Efficient Synthesis of Estriol 16-Glucuronide *via* 2,4,16α-Tribromoestrone

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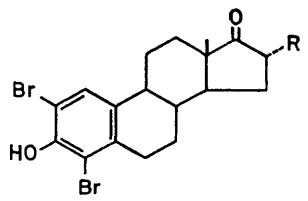
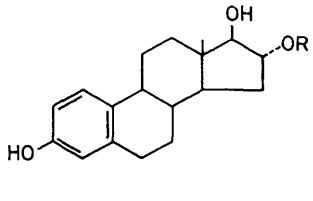
Summary A novel synthesis of estriol 16-glucuronide, a major estrogen involved in human pregnancy, has been accomplished using the controlled stereospecific alkaline hydrolysis of 2,4,16α-tribromoestrone and the selective glucuronidation of its hydrolysed product as key reactions.

THE considerable current clinical interest in the correlation of estriol 16-glucuronide concentration during pregnancy with foetal maturity has led to a number of approaches to its determination.[1] However, estriol 16-glucuronide is not readily available, primarily because of the difficulty involved in its synthesis. Previously reported methods[2] produce low yields, require many steps, or result in the formation of isomeric products (16- and 17-glucuronides) and are therefore not suitable as preparative procedures. We utilized the recently discovered stereospecific alkaline hydrolysis of androgen 16-bromoketones[3] and report here an efficient synthesis of estriol 16-glucuronide from estrone with a high overall yield.

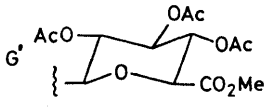
Bromination of estrone with a large excess of $CuBr_2$ (11 equiv., dry MeOH, reflux, 48 h) gave stereospecifically 2,4,16α-tribromoestrone (**1**) (85%) [m.p. 191—193 °C; ^{1}H n.m.r. δ ($CDCl_3$) 0·93 (3 H, s, 3 × 18-H), 4·58 (1H, m, 16β-H), and 7·40 (1 H, s, 1-H); ν_{max} (KBr) 1740 cm^{-1}] together with 2,4,16,16-tetrabromoestrone (5%). The tribromide (**1**) was subjected to controlled alkaline hydrolysis[3] (2·5 equiv. NaOH, 75% aq. pyridine, room temperature, 3 h) to give

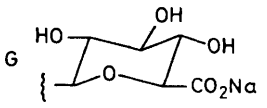


(1); R = Br
(2); R = OH
(3); R = OG'



(4); R = G'
(5); R = G





2,4-dibromo-16α-hydroxyestrone (**2**) (97%) [m.p. 205—206 °C; ^{1}H n.m.r. δ ($CDCl_3$) 0·97 (3 H, s, 3 × 18-H), 4·40 (1 H, m, 16β-H), and 7·36 (1 H, s, 1-H); ν_{max} (KBr) 1728 cm^{-1}]. The bromo-compounds (**1**) and (**2**) were readily isolated in a pure form by crystallization from acetone in very high yields.†

Treatment of the dibromo-derivative (**2**) with methyl 1-bromo-1-deoxy-2,3,4-tri-*O*-acetyl-α-D-glucopyranosuronate (6 equiv.) and Ag_2CO_3 (10 equiv.) (dry benzene, room temperature, 72 h) gave the 2,4-dibromo-16α-hydroxyestrone 16α-glucuronide triacetate methyl ester (**3**) (85%) as the sole product [m.p. 250 °C; ^{1}H n.m.r. δ ($CDCl_3$) 0·92 (3 H, s, 3 × 18-H), 2·02 and 2·07 (9 H, s, 3 × COMe), 4·51 (1 H, d, *J* 7 Hz, pyranose-1-H), and 7·36 (1 H, s, 1-H); ν_{max} (KBr) 1730—1750 cm^{-1}]. Reduction of the 17-carbonyl group and removal of the 2- and 4-bromine atoms of (**3**) were achieved simultaneously with $NaBH_4$ (7 equiv.) in the presence of 4 equiv. of $PdCl_2$[4] (MeOH, 0 °C, 30 min) to yield quantitatively the estriol 16-glucuronide acetate methyl ester (**4**), m.p. 229—231 °C (decomp.) [lit.[2b] m.p. 228—229 °C (decomp.)]. Finally, compound (**4**) was converted into estriol 16-glucuronide sodium salt (**5**), m.p. 246—250 °C (decomp.) (lit.[2a] m.p. 246—249 °C), in the usual manner in good yield. Amberlite XAD-2 resin was effective in isolating (**5**) in a pure form.‡ The glucuronide (**5**) was identical with an authentic sample in every respect.

In addition to its simplicity and high yield, this synthesis offers the advantage of permitting the regio- and stereospecific introduction of hydrogen isotopes at the 2,4,16β, and 17α positions[3,4] by choosing appropriately labelled reagents and solvents in the controlled alkaline hydrolysis and the reductive removal of bromine steps.

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† The brominated residue of estrone was triturated with ether to give the crude tribromide (**1**) which was recrystallized to give the pure compound.

‡ The mixtures obtained from the hydrolysis of the glucuronide acetate methyl ester (**4**) (1·0 g) were diluted with water and passed through a column of Amberlite XAD-2 (4 × 100 cm). After washing with water, the adsorbed glucuronide (**5**) was eluted with 50% aqueous methanol.

[1] For example: M. Numazawa, T. Tanaka, and T. Nambara, *Clin. Chim. Acta*, 1979, **91**, 169; J. Sugar, C. Dessy, S. Allexander, J.-J. Amy, F. Rodesch, and J. Schwers, *J. Clin. Endocrinol. Metab.*, 1980, **50**, 137 and references cited therein.
[2] (a) J. S. Elce, J. G. D. Carpenter, and A. E. Kellie, *J. Chem. Soc. C*, 1967, 542; (b) T. Nambara and K. Imai, *Chem. Pharm. Bull.*, 1967, **15**, 1323; (c) T. Nambara, T. Kawarada, K. Shibata, and T. Abe, *ibid.*, 1972, **20**, 1988.
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[4] M. Numazawa, N. Soeda, S. Moro, and T. Nambara, *Biochem. Pharmacol.*, 1977, **26**, 769.