Efficient Synthesis of 2-Methoxy- and 4-Methoxy-estrogens

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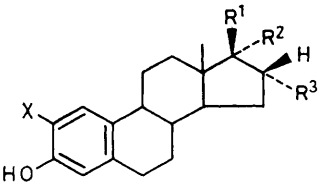
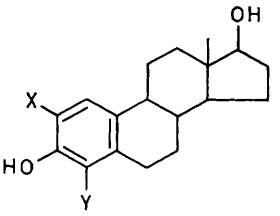
2-Methoxy- and 4-methoxy-estrogens are easily prepared from the corresponding 2-iodo or 4-bromo derivatives in high yields by a halogen–methoxy group exchange reaction using sodium methoxide–copper(II) chloride.

The physiological significance of catechol estrogens, a group of major estrogen metabolites formed by aromatic hydroxylation of primary estrogens at either the C-2 or C-4 position, is now well documented.[1] Catechol estrogens are further metab-



(1) R^1 = OH, R^2 = R^3 = H, X = H
(2) R^1 = OH, R^2 = R^3 = H, X = Br
(3) R^1 = OH, R^2 = R^3 = H, X = I
(4) R^1 = OH, R^2 = R^3 = H, X = OMe
(5) R^1, R^2 = O, R^3 = H, X = I
(6) R^1, R^2 = O, R^3 = H, X = OMe
(7) R^1 = R^3 = OH, R^2 = H, X = I
(8) R^1 = R^3 = OH, R^2 = H, X = OMe



(9) X = Y = Br
(10) X = H, Y = Br
(11) X = H, Y = OMe

olized to their monomethyl ethers, in which 2-methylation[1a,b] or 4-methylation[2] generally predominates. The biological activity of the 2-methyl ethers is becoming increasingly evident.[3]

A practical synthesis of 2-methoxy-estrogens was first reported by Fishman.[4] Since then many synthetic procedures have been reported for the 2-methoxy[5] and 4-methoxy[5a,6] derivatives, the most interesting of which[5d] involves a direct conversion of 2-bromoestradiol (**2**) into the corresponding methoxy derivative (**4**); this procedure, however, requires a long reaction time (22 h), and the yield is not satisfactory (50%). We now describe a new, efficient, and simple method for introducing a methoxy group at C-2 and C-4 of estrogens *via* the corresponding 2-iodo-[7] or 4-bromo-estrogens, which can be obtained regioselectively in high yields.

When 2,4-dibromoestradiol (**9**) was catalytically hydrogenated over 5% palladium-on-charcoal (EtOH, 1 atm, room temp.) until absorption of hydrogen (*ca.* 1 equiv.) stopped, selective debromination occurred at the C-2 position to give 4-bromoestradiol (**10**)[8] (80%).

Treatment[5d] of 2-iodoestradiol (**3**) with NaOMe (10 mol. equiv.) in MeOH–dimethylformamide (DMF) in the presence of CuI (0.33 mol. equiv.) unexpectedly gave the reductively dehalogenated product, estradiol (50%), along with the desired 2-methoxy compound (**4**) (3%). When the iodide (**3**) was submitted to the same reaction using $CuCl_2$[9] instead of CuI, however, the methoxyestrogen (**4**) [m.p. 188—189 °C (lit.[4] 188—190 °C); ^{1}H n.m.r. δ ($CDCl_3$–CD_3OD) 0.80 (3H, s, 3 × 18-H), 3.87 (3H, s, 2-OCH_3), 6.64 (1H, s, 4-H), and 6.80 (1H, s, 1-H)] was quantitatively obtained after only brief treatment (5 min). Other 2-iodo compounds (**5**) and (**7**) were also converted into the corresponding methoxyestrogen (**6**) (30%) [m.p. 185—187 °C (lit.[4] 188—191 °C), ^{1}H n.m.r. δ ($CDCl_3$) 0.90 (3H, s, 3 × 18-H), 3.83 (3H, s, 2-OCH_3), 6.62 (1H, s, 4-H), and 6.75 (1H, s, 1-H)] and (**8**) (45%) [m.p. 212—214 °C (lit.[5b] 211—214 °C), ^{1}H n.m.r. δ ($CDCl_3$–CD_3OD) 0.74 (3H, s, 3 × 18-H), 3.79 (3H, s, 2-OCH_3), 6.54 (1H, s, 4-H), and 6.70 (1H, s, 1-H)] using the same reaction (Table 1). Furthermore, the yield of the methoxyestrogen (**6**) (only) was much improved (65%) when pyridine was used as a solvent (Table 1).

Table 1. Conversion of halogeno into methoxy compounds.[a]

Substrate	Conditions: Solvent	Conditions: *t*/min	Product (isolated yield, %)
(**3**)	DMF	5	(**4**) (95)[b]
(**3**)	Pyridine	20	(**4**) (1.3)[c]
(**5**)	DMF	15	(**6**) (30)[c]
(**5**)	Pyridine	30	(**6**) (65)[b]
(**7**)	DMF	10	(**8**) (44)[b]
(**7**)	Pyridine	15	(**8**) (20)[c]
(**10**)	DMF	75	(**11**) (75)[b]

[a] Substrate (1 mmol) was dissolved in 4 ml of solvent. To this solution were added 2.0 ml of a 5.1 M solution of NaOMe in MeOH and $CuCl_2$ (0.33 mmol) and the reaction mixture was refluxed under an N_2 atmosphere. [b] The crude product obtained after the usual work-up was crystallized to give a pure product. [c] The product was purified by column chromatography.

When 4-bromoestradiol (**10**) was treated similarly with NaOMe in DMF, the corresponding 4-methoxyestradiol (**11**) [m.p. 166—168 °C (lit.[6] 167—169 °C), ^{1}H n.m.r. δ ($CDCl_3$–CD_3OD) 0.75 (3H, s, 3 × 18-H), 3.78 (3H, s, 4-OCH_3), 6.73 (1H, d, *J* 9 Hz, 2-H), and 6.98 (1H, d, *J* 9 Hz, 1-H)] was obtained in 75% yield.

In addition to its simplicity and the high yields obtained, the obvious advantages of this sequence are that substrates, 2-iodo- or 4-bromo-estrogens, can be obtained regioselectively in high yields and that catechol estrogens can be synthesized from primary estrogens in a relatively short step through the demethylation[5b] of the 2- or 4-methoxy derivatives.†

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† In a recent report (X. U-Z. Zheng, W. L. Wang, Z.-Z. Zhong, Z.-B. Xu, and H.-M. Zhao, *Steroids*, 1982, **40**, 121) 2,4-dibromoestradiol (**9**) was converted into the 2,4-dimethoxy analogue using NaOMe–CuI–benzo-15-crown-5–DMF in 40% yield. It is interesting to speculate on the results when using a crown ether in the reactions described in the present communication.