

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

David N. Kirk\* and Christopher J. Slade

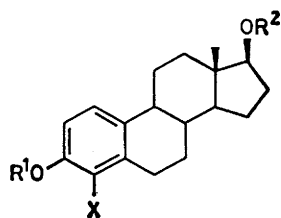
*Medical Research Council Steroid Reference Collection, Chemistry Department, Westfield College, Hampstead, London NW3 7ST, U.K.*

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.<sup>1</sup> 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<sup>2</sup> or involve oxidation-reduction steps<sup>3</sup> 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-<sup>4</sup> or 4-<sup>5</sup> 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)<sub>2</sub> in acetic acid, with perchloric acid an



(1)

a; R <sup>1</sup> = R <sup>2</sup> = Ac;	X = OAc
b; R <sup>1</sup> = R <sup>2</sup> = H;	X = HgOAc
c; R <sup>1</sup> = R <sup>2</sup> = Ac;	X = HgOAc
d; R <sup>1</sup> = R <sup>2</sup> = 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<sub>2</sub>O-pyridine) then afforded the corresponding 4-acetoxymercurio-oestradiol diacetate (**1c**), m.p. 198–200 °C, n.m.r. (CDCl<sub>3</sub>) 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,<sup>6</sup> produced the corresponding 4-

trifluoroacetate, which was not isolated but was hydrolysed during an aqueous-acidic work-up. The crude product was acetylated (Ac<sub>2</sub>O-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<sub>3</sub>) 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.,<sup>7</sup> 127–129 °C), arising from some protonolysis of the mercurio-acetate.

Received, 11th March 1982; Com. 285

## References

- 1 P. Ball and R. Knuppen, *Acta Endocrinologica*, Supplement 232, 1980, **93**, 1.
- 2 J. Fishman, *J. Am. Chem. Soc.*, 1958, **80**, 1213.
- 3 G. Stubenrauch and R. Knuppen, *Steroids*, 1976, **28**, 733.
- 4 E. Santaniello and P. Ferraboschi, *J. Chem. Soc., Chem. Commun.*, 1981, 217.
- 5 C. C. Chin and J. C. Warren, *J. Biol. Chem.*, 1968, **243**, 5056.
- 6 J. R. Kalman, J. T. Pinhey, and S. Sternhell, *Tetrahedron Lett.*, 1972, 5369.
- 7 C. Djerassi, G. Rosenkranz, J. Romo, S. Kaufman, and J. Pataki, *J. Am. Chem. Soc.*, 1950, **72**, 4534.