A Synthesis of 11β,18,21-Trihydroxypregn-4-ene-3,20-dione ('18-Hydroxy-corticosterone')

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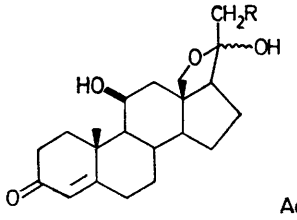
Summary 3β-Acetoxypregn-5-ene-11,20-dione has been converted through 3β-acetoxy-18,20-epoxy-20-hydroxypregn-5-en-11-one and '11β,18-dihydroxy-progesterone' into '18-hydroxy-corticosterone.'

11β,18,21-TRIHYDROXYPREGN-4-ENE-3,20-DIONE ('18-hydroxy-corticosterone'), which exists in the hemiacetal form (**1**), has been known for over a decade as one of the biosynthetic precursors of aldosterone.[1] A synthesis of racemic 18-hydroxy-corticosterone was reported in 1961 by the CIBA group,[2] but supplies of the natural enantiomer, required in medical and biochemical investigations, have had to be obtained by fungal[3,4] or adrenal incubation[5] of suitable steroids, no chemical synthesis having been reported. We now describe a synthesis from 3β-acetoxypregn-5-ene-11,20-dione (**2**), based in part on our recent preparation of 18,21-dihydroxypregn-4-ene-3,20-dione ('18-hydroxy-deoxycorticosterone').[6]

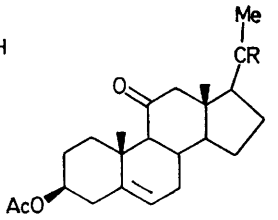
3β-Acetoxypregn-5-ene-11,20-dione (**2**) (Upjohn Co., Kalamazoo) was reduced with $NaBH_4$ in MeOH at 0 °C to give the 20β-alcohol (**3**), which was irradiated in cyclohexane containing $Pb(OAc)_4$ and iodine ('hypoiodite' reaction[7]) to give its 18-iodo-derivative. The crude 20-hydroxy-18-iodo-compound was oxidised with Jones' reagent in the usual way[6,7] to give the 18-iodo-20-ketone; silver ion-assisted hydrolysis then gave the hemiacetal (**4**) [m.p. 171—174 °C (from acetone–hexane), ν_{max} 3522, 1722, 1699, 1669, 1245, and 1042 cm^{-1}; τ ($CDCl_3$) 8·82 (s, 10β-Me), 8·50 (s, 21-H_3), 7·97 (s, AcO), 6·37 (s, 18-H_2), *ca.* 5·32 (m, 3α-H), and *ca.* 4·6 (m, 6-H)], isolated by chromatography on silica gel. Gradient elution with benzene containing up to 7% of Et_2O gave compound (**2**) and by-products. The hemiacetal (**4**) was obtained by increasing the amount of Et_2O from 7 to 10%. For optimum yield of the hemiacetal (12·5%), determined from n.m.r. and i.r. spectra of final products from a series of reactions, it was necessary to use a molar ratio (steroid : iodine) of 1·0 : 0·9, instead of 1·0 : 0·55 as for similar reactions in the 11-deoxy series.

To permit selective reduction of the 11-oxo-group, the hemiacetal was converted into the corresponding 20-methoxy compound (**5**) (88%) [m.p. 152—154 °C, ν_{max} (KBr) 1723, 1709, 1668, 1245, 1041, and 865 cm^{-1}; τ ($CDCl_3$) 8·85 (s, 10β-Me), 8·65 (s, 21-H_3), 7·98 (s, AcO), 6·83 (s, OMe), 6·66, 6·37 (dd, *J* 10 Hz, 18-CH_2), *ca.* 5·4 (m, 3α-H), and 4·65 (m, 6-H)] by methanolic HCl. [Hemiacetal (1·12 g) in anhydrous MeOH (50 ml), treated with HCl-saturated MeOH (0·1 ml) for 10 min at room temperature]. Reduction of the 11-oxo group with $NaBH_4$ in alkaline solution (tetrahydrofuran–EtOH 1 : 1) gave the 3β,11β-diol (**6**) (ν_{max} 3440 and 1650 cm^{-1}), which, without

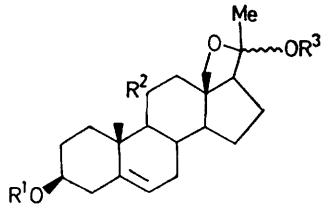
purification, was converted by Oppenauer oxidation [cyclohexanone and $Al(OPr^i)_3$ in toluene] into '11β,18-dihydroxy progesterone' [isolated by p.l.c. as the hemiacetal (**7**), 36%



(1) R = OH
(7) R = H
(8) R = OAc



(2) R = O
(3) R = β-OH, α-H



(4) R^1 = Ac, R^2 = O, R^3 = H
(5) R^1 = Ac, R^2 = O, R^3 = Me
(6) R^1 = H, R^2 = β-OH, R^3 = Me

from (**5**); ν_{max} 3420, 1662, 1615, 1162, and 1039 cm^{-1}, τ ($CDCl_3$) 8·59 and 8·53 (s, s, 10β and 20-Me), 6·24 and 5·73 (dd, *J* 10 Hz, 18-H_2), 5·62 (m, $W_{\frac{1}{2}}$ *ca.* 7 Hz, 11α-H), and 4·32 (s, 4-H)]. This compound is extremely sensitive to aqueous acids, which rapidly convert 11β,18-diols into 11β,18-ethers,[2,4,8] recognised by relatively low polarity (t.l.c.) and by the i.r. absorption (ν_{max} 1705 cm^{-1}) of the regenerated 20-oxo-group, and by n.m.r. characteristics.[9] The Oppenauer mixture was therefore worked up by extraction with aqueous sodium potassium tartrate to remove aluminium compounds in an alkaline-buffered medium, and cyclohexanone was removed as completely as possible under reduced pressure rather than by steam distillation. (The formation of 11β,18-ethers frustrated an alternative approach to 18-hydroxy-corticosterone *via* the 3-ethylene acetal of 11-oxoprogesterone; the hypoiodite reaction was also less satisfactory in this series.[10])

To minimise 11β,18-ether formation during 21-acetoxylation, solvent-free 11β,18-dihydroxyprogesterone, in the hemiacetal form (**7**), was treated with solid $Pb(OAc)_4$ followed *at once* by anhydrous AcOH. After swirling for 5 min to dissolve the reactants, the product was extracted with ether, which was washed neutral, dried, and evaporated to give crude 18-hydroxy-corticosterone 21-acetate (**8**) as a gum, τ ($CDCl_3$) 8·57 (s, 10β-Me), 7·67 (s, AcO), 6·5—5·9 (m, 18-H_2), 5·72 (s, 21-H_2), 5·53 (m, $W_{\frac{1}{2}}$ *ca.* 8 Hz, 11α-H), and 4·27 (s, 4-H). Alkaline hydrolysis of the 21-acetate with 0·1 M-NaOH in aqueous 90% MeOH under reflux for 30 min gave 18-hydroxy-corticosterone (**1**), purified by preparative t.l.c. (on Merck Kieselgel, HF 254; multiple development with benzene–Et_2O, 4 : 1) and crystallisation from acetone–hexane containing a trace of Et_3N [m.p. 148—150 °C (*cf.* m.p. 163—164 °C or 170 °C reported[2] for the racemate), ν_{max} (KBr) *ca.* 3400 br, 1661 and 1614 (4-en-3-one), 1281, 1230, 1061, 1040, 1032, 1018—998 br, and 895 cm^{-1}].

This route, and method of purification, avoids the formation of the useless dimer, which can result from contact with acid, or apparently from fermentation procedures for the preparation of 18-hydroxy-corticosterone.[4] The product was identical with a sample provided by G. D. Searle and Co. Ltd. The identity was further confirmed by a mass spectral study, kindly carried out by Dr. C. J. W. Brooks, Glasgow; details will be given in our definitive paper, following work now in progress to optimise yields in the later stages of the synthesis.

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