Potential Oestrogen Precursors: The Synthesis of 7,19-Disubstituted Androgens

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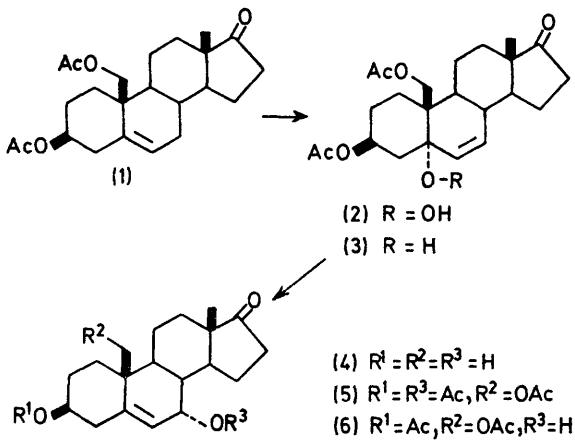
Summary The synthesis of 7α-substituted steroids in good yield by allylic rearrangement of Δ^6-5α-hydroxy-steroids is described.

3β,7α-DIHYDROXYANDROST-5-EN-17-ONE (**4**) can be converted by human and equine placenta into equilin and equilenin.[1] However, there remains considerable doubt as to the

exact sequence of the intermediates involved in the biosynthesis[2] of these oestrogens. For ring B saturated oestrogens such as oestrone, it is known[3] that 19-hydroxy-androgens are obligatory intermediates. It was of interest, therefore, to prepare the corresponding compounds substituted at C-7 and C-19 in order to determine their efficiency in the biosynthesis of ring B unsaturated oestrogens as compared with compounds substituted only at C-7.



Schenk and his co-workers[4] have reported the conversion of cholesterol into cholest-5-ene-3β,7α-diol in reasonable yield by photosensitized oxygenation to give the 5α-hydroperoxide, which, on rearrangement and subsequent reduction, yields exclusively the 7α-hydroxy-compound. By use of Schenk's conditions, we converted 3β,19-diacetoxyandrost-5-en-17-one (**1**) into the 5α-hydroperoxide (**2**), reduction of which gave the 5α-hydroxy-compound (**3**) in an overall yield of 78% based on recovered starting material. However, all attempts to rearrange the 5α-hydroperoxide to the 7α-isomer failed.

Treatment of the 5α-alcohol (**3**) with aqueous acetic acid (1 : 4) at room temperature for 1·5 h gave 3β,7α,19-triacetoxyandrost-5-en-17-one† (**5**) (14%),δ ($CDCl_3$) 0·87 (3H, s, 13-CH_3), 1·99 (9H, s, 3 × OAc), 5·10 (1H, t, 7β-H), 3·90, 4·65 (2H, q, 10-CH_2·OAc, J 12 Hz), and 5·82 p.p.m. (1H, d, 6-H, J 5·0 Hz); $[\alpha]_D$ −99·5° (c 0·28 in $CHCl_3$)]; and 3β,19-diacetoxy-7α-hydroxyandrost-5-en-17-one (**6**) (70%), m.p. 139–140°; $[\alpha]_D$ −94·7° (c 0·49 in $CHCl_3$) δ ($CDCl_3$) 0·89 (3H, s, 13-CH_3), 2·00 (6H, s, 2 × OAc), 3·90 (1H, m, 7β-H), 3·90, 4·60 (2H, q, 10-CH_2·OAc, J 12 Hz), and 5·86 p.p.m. (1H, d, 6-H, J 5·5‡ Hz)]. Although initially it is the 7α-hydroxy- and 7α-acetoxy-compounds that are formed exclusively, prolongation of the reaction under the conditions used for the rearrangement gives the 7β-epimers. Experiments are in progress to determine the mechanism of this allylic rearrangement.

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† Satisfactory analyses were obtained for the compounds reported.

‡ The coupling constants $J_{6,7\alpha}$ and $J_{6,7\beta}$ in Δ^5-7-acetates have been reported[5] to be 4·5 and 9·0 Hz, respectively. These values are greater by a factor of *ca.* 2 than those observed by us for our compounds. On communicating this information to Professor Shoppee, the latter indicated that the values reported in his paper should be halved.