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Synthesis of isomeric 5α-androstane-3,15,17β-triols*

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In a paper dealing with the biliary metabolites of testosterone sulphate in the rat, we reported the production of considerable quantities of disulphates of 5α-androstane-3α,17β-diol and polar hydroxylated steroids in the female. Gustafsson and Ingelman-Sundberg recently described the 15β-hydroxylation of the 3,17-disulphates of 5α-androstane-3α,17β-diol and the corresponding 3β-epimer in female rat liver microsomes. These results strongly suggest the occurrence of 15β-hydroxylated steroids in biliary metabolites. As authentic standards, 5α-androstane-3,15,17β-triols were prepared by incubation of 15α- and 15β-hydroxyandrost-4-ene-3,17-dione with rat liver microsomes, and the respective trimethylsilyl ethers were subjected to glc-mass spectrometric analysis. Of the four isomeric 3,15,17β-triols, 5α-androstane-3β,15α,17β-triol (15) has been prepared by Nussim and his co-workers. We now describe the synthesis of 5α-androstane-3α,15β,17β-triol(8), -3β,15β,17β-triol(10), and -3α,15α,17β-triol(13).

The 15β-hydroxy-group has been introduced into the steroid nucleus by nucleophilic addition of a benzyl alcohol to a Δ^{15}-17-oxo steroid, followed by catalytic hydrogenolysis, and 15α-hydroxysteroids have been prepared by hydroboration of Δ^{14}-steroids. We have applied these reactions to the synthesis of the 5α-androstane-3,15,17β-triols.

3α-Acetoxy-16α-bromo-5α-androstan-17-one (1) was acetalised with ethylene glycol; dehydrobromination of the bromo-acetal (2) with potassium *t*-butoxide in refluxing xylene then gave the unexpected 3β-epimerisation product, 3β-hydroxy-5α-androst-15-en-17-one (3) (after hydrolysis of the acetal with toluene-*p*-sulphonic acid). The structure (3) was confirmed by catalytic hydrogenation to give 3β-hydroxy-5α-androstan-17-one (4), identical with an authentic sample. However, mild dehydrobromination of the bromo-acetal (2) with potassium *t*-butoxide in dimethyl sulphoxide at 37°C and subsequent deacetalisation provided a route to 3α-hydroxy-5α-androst-15-en-17-one (5), catalytic hydrogenation of the 15,16-double bond affording 3α-hydroxy-5α-androstan-17-one (6). Base-catalysed addition of benzyl alcohol to the Δ^{15}-3α-ol (5) followed by hydrogenolysis over palladium-charcoal gave 3α,15β-dihydroxy-5α-androstan-17-one (7), which was converted into the 3α,15β,17β-triol (8) with sodium borohydride. Similarly, condensation of the Δ^{15}-3β-ol (3) with benzyl alcohol and hydrogenolysis yielded 3β,15β-dihydroxy-5α-androstan-17-one (9), which was reduced

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with sodium borohydride to the 3β,15β,17β-triol (10).

3α-Hydroxy-5α-androst-14-en-17-one (11), prepared by acid-catalysed epimerisation of the Δ^{15}-3α-ol (5), was reduced with sodium borohydride to give 5α-androst-14-ene-3α,17β-diol (12). Hydroboration followed by oxidation with alkaline hydrogen peroxide then afforded the 3α,15α,17β-triol (3). The 3β,15α,17β-triol (15) was also prepared from 5α-androst-14-ene-3β,17β-diol (14) by the hydroboration method.

The spectral properties of the isomeric 3,15,17β-triols are markedly affected by the configuration of the C-15 hydroxy-group. Molecular rotation analysis indicated that the 15α-ols [(13) and (15)] were more dextrorotatory than the 15β-epimers [(8) and (10)], in accord with other epimeric 15-hydroxy-steroids. The ^{1}H n.m.r. data showed a large downfield shift of the 13-methyl signal of the 15β-ols due to pseudo-1,3-diaxial deshielding by the 15β-hydroxy-group. The mass spectrometric fragmentations provided strong evidence for the configuration of the 15-hydroxy-group. Prominent ions at m/e 107 and 264 are characteristic of 15α-ols, whereas the mass spectra of the 15β-ols are dominated by fragments of m/e 107, 217, and 290. Generally the 15α-hydroxy-group confers greater polarity than does the 15β-hydroxy-group. Tlc showed that the 15β-ols were more mobile than the 15α-ols. Glc of the trimethylsilyl ether derivatives on 0.5% CHDMS (or 1.5% SE-30) gave retention times (relative to 5α-cholestane) of 0.34(0.70), 0.43 (0.71), 0.55 (0.90), and 0.68(0.99) for the 3α,15β,17β-triol (8), the 3α,15α,17β-triol (13), the 3β,15β,17β-triol (10), and the 3β,15α,17β-triol (15), respectively.