

New Approach to the Aromatization of Ring B in 19-Norsteroids and to the Synthesis of Equilenin-type Compounds

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Summary When 7α -acetoxy-3,3:17,17-bis(ethylenedioxy)-5,10-epoxy- 5β ,10 β -oestrane-6-one (**2**), formed by lead tetra-acetate acetoxylation of the parent compound (**1**), is heated with alkali, it undergoes ring B aromatization to give 3,3:17,17-bis(ethylenedioxy)-5(10),6,8-oestratriene-6,7-diol (**3**), without configurational change

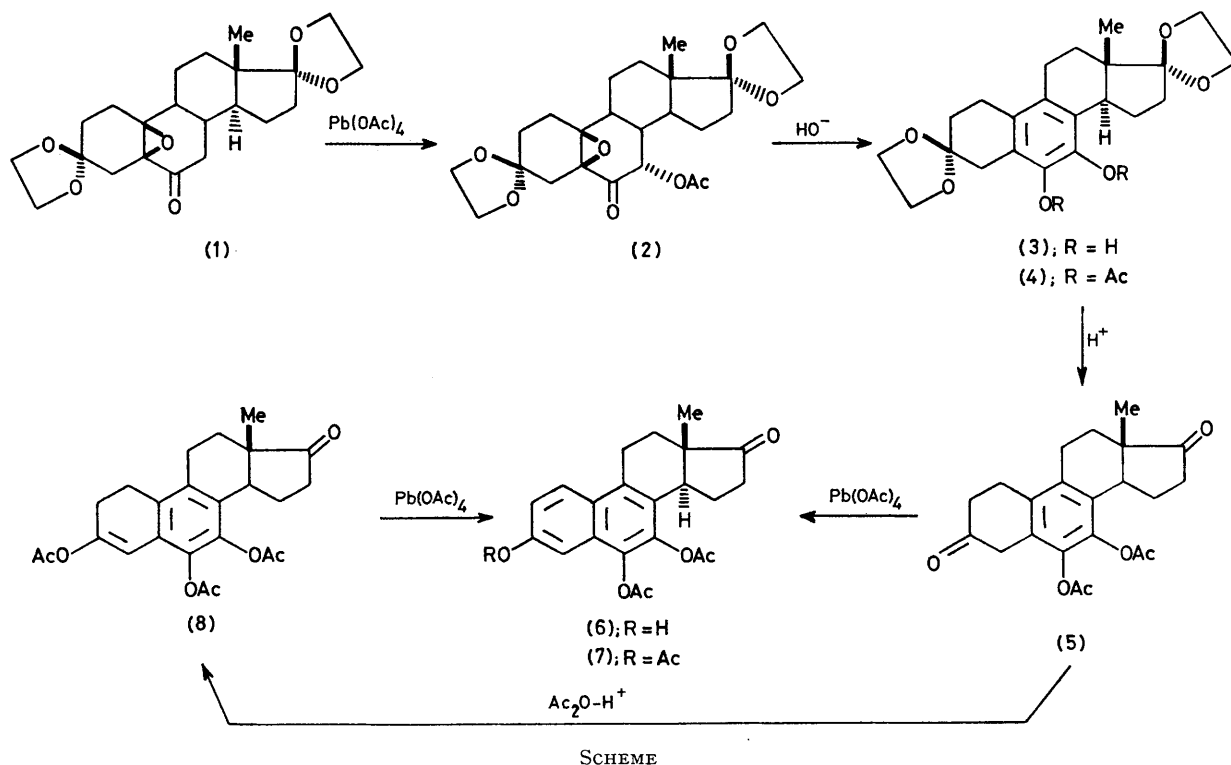
at C(14); deacetalization of the corresponding diacetate (**4**), followed by lead tetra-acetate aromatization of ring A in the resulting diketone (**5**), produces 6,7-diacetoxy-equilenin (**6**), which is finally converted into its 3-acetate (**7**).

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THE aromatization of ring B in 19-norsteroids has been achieved, so far, by methods (involving dehydrogenation and/or elimination) requiring the substrate to be aromatic in ring A^{1,2} or (in one case) to contain a 3,5-diene system,² so that the products obtained were always aromatic in both rings A and B. Here we describe a different, new approach to aromatization of ring B alone, starting from non-aromatic and non-olefinic 19-norsteroid compounds. The procedure used is based on the lead tetra-acetate α' -acetoxylation of α,β -epoxy ketones followed by *O*-acetyl and epoxide oxygen elimination, reactions which have been successfully applied for the preparation of steroidal 1,4-dien-2-ol-3-ones³ and the aromatization of ring A in 19-nortestosterone.⁴

5(10),6,8-oestratriene-6,7-diol (**3**), m.p. 195 °C, $[\alpha]_D -48^\circ$, was obtained in 80% yield. Acetylation of (**3**) to the corresponding diacetate (**4**) (92% yield), m.p. 113 °C, $[\alpha]_D -36^\circ$, followed by bis-deacetalization (effected by heating in 85% acetic acid at 100 °C for 2 h) afforded *ca.* 76% of 6,7-diacetoxy-5(10),6,8-oestratriene-3,17-dione (**5**), m.p. 220 °C, $[\alpha]_D +25^\circ$.

When the diketone (**5**) was treated, under nitrogen, with 1.35 mol equiv. of lead tetra-acetate in glacial acetic acid at 80 °C for 2 h, it readily underwent aromatization of ring A to give 6,7-diacetoxyequilenin (**6**), m.p. 270–274 °C, $[\alpha]_D +41^\circ$ (MeOH) which, upon acetylation, afforded 3,6,7-triacetoxyoestra-1,3,5(10),6,8-pentaen-17-one (**7**), m.p. 212–214 °C, $[\alpha]_D +35^\circ$, in 50% yield [based on (**5**)].§



SCHEME

Thus, when the readily accessible 3,3:17,17-bis(ethylenedioxy)-5,10-epoxy-5 β ,10 β -oestrane-6-one (**1**), m.p. 140–141 °C, $[\alpha]_D -93^\circ$,⁵ was treated with an excess of lead tetra-acetate (4 mol equiv.) in the presence of calcium carbonate in refluxing benzene for a prolonged period (*ca.* 12 days), it underwent acetoxylation to give the 7 α -acetoxy derivative (**2**), m.p. 126 °C, $[\alpha]_D -159^\circ$, in 50–60% yield (Scheme).[†] When a solution of this product in 1% methanolic potassium hydroxide was heated to reflux for 1 h under nitrogen, the desired transformation resulting in ring B aromatization took place and, upon column chromatography on silica gel, 3,3:17,17-bis(ethylenedioxy)-

Aromatization of ring A could also be achieved by conversion of the diketone (**5**) into its 3-enol acetate (**8**), m.p. 195–197 °C, $[\alpha]_D +27^\circ$, followed by lead tetra-acetate dehydrogenation, but in that case the yield of (**7**) was considerably lower (*ca.* 15%).

It should be emphasized that in the course of the aromatization of ring B the configuration at C(14) remained unchanged (according to the ¹H and, particularly, ¹³C n.m.r. spectra), so that the synthetic sequence described above leads exclusively to normal equilenin-type compounds.

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[†] All yields refer to recrystallized (from diethyl ether–light petroleum or acetone–light petroleum) and analytically pure compounds (**2**)–(**8**). The yields of products isolated and purified only by column chromatography (and which could be used, in most cases, directly for further work) were *ca.* 10–15% higher. All new compounds gave elemental analyses and i.r., u.v., ¹H and ¹³C n.m.r., and mass spectra in accord with the structures proposed. Optical rotations are for CHCl₃ solutions unless stated otherwise.

[§] The triacetate (**7**) is a weak oestrogen. When administered subcutaneously in the Bülbring-Burn test (E. Bülbring and J. H. Burn, *J. Physiol.*, 1935, **85**, 320) its activity was *ca.* 1/1000 that of oestradiol.

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