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Electrochemical Reduction of 7-Oxo Steroids: Route to Multideuterated Biological Steroids

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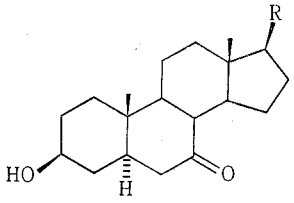
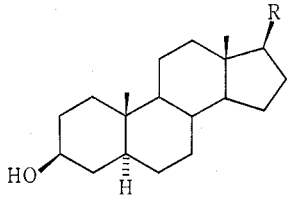
Abstract

Electrochemical reduction of saturated 7-oxo steroids is shown to be an efficient procedure for the preparation of the respective deoxygenated analogues. Use of deuterated reagents allows a facile route to the corresponding deuterated steroids.

Electrochemical deoxygenation of carbonyl groups has been reported as an efficient procedure for the deuterium labelling of steroids.[1,2] As part of a continuing program[2–4] aimed at preparing deuterated steroids for biomedical studies we envisaged that a similar reduction of saturated 7-oxo steroids would allow a facile route to biologically relevant compounds labelled in the B ring.





(1) R = $CH(Me)CH_2CH_2CH_2CHMe_2$
(2) R = OH
(3) R = CHOHMe

(4) R = $CH(Me)CH_2CH_2CH_2CHMe$
(5) R = OH
(6) R = CHOHMe

The required ketones (1)–(3) were obtained by successive hydrogenation and hydrolysis of 3β-acetoxycholest-5-en-7-one, 3β,17β-diacetoxyandrost-5-en-7-one and 3β,20β-diacetoxypregn-5-en-7-one respectively. The latter compounds were prepared by allylic oxidation as previously reported.[4]

[1] Tokes, L., and Throop, L. J., in 'Organic Reactions in Steroid Chemistry' (Eds J. Fried and J. A. Edwards) Vol. 1, p. 166 (Van Nostrand Reinhold: New York 1972).
[2] Blair, I. A., Frith, R. G., Phillipou, G., and Seaborn, C. J., *Aust. J. Chem.*, 1979 **32**, 2327.
[3] Seamark, R. F., Phillipou, G., and McIntosh, J. E. A., *J. Steroid Biochem.*, 1977, **8**, 885.
[4] Blair, I. A., Phillipou, G., and Seaborn, C. J., *J. Labelled Compd.*, 1978, **15**, 645.

Electrochemical reductions of (1)–(3) in all cases provided the respective deoxygenated analogues (4)–(6) in 60–70% yield. Only trace amounts of products arising from reduction of the CO groups to CHOH were evident. It has been shown previously that, where the oxo group is sterically hindered, reduction to the corresponding alcohol is the major reaction pathway.[1]

Reduction of (2) in the appropriate deuterated reagents, followed by oxidation of the diol (5),[5] yielded [7,7-$^2H_2$]-5α-androstane-3,17-dione in 88·4% isotopic purity. Preparation of 3β,20β-dihydroxy[6,6,8β-$^2H_3$]-5α-pregnan-7-one by base-catalysed exchange,[6] followed by electrochemical reduction in deuterated reagents and subsequent oxidation,[5] gave [6,6,7,7,8β-$^2H_5$]-5α-pregnane-3,20-dione in 76·0% isotopic purity.

The electrochemical reduction of C 7 oxo steroids is therefore shown as an efficient route leading to biologically important deuterated steroids in high isotopic purity. As such it represents a considerable improvement over previously reported methodology based on the elaboration of pregnan-12-ones prepared through degradation of hecogenin.[7]

Experimental

Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. Steroid precursors were purchased from Steraloids Inc. (Wilton, U.S.A.). Thin-layer chromatography was carried out on Eastman precoated silica gel sheets. Mass spectral data were obtained on an A.E.I. MS-30 mass spectrometer interfaced to a Pye 104 gas chromatograph (column 2 m by 2 mm i.d., 1·6% OV-101). Elementary analyses were performed by the Australian Microanalytical Service, Melbourne. The homogeneity of all products was checked by t.l.c. and g.l.c.–m.s.

Hydrogenation

The α,β-unsaturated ketone (1·0 g) was dissolved in ethyl acetate (20 ml) and hydrogenated in the presence of Adams catalyst (0·02 g) for 1 h at room temperature. If t.l.c. indicated the formation of the respective 7-hydroxy compound, the mixture was oxidized with Brown's reagent.[5] Isolation in the usual manner gave the following steroids.

3β-Acetoxy-5α-cholestan-7-one (65%), m.p. 144–145° (lit.[8] 143°).

3β,17β-Diacetoxy-5α-androstan-7-one (73%), m.p. 198–201° (Found: C, 70·4; H, 8·6. $C_{23}H_{34}O_5$ requires C, 70·7; H, 8·8%).

3β,20β-Diacetoxy-5α-pregnan-7-one (80%), m.p. 154–155° (Found: C, 71·7; H, 9·1. $C_{25}H_{38}O_5$ requires C, 71·7; H, 9·2%).

Hydrolysis

The acetate (1 g) and potassium carbonate (10 equiv.) in methanol (50 ml) were stirred at room temperature for varying periods (cholestane, 3 h; androstane, 18 h; pregnane, 140 h). The mixture was then neutralized with 10% hydrochloric acid and repeatedly extracted with chloroform. The chloroform extract was washed with brine, dried and the solvent removed to give the following compounds.

3β-Hydroxy-5α-cholestan-7-one (1) (90%), m.p. 170–171° (lit.[8] 163°).

3β,17β-Dihydroxy-5α-androstan-7-one (2) (90%), m.p. 203–206° (Found: C, 74·3; H, 9·9. $C_{19}H_{30}O_3$ requires C, 74·5; H, 9·9%).

3β,20β-Dihydroxy-5α-pregnan-7-one (3) (86%), m.p. 207–207·5°. Although a satisfactory combustion analysis could not be obtained, the compound was pure by t.l.c. and g.l.c.–m.s., as was its respective di(trimethylsilyl) ether.

[5] Brown, H. C., Garg, C. P., and Liu, K. T., *J. Org. Chem.*, 1971, **36**, 387.
[6] Williams, D. H., Bhacca, N. S., and Djerassi, C., *J. Am. Chem. Soc.*, 1963, **85**, 2810.
[7] Baille, T. A., Sjovall, J., and Herz, J. E., *Steroids*, 1975, **26**, 438.
[8] Fieser, L. F., and Fieser, M., 'Steroids' (Reinhold: New York 1959).

Electrochemical Reduction

The apparatus consisted of a 100-ml round-bottom flask, with a B34 glass stopper through which two holes were bored to accommodate the electrodes. The anode (lead, 2·3 cm by 4·4 cm) was defined by a dialysis bag. The cathode (lead, 2·7 cm by 6·0 cm) was defined by the flask volume. All experiments used dioxan/10% sulfuric acid (3:2) as reaction medium, except for deuterated runs in which 10% $^2H_2SO_4/^2H_2O$ was employed. Typically 0·1–0·25 g of steroid was dissolved in the cathode compartment and treated until t.l.c. indicated the absence of starting material. Reactions were conducted at approximately 500 mA and 3–5 V. Workup of the cathode chamber in the normal manner, and chromatography of the crude product on Sorbsil (5 g) gave the following steroids: 5α-cholestan-3β-ol (70%), m.p. 143–144° (lit.[8] 142°); 5α-androstane-3β,17β-diol (60%), m.p. 168–169° (lit.[8] 164°); 5α-pregnane-3β,20β-diol (60%), m.p. 194–195° (lit.[8] 194°).

Deuterated Compounds

Electrochemical reduction of (2) (0·15 g) as above in dioxan/(10% $^2H_2SO_4/^2H_2O$) and chromatographic purification of the product on Sorbsil (5 g) (ether/n-hexane 2:5) gave [7,7-$^2H_2$]-5α-androstane-3β,17β-diol (0·08 g, 50%), m.p. 167–169° (lit.[8] 164°). Oxidation[5] of the diol (0·05 g) gave [7,7-$^2H_2$]-5α-androstane-3,17-dione (0·032 g, 64%), m.p. 133–135° (lit.[8] 133°). Mass spectral analysis showed it to be 0·7% $^2H_0$, 7·8% $^2H_1$, 88·4% $^2H_2$ and 3·1% $^2H_3$ isotopically labelled.

3β,20β-Diacetoxy-5α-pregnan-7-one (0·1 g) was dissolved in $CH_3O^2H/^2H_2O$ (5:2, 7 ml), containing dissolved sodium (0·2 g), and heated under reflux for 3 days. Workup in the usual manner gave 0·071 g of a white solid which was subjected to electrochemical reduction in dioxan/(10% $^2H_2SO_4/^2H_2O$) without further purification. Isolation of the product on Sorbsil (2 g; ether/n-hexane 1:5) gave [6,6,7,7,8β-$^2H_5$]-5α-pregnane-3β,20β-diol (0·037 g, 50%), m.p. 194–196°. Oxidation[5] of the diol (0·03 g) gave [6,6,7,7,8β-$^2H_5$]-5α-pregnane-3,20-dione (0·025 g, 80%), m.p. 197–199° (lit.[8] 199–200°). Mass spectral analysis showed it to be 2·0% $^2H_3$, 22·0% $^2H_4$ and 76·0% $^2H_5$ isotopically labelled.

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