# A Convenient Synthesis of 4-Hydroxyoestradiol Triacetate [Oestra-1,3,5(10)-triene-3,4,17β-triol Triacetate]

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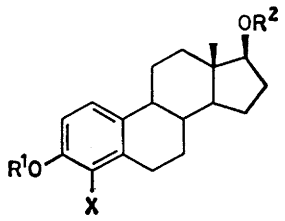
4-Hydroxyoestradiol triacetate is easily prepared from the 4-acetoxymercurio derivative of oestradiol by using lead tetra-acetate in a metal–metal exchange reaction to introduce the oxygen substituent at C-4.

The biological importance of the catechol oestrogens (2-and 4-hydroxy-oestrogens) is becoming increasingly evident.[1] We describe a new, efficient, and simple method for introducing a hydroxy-group into oestrogens, in the present example specifically at C-4. This route offers advantages over published procedures which are either long and low yielding[2] or involve oxidation–reduction steps[3] which we wished to avoid.

The aromatic A ring of oestrogens has been reported to be mercurated under mild conditions to give either the 2-[4] or 4-[5] acetoxy-mercurio-oestradiol derivatives, apparently depending upon whether the 3-methyl ether or the free phenol, respectively, is used.

We have found that by catalysing the mercuration of oestradiol, by $Hg(OAc)_2$ in acetic acid, with perchloric acid an




(1)

**a**; $R^1 = R^2 = Ac$; X = OAc
**b**; $R^1 = R^2 = H$; X = HgOAc
**c**; $R^1 = R^2 = Ac$; X = HgOAc
**d**; $R^1 = R^2 = Ac$; X = H

improved yield (>90%) of nearly pure (n.m.r.) 4-acetoxymercurio-oestradiol (**1b**) would precipitate out of solution in two crops. Acetylation ($Ac_2O$–pyridine) then afforded the corresponding 4-acetoxymercurio-oestradiol diacetate (**1c**), m.p. 198—200 °C, n.m.r. ($CDCl_3$) δ 0.81 (s, 13-Me), 2.04 and 2.08 (s,s, HgOAc and 17-OAc), 2.32 (s,3-OAc), 4.65 (m, 17α-H), and 6.94 and 7.26 (ABq, *J* 10 Hz, 1-H and 2-H).

Treatment of (**1c**) with lead tetra-acetate (2 equiv.) in trifluoroacetic acid for 15 h, according to the method of Kalman and co-workers,[6] produced the corresponding 4-trifluoroacetate, which was not isolated but was hydrolysed during an aqueous-acidic work-up. The crude product was acetylated ($Ac_2O$–pyridine) and purified by preparative h.p.l.c. to give 4-hydroxyoestradiol triacetate (**1a**) [48% from (**1c**)], m.p. 192—196 °C, n.m.r. ($CDCl_3$) δ 0.81 (s, 13-Me), 2.05 (s, 17-OAc), 2.26 and 2.29 (s,s, 3- and 4-OAc), 4.7 (m, 17α-H), and 6.94 and 7.18 (ABq, *J* 10 Hz, 1-H and 2-H). A less polar fraction afforded oestradiol diacetate (**1d**) [25% from (**1c**)], m.p. 122—125 °C (lit.,[7] 127—129 °C), arising from some protonolysis of the mercurio-acetate.

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