

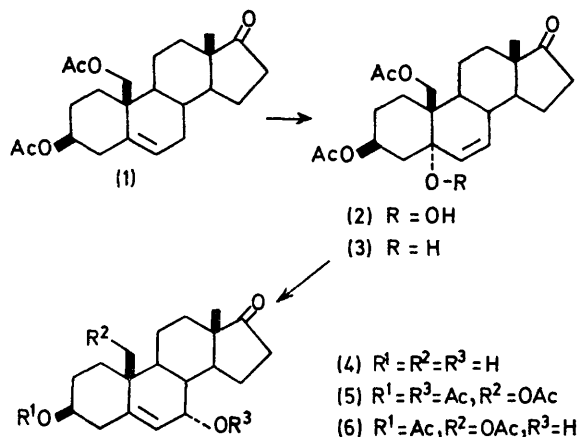
## Potential Oestrogen Precursors: The Synthesis of 7,19-Disubstituted Androgens

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**Summary** The synthesis of  $7\alpha$ -substituted steroids in good yield by allylic rearrangement of  $\Delta^6$ -5 $\alpha$ -hydroxy-steroids is described.  $3\beta,7\alpha$ -DIHYDROXYANDROST-5-EN-17-ONE (4) can be converted by human and equine placenta into equilin and equilenin.<sup>1</sup> However, there remains considerable doubt as to the

exact sequence of the intermediates involved in the biosynthesis<sup>2</sup> of these oestrogens. For ring B saturated oestrogens such as oestrone, it is known<sup>3</sup> 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<sup>4</sup> 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<sub>3</sub>) 0.87 (3H, s, 13-CH<sub>3</sub>), 1.99 (9H, s, 3 × OAc), 5.10 (1H, t, 7β-H), 3.90, 4.65 (2H, q, 10-CH<sub>2</sub>·OAc, J 12 Hz), and 5.82 p.p.m. (1H, d, 6-H, J 5.0 Hz); [α]<sub>D</sub> -99.5° (c 0.28 in CHCl<sub>3</sub>); and 3β,19-diacetoxy-7α-hydroxyandrost-5-en-17-one (6) (70%), m.p. 139–140°; [α]<sub>D</sub> -94.7° (c 0.49 in CHCl<sub>3</sub>) δ (CDCl<sub>3</sub>) 0.89 (3H, s, 13-CH<sub>3</sub>), 2.00 (6H, s, 2 × OAc), 3.90 (1H, m, 7β-H), 3.90, 4.60 (2H, q, 10-CH<sub>2</sub>·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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<sup>1</sup> L. Stárka and H. Breuer, *Biochim. Biophys. Acta*, 1966, **115**, 306; *Z. physiol. Chem.*, 1966, **344**, 124.

<sup>2</sup> For a review of the biosynthesis of oestrogens see P. Morand and J. Lyall, *Chem. Rev.*, 1968, **68**, 85.

<sup>3</sup> J. E. Longchamp, C. Gual, M. Ehrenstein, and R. I. Dorfman, *Endocrinol.*, 1960, **66**, 416; R. B. Wilcox and L. L. Engle, *Steroids, Suppl. I*, 1965, 49.

<sup>4</sup> G. O. Schenk, O. A. Neumüller, and W. Eisfeld, *Annalen*, 1958, **618**, 202.

<sup>5</sup> C. W. Shoppee and B. C. Newman, *J. Chem. Soc. (C)*, 1968, 981.

† Satisfactory analyses were obtained for the compounds reported.

‡ The coupling constants  $J_{6,7\alpha}$  and  $J_{6,7\beta}$  in Δ<sup>5</sup>-7-acetates have been reported<sup>5</sup> 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.