A New Synthesis of 19-Nor Steroids *via* 2,4-Dibromoestrogens

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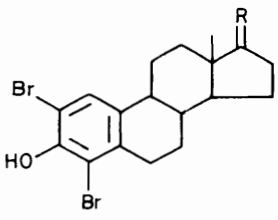
19-Nor steroids (**7**) and (**8**) have been synthesised *via* oxidation of 2,4-dibromoestrogens (**1**) and (**2**) with nitric acid followed by hydrogenation over palladium-on-charcoal and subsequent treatment with Nafion-H.

19-Nor steroids, of considerable importance owing to their biological activity, have traditionally been prepared by the Birch reduction of estradiol derivative.[1] While this method is useful, it has some limitations.[1] Lupon *et al.*[2] recently reported a short synthesis of 19-nor steroids using the photo-oxygenation of estrogens as the key reaction.

Recently, we[3] reported the use of 2,4-dihalogeno-estrogens for the synthesis of the major metabolites of estrogens, the 2- and 16α-hydroxy derivatives. In conjunction with our investigation of the utility of the 2,4-halogeno compounds, we have developed a new application of the 2,4-dibromides for the synthesis of 19-nor steroids. Our alternative procedure involves the oxidation of the 2,4-dibromide with HNO_3 and a subsequent hydrogenation followed by treatment with a superacidic, perfluorinated resin–sulphonic acid (Nafion-H).

Reaction of 2,4-dibromoestrogens (**1**) and (**2**) with 70% HNO_3 [2.5 mol. equiv., AcOH–$CHCl_3$ for (**1**) or AcOH for (**2**), room temperature, 2 h] gave the 2,4-dibromo-10β-hydroxy-1,4-dien-3-one derivatives (**3**) (90%) {m.p. 230—232 °C; [α] +53° (*c* 1.13 in $CHCl_3$–MeOH, 9 : 1, v/v); ^{1}H n.m.r. δ ($CDCl_3$) 0.99 (3H, s, Me-18) and 7.64 (1H, s, 1-H); $\nu_{max.}$ (KBr) 1736 and 1653 cm^{-1}; $\lambda_{max.}$ (EtOH) 265 nm (ε 10 800)} and (**4**) (96%) {m.p. 221—224 °C (decomp.); [α] +54° (*c* 1.0 in $CHCl_3$–MeOH, 9 : 1, v/v); ^{1}H n.m.r. δ ($CDCl_3$) 0.89 (3H, s, Me-18), 3.67 (1H, t, *J* 8 Hz, 17α-H), and 7.67 (1H, s, 1-H); $\nu_{max.}$ (KBr) 3250—3500 and 1653 cm^{-1}; $\lambda_{max.}$ (EtOH) 266 nm (ε 10 600)}, respectively. The stereochemistry at C-10 was established on the basis of previous results for the reaction of estrogens with lead(IV) acetate[4] or thallium(III) trifluoroacetate.[5] Compounds (**3**) and (**4**) were catalytically hydrogenated over palladium-on-charcoal in EtOH containing 5% of pyridine until absorption of hydrogen (*ca.* 4 mol. equiv.) stopped, giving the corresponding debrominated tetrahydro derivatives (**5**) (92%) [m.p. 190—192 °C; ^{1}H n.m.r. δ ($CDCl_3$) 0.93 (3H, s, Me-18); $\nu_{max.}$ (KBr) 3520, 1741, and 1713 cm^{-1}] and (**6**) (95%) [semi-solid; ^{1}H n.m.r. δ ($CDCl_3$) 0.81 (3H, s, Me-18) and 3.67 (1H, t, *J* 8 Hz, 17α-H); $\nu_{max.}$ (KBr) 3400 and 1704 cm^{-1}] along with small amounts (*ca.* 5%) of the corresponding primary estrogens (estrone and estradiol). Considering the stereochemistry of the catalytic



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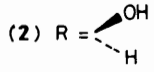
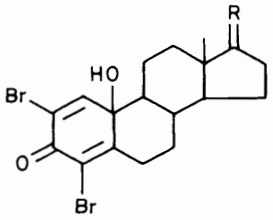
(2) R = 



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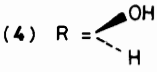
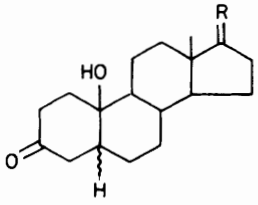
(4) R = 



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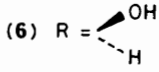
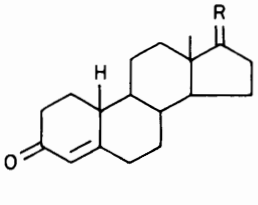
(6) R = 



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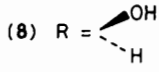
(8) R = 

hydrogenation,[6] compounds (**5**) and (**6**) would be a mixture of the 5α- and 5β-reduced products. The saturated derivatives (**5**) and (**6**) were then converted into the 19-nor steroids (**7**) (65%) [m.p. 170—173 °C (lit.[7] 171 °C); ^{1}H n.m.r. δ ($CDCl_3$) 0.93 (3H, s, Me-18) and 5.82 (1H, br.s, 4-H); $\nu_{max.}$ 1730 and 1680 cm^{-1}] and (**8**) (61%) [m.p. 122—123 °C (lit.[2] 114—115 °C); ^{1}H n.m.r. δ ($CDCl_3$) 0.82 (3H, s, Me-18), 3.70 (1H, t, *J* 8 Hz, 17α-H), and 5.85 (1H, br.s, 4-H); $\nu_{max.}$ 3400 and 1660 cm^{-1}] by treatment with Nafion-H[8] ($CHCl_3$, reflux with stirring, 24 h). The products (**7**) and (**8**) were identical with the corresponding authentic samples in every respect. In this sequence, the 19-nor steroids (**7**) and (**8**) were each obtained in *ca.* 50% yield from estrone and estradiol, respectively, without isolation of the intermediates.

In addition to easier handling, the obvious advantages of this sequence are that it takes place in higher yield and avoids the use of poisonous lead or thallium reagents.

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