Marine Steroids. Part II.[1] A Synthesis of 3β,6α-Dihydroxy-5α-pregn-9(11)-en-20-one

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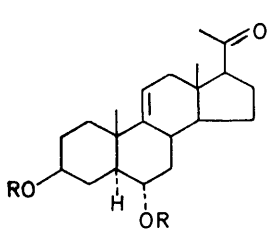
The title compound has been obtained in nine stages from 11α-hydroxyprogesterone, in an overall yield of 4%.

3β,6α-DIHYDROXY-5α-PREGN-9(11)-EN-20-ONE (1) has been obtained by acid-catalysed hydrolysis of the saponins from several species of starfish,[2,3] and routes have been developed for its conversion into various corticosteroids.[4] 11α-Hydroxyprogesterone (2) appeared to be a convenient starting point for the synthesis of the pregnene (1), since methods were available for conversion of the 4-en-3-one system into the required 5α-3β,6α-diol system and for dehydration of the 11α-alcohol function to give the 9,11-double bond.

Acid-catalysed reaction of 11α-hydroxyprogesterone (2) with isopropenyl acetate gave the dienol diacetate (3), the 20-oxo-group of which was protected by formation of the ethylene acetal (4). Some degree of hydrolysis of the enol acetate system during acetalisation was evident from the n.m.r. spectrum of the crude product, which indicated that some of the 3,20-diacetal had been formed. (The signals in the acetal region at τ 6.07 integrated for rather more than four protons.) The crude 20-acetal (4) was converted into the 5-en-3β-ol (5) by the method of Belleau and Gallagher,[5] employing the weakly alkaline nature of sodium borohydride in aqueous ethanol for selective hydrolysis of the 3,5-dienol acetate system, without affecting the acetoxy-group in ring C. Reduction of the carbonyl group of the resulting deconjugated ketone by borohydride gave the 5-en-3β-ol (5). The alcohol (5) was obtained in 50% overall yield from 11α-hydroxyprogesterone, but a substantial amount of the 3,20-diacetal (6) was also isolated.



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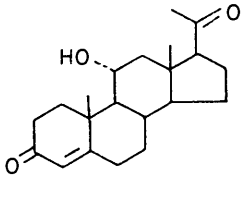
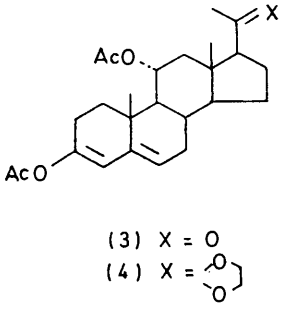
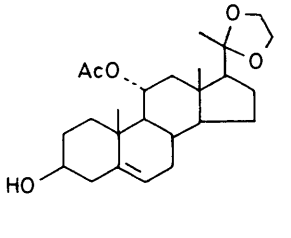
(12) R = Ac



(2)



(3) X = O
(4) X = O,O



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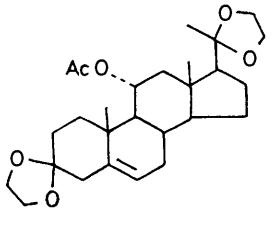

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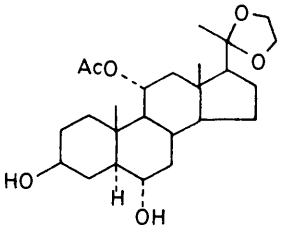

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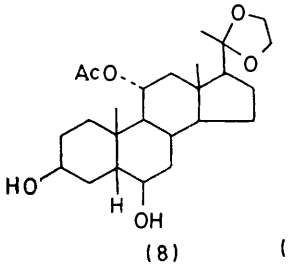

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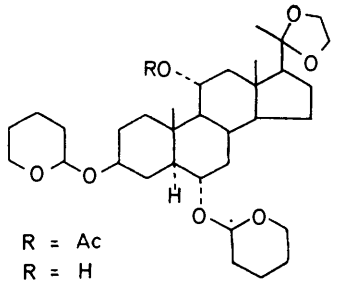

(9) R = Ac
(10) R = H
(11) R = p-MeC$_6$H$_4$·SO$_2$

Hydroboration of the 5-en-3β-ol (5) with diborane in tetrahydrofuran,[6] followed by oxidation with alkaline hydrogen peroxide, yielded a mixture of the 3β,6α-dihydroxy-5α-pregnane (7) and the 3β,6β-dihydroxy-5β-pregnane (8). After separation by t.l.c. (multiple development), these diols were obtained in the ratio *ca.* 2 : 1. The isomers were identified initially on the basis of their relative amounts, since the α-face of the

[1] Part I, D. S. H. Smith, A. B. Turner, and A. M. Mackie, *J.C.S. Perkin I*, 1973, 1745.

[2] (*a*) S. Ikegami, Y. Kamiya, and S. Tamura, *Tetrahedron Letters*, 1972, 1601; *Agric. and Biol. Chem. (Japan)*, 1972, **36**, 1777; (*b*) Y. M. Sheikh, B. M. Tursch, and C. Djerassi, *J. Amer. Chem. Soc.*, 1972, **94**, 3278; (*c*) Y. Shimizu, *ibid.*, p. 4051; (*d*) J. W. ApSimon, J. A. Buccini, and S. Badripersaud, *Canad. J. Chem.*, 1973, **51**, 850; (*e*) G. Habermehl and B. Christ, *Z. Naturforsch.*, 1973, **28c**, 225.

[3] Preliminary communication, D. S. H. Smith and A. B. Turner, *Tetrahedron Letters*, 1972, 5263.

[4] J. E. Gurst, Y. M. Shiekh, and C. Djerassi, *J. Amer. Chem. Soc.*, 1973, **95**, 628.

[5] B. Belleau and T. F. Gallagher, *J. Amer. Chem. Soc.*, 1951, **73**, 4458; *cf.* B. R. Bhavnani and F. Z. Stanczyk, *Steroids*, 1972, **20**, 129.

[6] S. Wolfe, M. Nussim, Y. Mazur, and F. Sondheimer, *J. Org. Chem.*, 1959, **24**, 1034.

steroid nucleus is much less hindered than the β-face, and hydroboration–oxidation of a 5,6-double bond gives mainly the 6α-alcohol of the 5α-series.[6,7] Steric hindrance arising from the 11α-acetoxy-group may account for the formation of a greater proportion of the 6β-hydroxy-5β-pregnane (8) than is usual in this type of hydroboration. The structural assignments were confirmed by the n.m.r. spectra of the two diols, which differed markedly in the chemical shifts of their 10-methyl protons, as expected from calculated values[8] (see Table). The mass spectral fragmentation patterns

Chemical shifts (τ values) of angular methyl protons of pregnanes

	Observed		Calculated [8]	
Steroid	19-H	18-H	19-H	18-H
(4)	8.87	9.12	8.87	9.13
(5)	8.90	9.15	8.86	9.15
(6)	8.87	9.14	8.87	9.14
(7)	9.06	9.19	9.08	9.18
(8)	8.74	9.16	8.75	9.15
(12)	8.98	9.45	8.98	9.44
(1)	9.04	9.44	9.05	9.44

of the two compounds were very similar, in keeping with the dominant influence of the acetal grouping.[9] The molecular ions are very weak and prominent fragments of *m/e* 421, 99, and 87 (base peak) can be ascribed to oxonium ions of the acetal system formed by cleavage of the 20,21-, 13,17-, and 15,16-, and 17,20-bonds, respectively.

The diol (7) was finally transformed into the pregnene (1) by standard methods,[10] without purification of intermediates [(9)—(11)]. The hydroxy-groups were protected by formation of their tetrahydropyranyl ethers, thereby allowing the use of base to hydrolyse selectively the 11α-acetoxy-group. Tosylation of the resulting 11α-alcohol, followed by elimination of toluene-*p*-sulphonic acid with sodium acetate in acetic acid,[11] introduced the desired 9,11-double bond. This treatment also removed all the acid-sensitive protecting groups and gave the diacetate (12). Finally, hydrolysis of this diacetate with base gave 3β,6α-dihydroxy-5α-pregn-9(11)-en-20-one (1).

Two other synthetic routes to the pregnene (1) have appeared. Gurst *et al.*[4] utilised Breslow's iodobenzene dichloride method for the introduction of the 9,11-double bond into the 20-acetal of 3β,6α-diacetoxy-5α-pregnan-20-one, and ApSimon and Eenkhoorn [12] developed a seven-stage synthesis from 11-oxoprogesterone, and obtained the pregnene (1) in 13.5% overall yield. The Carleton route differs from our own in that it involves reduction of the 11-oxo-group to the 11β-alcohol with lithium aluminium hydride, followed by elimination of the axial hydroxy-group to form the 9,11-double bond. The Stanford route produced the pregnene (1) in *ca.* 11% yield from the 20-ethylene acetal of pregnenolone acetate, but requires argentation chromatography to separate the 9(11)-olefin from its Δ^{14}-isomer, which is also formed in substantial proportion.

EXPERIMENTAL

For general directions see ref. 1.

11α-Acetoxy-20,20-ethylenedioxypregn-5-en-3β-ol (5).—A solution of 11α-hydroxyprogesterone (16 g) in dry benzene was heated under reflux for 16 h with isopropenyl acetate (80 ml) and toluene-*p*-sulphonic acid (2.4 g). The solution was poured into water, and the organic layer was separated, washed with saturated aqueous sodium hydrogen carbonate, then with water, and dried ($MgSO_4$). Evaporation *in vacuo* gave an oil (20 g) which slowly crystallised. [A sample of this material, recrystallised from methanol, had m.p. 142—144°, undepressed upon admixture with 3,11α-diacetoxypregna-3,5-dien-20-one, m.p. 144—145° (lit.,[13] 145—146°) prepared [13] from 11α-acetoxyprogesterone.] The crude product was dissolved in benzene (800 ml) and ethane-1,2-diol (120 ml) containing toluene-*p*-sulphonic acid (1.2 g), and the mixture was heated under reflux (with water separator) for 8 h. The cooled solution was washed with saturated aqueous sodium hydrogen carbonate, then with water, and dried ($MgSO_4$). Evaporation yielded crude 3,11α-diacetoxy-20,20-ethylenedioxypregna-3,5-diene (4) as a viscous oil [τ 9.12 (s, 13-Me), 8.87 (s, 10-Me), 7.99 (s, 11α-OAc), 7.86 (s, 3-OAc), 6.05 (m, 20-acetal), 4.70br (m, 11β-H), 4.56 (m, olefinic 6-H), and 4.31 (s, olefinic 4-H)].

The crude diacetoxy-acetal (4) was dissolved in 95% ethanol (2.5 l) and sodium borohydride (6.5 g) was added. The solution was stirred at ambient temperature for 24 h. Most of the ethanol was removed *in vacuo* and the resulting suspension was partitioned between ethyl acetate and water. The organic layer was separated, washed thoroughly with water, dried ($MgSO_4$), and evaporated. The resulting yellow gum was chromatographed on a column of silica gel (500 g), which was eluted with benzene–hexane (3 : 1; 5 l) and then with benzene alone until elution of the first component began. This component was then eluted with benzene–ether (9 : 1), and, after treatment with charcoal in boiling hexane followed by crystallisation from ethanol, gave 11α-acetoxy-3,3:20,20-bisethylenedioxypregn-5-ene (2.5 g, 11%), m.p. 193—194° (lit.,[14] 186—190°), τ 9.14 (s, 13-Me), 8.87 (s, 10-Me), 8.73 (s, 20-Me), 7.99 (s, 11α-OAc), 6.05 (s, 3- and 20-acetals), 4.71br (m, 11β-H), and 4.59br (d, *J* 4 Hz, olefinic 6-H). Further elution with benzene–ether (9 : 1) gave, after similar treatment with charcoal and crystallisation from ethanol, *11α-acetoxy-20,20-ethylenedioxypregn-5-en-3β-ol* (12.2 g, 60%) as needles, m.p. 152—154° (Found: C, 69.1; H, 8.8. $C_{25}H_{38}O_5$ requires C, 69.1; H, 8.8%), $\nu_{max.}$ 1 730, 1 250, and 1 050 cm^{-1}, τ 9.15 (s, 13-Me), 8.90 (s, 10-Me), 8.74 (s, 20-Me), 8.00 (s, 11α-OAc), 6.50br (m, 3α-H), 6.07 (m, 20-acetal), 4.67br (m, 11β-H), and 4.59br (d, *J* 5 Hz, olefinic 6-H). Elution with benzene–

[7] *Cf.* E. R. H. Jones, G. D. Meakins, J. Pragnell, W. E. Müller, and A. L. Wilkins, *J.C.S. Perkin I*, 1974, 2376.

[8] R. F. Zürcher, *Helv. Chim. Acta*, 1961, **44**, 1380; 1963, **46**, 2054.

[9] H. Budzikiewicz, C. Djerassi, and D. H. Williams, 'Interpretation of Mass Spectra of Organic Compounds,' Holden-Day, San Francisco, 1964, pp. 54—58.

[10] D. N. Kirk and M. P. Hartshorn, 'Steroid Reaction Mechanisms,' Elsevier, Amsterdam, 1968, p. 107.

[11] *Cf.* K. Takeda, H. Tanida, and K. Horiki, *J. Org. Chem.*, 1966, **31**, 734.

[12] J. W. ApSimon and J. A. Eenkhoorn, *Canad. J. Chem.*, 1974, **52**, 4113.

[13] M. S. Heller, H. Wehrli, K. Schaffner, and O. Jeger, *Helv. Chim. Acta*, 1962, **45**, 1261.

[14] G. B. Spero, J. L. Thompson, B. J. Magerlein, A. R. Hanze, H. C. Murray, O. K. Sebek, and J. A. Hogg, *J. Amer. Chem. Soc.*, 1956, **78**, 6213.

ether (1 : 1) gave a yellow gum (0.8 g) which appeared to be 3,3:20,20-bisethylenedioxypregn-5-en-11α-ol, $\nu_{max.}$ 3 460 cm^{-1}, τ 9.20 (s, 13-Me), 8.82 (s, 10-Me), 8.71 (s, 20-Me), 6.28br (m, 11β-H), 6.07 (m, 3- and 20-acetals), and 4.50 (m, olefinic 6-H).

11α-*Acetoxy*-20,20-*ethylenedioxy*-5α-*pregnane*-3β,6α-*diol* (7).—To a solution of 11α-acetoxy-20,20-ethylenedioxypregn-5-en-3β-ol (500 mg) in dry tetrahydrofuran (15 ml) at 5 °C was added a freshly prepared 0.1M-solution of diborane in tetrahydrofuran (15 ml). After 1 h at 5 °C, potassium carbonate (1 g) in water (5 ml) was added dropwise, followed by aqueous 30% hydrogen peroxide (25 ml), and the mixture was stirred for 40 min at ambient temperature. Ethyl acetate (20 ml) was added and the organic layer was separated, washed successively with water, iron(II) sulphate solution, and water again, and dried ($MgSO_4$). Evaporation *in vacuo* gave a foam which, by t.l.c., was found to contain two major polar components and some minor mobile impurities. The main components were separated by multiple-development t.l.c. [acetone–benzene (2 : 1)] to give 11α-*acetoxy*-20,20-*ethylenedioxy*-5α-*pregnane*-3β,6α-*diol* (180 mg, 35%), m.p. 216—218°, raised by recrystallisation from acetone–hexane to 221—222° (Found: C, 68.6; H, 8.9. $C_{25}H_{40}O_6$ requires C, 68.8; H, 9.2%), R_F 0.61 (three developments), $\nu_{max.}$ 3 520, 3 290, 1 732, 1 715, and 1 260 cm^{-1}, τ 9.19 (s, 13-Me), 9.06 (s, 10-Me), 8.74 (s, 20-Me), 8.01 (s, 11α-OAc), 6.52br (m, 3α- and 6β-H), 6.08 (m, 20-acetal), and 4.86br (m, 11β-H), *m/e* 436 (0.05%), 421 (10), 274 (20), 145 (18), 118 (10), 117 (14), 105 (13), 99 (40), and 87 (100); and 11α-*acetoxy*-20,20-*ethylenedioxy*-5β-*pregnane*-3β,6β-*diol* (8) (96 mg, 19%), m.p. 203—206°, raised on repeated recrystallisation from acetone–hexane to 214—215° (Found: C, 68.5; H, 9.0. $C_{25}H_{40}O_6$ requires C, 68.8; H, 9.2%), R_F 0.72 (three developments), $\nu_{max.}$ 3 450, 1 715, and 1 255 cm^{-1}, τ 9.16 (s, 13-Me), 8.74 (s, 10- and 20-Me), 8.05 (s, 11α-OAc), 6.29 (m, 3α-H), 6.08 (m, 20-acetal), 5.90 (m, 6α-H), and 4.86br (m, 11β-H), *m/e* 436 (0.1%), 421 (9), 145 (14), 117 (9), 105 (11), 99 (25), and 87 (100).

3β,6α-*Diacetoxy*-5α-*pregn*-9(11)-*en*-20-*one* (12).—A solution of the above 3β,6α-diol (100 mg) in 2,3-dihydropyran (10 ml) containing phosphoryl chloride (5 μl) was left at ambient temperature for 30 min, and then diluted with ether (100 ml), washed with water, dried ($MgSO_4$), and evaporated. The resulting bistetrahydropyranyl ether was dissolved in methanolic potassium hydroxide (1.0M; 10 ml) and heated under reflux for 3 days. Most of the ethanol was removed *in vacuo* and the 11α-alcohol was isolated with ether.[15] The alcohol (10) was dissolved in dry pyridine (5 ml), cooled to 4 °C, and treated with toluene-*p*-sulphonyl chloride (200 mg). After 24 h at this temperature the mixture was worked up in the usual way [16] to give the crude tosylate (11) as an oil. A solution of this tosylate in glacial acetic acid (10 ml) was boiled under reflux with sodium acetate (200 mg) for 18 h. The mixture was poured into water and neutralised with sodium hydroxide, and the product was isolated with ethyl acetate. It was purified by t.l.c. (two developments with benzene–ethyl acetate, 9 : 1) to give 3β,6α-diacetoxy-5α-pregn-9(11)-en-20-one (28 mg, 29%) as an oil, t_R 0.88, $\nu_{max.}$ (film) 1 735, 1 700, 1 250, and 1 035 cm^{-1}, τ 9.45 (s, 13-Me), 8.98 (s, 10-Me), 7.98 (s, 3β- and 6α-OAc), 7.88 (s, 20-Me), 5.28br (m, 3α- and 6β-H), and 4.62 (m, olefinic 11-H).

3β,6α-*Dihydroxy*-5α-*pregn*-9(11)-*en*-20-*one* (1).—A solution of the above diacetate (50 mg) in methanolic potassium hydroxide (0.5M; 10 ml) was left at room temperature for 24 h. Most of the solvent was evaporated off *in vacuo* and water and dichloromethane were added to the residue. The organic layer was separated, washed with water, dried (Na_2SO_4), and evaporated to give a solid (42 mg). This was purified by t.l.c. and material from the main band (R_F 0.60 after two developments in chloroform–ethanol, 9 : 1) was crystallised from aqueous methanol to give the *diol* (30 mg, 75%), m.p. 158—162°, raised after two recrystallisations from aqueous methanol to 194—196° (lit.,[1c] 193—196°; lit.,[12] 196—198°), M^+ 332.2350 ($C_{21}H_{32}O_3$), t_R 0.65, $\nu_{max.}$ 3 240 and 1 700 cm^{-1}, τ 9.44 (s, 13-Me), 9.04 (s, 10-Me), 7.87 (s, 20-Me), 6.42 (m, 3α- and 6β-H), and 4.62 (m, olefinic 11-H), *m/e* 332 (M^+, 3%), 314 (6), 299 (15), 281 (16), 230 (45), 211 (18), 95 (100), and 43 (100).

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[15] M. S. Rajagopalan and A. B. Turner, *J. Chem. Soc.* (*C*), 1970, 2266.

[16] L. F. Fieser and M. Fieser, ' Reagents for Organic Synthesis,' Wiley, New York, 1967, p. 1180.