.1 (t), 64.2 (t), 109.3 (s, C-3), 121.8 (d, C-6), 123.6 (d, C-16), 124.8 (d), 134.0 (s), 140.3 (s, C-5), and 147.0 (s, C-17).

21-*Hydroxypregna*-5,16-*diene*-3,20-*dione* (**7**).—To a solution of (**5**) (160 mg, 0.40 mmol), in methanol (20 ml) and dichloromethane (10 ml) cooled in an ice-bath was added dropwise a solution of 80% *m*-chloroperbenzoic acid (95 mg, 0.44 mmol) in methanol (5 ml). The solution was stirred at 0 °C for 15 min and then neutralized with saturated aqueous sodium hydrogen carbonate. Methanol was removed under reduced pressure and the product was extracted with dichloromethane. The crude product [the hemiacetal (**8**)] was then taken up in ethanol (30 ml) and reduced with $NaBH_4$ (20 mg) for 2 h. The solvent was removed under reduced pressure and the product was extracted with dichloromethane and worked up. The crude diol was then taken in 1% aqueous acetone (20 ml); toluene-p-sulphonic acid (10 mg) was added and the solution was heated at 40–50 °C for 2 h, neutralized with saturated solution of $NaHCO_3$ and the product was extracted with ethyl acetate. Work-up of the extract and flash chromatography of the crude product (1:2) as eluant) yielded (**7**) as white crystals (90 mg, 68%); m.p. 217–220 °C (methanol–acetone) (lit.,[3g] 215–220 °C), $[\alpha]_D$ +146 (*c* 0.94) (lit.,[3g] $[\alpha]_D$ +145); ν_{max}($CHCl_3$) 3 480 and 1 680 cm^{-1}; δ_H(200 MHz) 0.93 (3 H, s), 1.17 (3 H, s), 3.3 (1 H, m, OH), 4.32 (1 H, d, *J* 18 Hz), 4.50 (1 H, d, *J* 18 Hz), 5.67 (1 H, s), and 6.70 (1 H, m); δ_C 16.1 (q, C-18), 17.3 (q, C-19), 20.8 (t), 31.8 (t), 32.6 (t), 32.7 (t), 33.9 (t), 34.0 (t), 34.4 (t), 35.6 (t), 38.8 (s), 46.7 (s), 54.2 (d), 55.5 (d), 65.1 (t, C-21), 124.1 (d, C-4), 144.3 (d, C-16), 151.4 (s, C-17), 170.6 (s, C-5), 196.5 (s, C-20), and 199.4 (s, C-3).

17β,21-*Dihydroxypregn*-4-*ene*-3,11,20-*trione* (17-*Epicortisone*) (**11**).—To a solution of (**9a**) (564 mg, 1.31 mmol) in methanol (40 ml) cooled in an ice-bath, was added dropwise a solution of 85% *m*-chloroperbenzoic acid (270 mg, 1.33 mmol) in methanol (10 ml). After the solution had been allowed to warm to room temperature, it was stirred for 30 min and then neutralized with saturated aqueous $NaHCO_3$. The solvent was removed under reduced pressure and the product was extracted with dichloromethane. After work-up of the extract flash chromatography of the residue yielded the hemiacetal (**10**) as a mixture of diastereoisomers (630 mg, 82%). This product (400 mg, 0.83 mmol) was reduced with $NaBH_4$ (30 mg) in ethanol (20 ml) at room temperature for 1 h. The solvent was removed under reduced pressure and the product was extracted with dichloromethane. The crude product was then treated with 1% aqueous acetone (10 ml) and toluene-p-sulphonic acid (5 mg) at room temperature for 12 h. The mixture was neutralized with $NaHCO_3$ and extracted with ethyl acetate and the extract was worked up; flash chromatography (2:1) of the residue afforded pure (**11**) as white solid (235 mg, 78%); m.p. 179–180 °C (benzene); $[\alpha]_D$ +108 (*c* 0.27, ethanol) (Found: C,70.05; H, 7.8. $C_{21}H_{28}O_5$ requires C, 70.00; H, 7.77%); ν_{max}($CHCl_3$) 3 420, 1 710, and 1 665 cm^{-1}; δ_H(200 MHz) 0.90 (s, 3 H, 18-Me), 1.40 (3 H, s, 19-Me), 4.39 (1 H, d, *J* 20 Hz), 4.59 (1 H, d, *J* 20 Hz), and 5.71 (1 H, s); δ_C 14.7 (q, C-18), 16.9 (q, C-19), 23.6, 29.5, 31.6, 32.0, 33.5, 34.2, 36.6, 37.2, 38.0, 47.7, 50.8, 62.0 (d, C-9), 67.0 (t, C-21), 88.2 (s, C-17), 124.3 (d, C-4), 169.0 (s, C-5), 200.1 (s, C-3), 207.8 (s, C-20), and 215.5 (s, C-11).

17α,21-*Dihydroxy*-5α-*pregnan*-20-*one Ethylene Ketal* (**13**).—To a solution of the tertiary alcohol (**9b**) (344 mg, 0.95 mmol) in 10% aqueous acetone (20 ml) was added toluene-*p*-sulphonic acid (10 mg). The solution was heated at 30–40 °C for 1 h (controlled by TLC), and then neutralized with saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The extract was worked-up and the crude product was reduced with $NaBH_4$ (15 mg) in methanol (10 ml) for 10 min. The solvent was evaporated and the product was extracted with CH_2Cl_2. The extract was worked-up and rapid chromatography (AcOEt as eluant) of the crude product gave the diol (**12**) (240 mg, 69%) as a mixture of stereoisomers. A solution of (**12**) (85 mg) in CH_2Cl_2 (6 ml) was oxidized with 80% MCPBA (58 mg) in CH_2Cl_2 (4 ml) at 0 °C for 5 min. The solution was neutralized with saturated aqueous $NaHCO_3$ and worked-up and flash chromatography of the crude product (1:1) as eluant yielded pure (**13**) as white solid (80 mg, 90%); ν_{max} 3 605 cm^{-1}; δ_H (200 MHz) 0.75 (3 H, s, 19-Me), 0.77 (3 H, s, 18-Me), 3.63 (1 H, d, *J* 12 Hz), 3.82 (1 H, d, *J* 12 Hz), and 4.10–3.90 (4 H, m); δ_C 12.3 (q, C-19), 14.6 (q, C-18), 20.4 (t), 22.3 (t), 23.0 ('t), 26.9 (t), 29.2 ('t), 31.4 (t), 32.2 (t), 33.3 (t), 35.3 (d), 36.4 (s), 38.8 (t), 46.4 (s), 47.1 (d), 50.9 (d), 54.4 (d), 64.8 (t), 65.1 (t), 67.5 (t, C-21), 88.8 (s, C.17), and 111.5 (s, C-20).

17α,21-*Dihydroxypregnan*-20-*one* (**14**).—A solution of (**13**) (80 mg) in 1% aqueous acetone and TsOH (1 mg) was refluxed for 3 h. The product which precipitated on cooling, was isolated by filtration as white solid (65 mg, 92%); R_f 0.75 (1:2); m.p. 168–170 °C (benzene); $[\alpha]_D$ +84.9 (c 0.38); ν_{max}($CHCl_3$) 3 605 and 1 710 cm^{-1}; δ_H(200 MHz) 0.62 (3 H, s, 18-Me), 0.75 (3 H, s, 19-Me), 2.1 (1 H, br s), 2.7–2.5 (1 H, m), 3.1 (1 H, m, OH), 4.24 (1 H, dd, *J* 20 and 4 Hz), and 4.64 (dd, *J* 20 and 4 Hz, 1 H); δ_C 12.3 (q, C-19), 15.3 (q, C-18), 20.4 (t), 22.3 (t), 23.9 (t), 26.9 (t), 29.1 (t), 30.6 (t), 32.4 (t), 34.6 (t), 35.7 (d), 36.4 (s), 38.8 (t), 47.1 (d), 49.1 (s), 51.2 (d), 54.4 (d), 67.6 (t, C-21), 89.5 (s, C-17), and 212.6 (s, C-20).

References

1 Part 8, see ref. 5.
2 M. G. Wovcha, F. J. Antosz, J. C. Knight, L. A. Komineck, and T. R. Pyke, *Biochem. Biophys. Acta*, 1978, **539**, 308.
3 L. F. Fieser and M. Fieser, 'Steroids,' Reinhold, New York, 1959.
4 (*a*) J. E. Baldwin, O. W. Lever, Jr., and N. R. Tzodikov, *J. Org. Chem.*,

1976, **41**, 2312; (*b*) V. Van Rheenen and K. P. Shephard, *J. Org. Chem.*, 1979, **44**, 1582; (*c*) G. Neef, U. Eder, A. Seeger, and R. Wiechert, *Chem. Ber.*, 1980, **113**, 1184; (*d*) D. H. R. Barton, W. B. Motherwell, and S. Z. Zard, *J. Chem. Soc., Chem. Commun.*, 1981, 774; *ibid.* 1982, 551; *Nouv. J. Chim.*, 1982, **6**, 295; *Bull. Soc. Chim. Fr.*, II, 1983, **61**; (*e*) L. Nedelec, V. Torelli, and M. Hardy, *J. Chem. Soc., Chem. Commun.*, 1981, 775; (*f*) A. R. Daniewski and W. Wojciechowska, *Synthesis*, 1984, 132; *J. Org. Chem.*, 1982, **47**, 2993. (*g*) D. Van Leusen and A. M. Van Leusen, *Tetrahedron Lett.*, 1984, **25**, 2581; (*h*) D. H. R. Barton and S. Z. Zard, *J. Chem. Soc., Perkin Trans. 1*, 1985, 2191; (*i*) R. Nikolson, G. P. 2521231 (*Chem. Abstr.*, 1977, **86**, 90139e); (*j*) H. A. F. Heinemann and W. Kreiser, G. P. 1655104 (*Chem. Abstr.*, 1978, **89**, 129802e); (*k*) A. Henning, F. Heinemann, and W. Kreiser, G. P. 2603266 (*Chem. Abstr.*, 1978, **88**, 23263u, (*l*) E. J. Hessler and V. H. Van Rheenen, G. P. 2920290 (*Chem. Abstr.*, 1980, **92**, 215642w); (*m*) J. A. Walker and E. J. Hessler, U. S. P. 4357279 (*Chem. Abstr.*, 1983, **98**, 72566k).

5 For a review, see M. Fétizon, P. Goulaouic, and I. Hanna, *Heterocycles*, 1989, **28**, 521.

6 H. J. Dauben, J. B. Löken, and H. J. Ringold, *J. Am. Chem. Soc.*, 1954, **76**, 1359.

7 J. A. Zderic, E. Batres, D. C. Limon, H. Carpio, J. Lisci, G. Monroy, E. Nicoechea, and H. J. Ringold, *J. Am. Chem. Soc.*, 1960, **82**, 3404.

8 T. J. Nitz and L. A. Paquette, *Tetrahedron Lett.*, 1984, **25**, 3047.

9 R. D. Moss and J. Page, *J. Chem. Eng. Data*, 1967, **12**, 452.

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