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SYNTHESIS OF 15β-HYDROXYLATED DERIVATIVES OF DEHYDROISOANDROSTERONE AND ISOANDROSTERONE

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A number of steroid metabolites excreted by the human newborn have been characterized as C-19 and C-21 polyhydroxylated structures (1). Among these metabolites, 15-hydroxylated compounds are of special interest since they may be foetal precursors of the corresponding estrogenic derivatives in the foeto-placental unit (2). In addition, 15-hydroxylation may be an enzymatic marker of sexual differentiation (3).

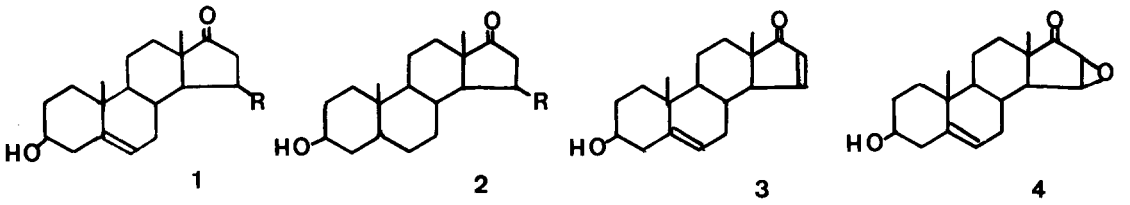
Microbiological hydroxylation has been used for the introduction of a 15-hydroxy group into a steroid nucleus. Thus, 15-hydroxycortexone has been obtained from cortexone by incubation with *Gibberella baccata* (4), and a 15β-hydroxypregnene has been obtained from the corresponding pregnene derivative with *Spicaria Simplicissima* (5). However, we found that dehydroioandrosterone (DHA) 1a and isoandrosterone (isoA) 2a could not be hydroxylated with *Gibberella Baccata*. It appears that microbiological 15β-hydroxylation may not always be a simple and straightforward general procedure, probably due to different stereospecificities of the involved enzymes. Chemical approaches were therefore examined and the syntheses of 15β-hydroxy-DHA 1b and 15β-hydroxy-isoA 2b are reported in this communication.

Starting from the Δ-15 derivative 3 of DHA a chemical synthesis of 5-androsten-3β,15β, 17β-triol has been described (6) but the corresponding 17-ketone was not prepared. Our first attempt to introduce a 15β-substituant was by treatment of the α,β-unsaturated ketones 3 and Δ-15-isoA with sodium hydroxyde in methanol (7), which afforded 15β-methoxy-DHA 1c and 15β-methoxy isoA 2c. Compound 1c showed m.p. 120-122°, $[\alpha]_D$ = -30° (c=0,4) ; mass spectrum : m/e 318 ; nmr (60 MHz): δ 1,08 (3H,s,Me-19), 1,12 (3H,s,Me-18), 3,30 (3H,s,O-CH_3). Compound 2c exhibited m.p. 151-154° ; $[\alpha]_D$ = +37° (c=1) ; mass spectrum : m/e 320 ; nmr (250 MHz) : δ 0,88 (3H, s,Me-18) ; 1,12 (3H,s,Me-19), 2,28 (1H,q,J16a-16b 18Hz, J16a-15 5Hz, H-16a), 2,65 (1H,q,J16a-16b 18Hz, J16b-15 1Hz, H-16b), 3,28 (3H,s,O-CH_3), 3,61 (1H,m,J14-15 = J16a-15 5Hz, J16b-15 1Hz, H-15). However, it proved difficult to cleave these methyl ethers, and the free hydroxyl analog could not be obtained by this route. The epoxidation of the Δ-15 bond followed by reduction was more successful.

With alkaline hydrogen peroxide in t-butanol (8) compound 3 selectively afforded the 15β, 16β-epoxide 4, in contrast to the 5α, 6α-epoxyde which was formed (6) by action of a peracid.

3β-Hydroxy-15β,16β-oxydo-5-androst-en-17-one 4 had m.p. 111-112° ; $[\alpha]_D$ = -120° (c=1,3) ; mass spectrum : m/e 302 (M^+) ; nmr (250 MHz) : δ 1,18 (3H,s,Me-18), 1,10 (3H,s,Me-19), 3,33 (1H, d,J15-16 2,8Hz, H-16), 3,63 (1H,m,H-3), 3,91 (1H,d,J15-16 2,8Hz,H-15).

3β-Hydroxy-15β,16β-oxidoandrostan-17-one was prepared in the same manner : m.p. 135-137°, $[\alpha]_D$ = -41° (c=1,3) ; mass spectrum : m/e 304 (M^+) ; nmr (60 MHz) : δ 1,15 (3H,s,Me-18), 0,88 (3H,s,Me-19).



1 2 3 4

a R = H, b R = OH, c R = OCH_3

Reduction of 5 and 15β-16β-oxido-isoA by chromous acetate (9) as previously described (10) afforded the desired 15β-hydroxy-compounds 1b and 2b.

3β,15β-Dihydroxy-5-androsten-17-one 1b had m.p. 182-184° ; $|\alpha|_D$ = -28° (c=0,8) ; mass spectrum : m/e 304 (M^+) ; nmr (250 MHz) : δ 1,09 (3H,s,Me-19), 1,21 (3H,s,Me-18), 2,67 (2H,d,H-16), 3,53 (1H,m,H-13), 4,68 (1H,m,J14-15 = J15-16a 4Hz, J15-16b 1,5Hz, H-15), 5,36 (1H,m,H-6), circular dichroim : 296 nm (Δε = + 2,43).

The mnr spectrum confirmed the 15β configuration and the circular dichroism data agreed well with the keto group in the 17-position and an intact C/D trans ring junction. The structure of 1b was also confirmed by sodium borohydride reduction giving known 5-androsten-3β,15β,17β-triol identified by melting point, optical rotation and nmr data (6, 11).

3β,15β-Dihydroxyandrostan-17-one (2b) showed m.p. 223-224° ; $|\alpha|_D$ = 46° (c=0,5) mass spectrum : m/e 306 ; nmr (250 MHz) (diacetoxy compound) : δ 0,9 (3H,s,Me-19), 1,12 (3H,s,Me-18), 4,72 (1H,m,H-3), 5,37 (1H,m,J15-16 4Hz, H-15) ; circular dichroism, 296 nm (Δε = + 2,80).

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(11) NMR spectra were obtained with deuteriochloroform as solvent. Optical rotations were measured in chloroform and dichroic spectra in ethanol. Retention times, GLC (as methylene units) (12) : 3β,15β,17β-trihydroxy-A-5-ene (tri-TMS) : OV-1 : 27,48 ; 15β-hydroxy-DHA (MO-di-TMS) : OV-1 : 27,72 ; 15β-hydroxy-isoA (di-TMS) : OV-1 : 27,62 ; OV-17 : 29,27.

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