A Novel, Two-Step Synthesis of 2-Methoxyestradiol

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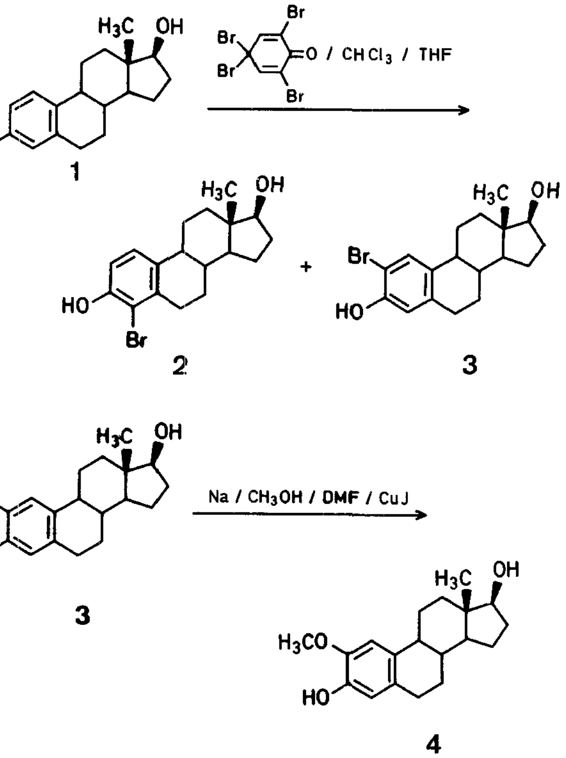
Since the initial demonstration by Kraychy and Gallagher[1] that 2-methoxyestrone was a normal metabolite of estradiol, a number of investigators subsequently have demonstrated the presence of other 2-methoxyestrogens as metabolites in the urine. A practical synthesis of 2-methoxyestradiol and 2-methoxyestrone by Fishman[2] helped greatly in positive identification of these metabolites. Since then many new synthetic procedures have been reported for 2-hydroxy- and 2-methoxyestrogens[3-14]. Estrogen metabolism studies in our laboratories and elsewhere require a regular supply of 2-methoxyestrogens for reverse isotope-dilution procedure.

We now present a novel two step synthesis of 2-methoxyestradiol (4) from estradiol (1).



Estradiol (1) was brominated[15] with 2,4,4,6-tetrabromocyclohexa-2,5-dienone[16] to give a mixture of 2-bromo- and 4-bromoestradiol derivatives. Fractional crystallization of the mixture readily separated both 4-bromoestradiol (2) and 2-bromoestradiol (3). Treatment of 2-bromoestradiol (3) with sodium methoxide in methanol/dimethylformamide in the presence of copper(I) iodide[17] led to 2-methoxyestradiol (4).

2-Bromo-3,17β-dihydroxyestra-1,3,5(10)-triene (3):
To a solution of estradiol (1; 6.5 g) in a mixture of chloroform (320 ml) and tetrahydrofuran (100 ml), 2,4,4,6-tetrabromocyclohexa-2,5-dienone (10.6 g) dissolved in a mixture of chloroform (250 ml) and tetrahydrofuran (100 ml) was added dropwise over an 80 minute period while the contents stirred at 0°. After the addition was complete the reaction mixture was removed from the ice bath and an additional 30 minutes stirring completed the reaction. The mixture was then washed with 10% sodium thiosulfate, water, and brine, dried over sodium sulfate, and the

solvent evaporated. Treatment of the reaction product with ethanol (37 ml) precipitated 4-bromoestradiol (**2**) which was recrystallized from ethanol; yield: 2.75 g (40%); m.p. 211–212°; Lit.[15] m.p. 215–216.5°.

$C_{18}H_{23}BrO_2$	calc.	C 61.54	H 6.60
(351.3)	found	61.74	6.60

I.R. (KBr): ν_{max} = 3585, 3520, 3230, 1600, 1560 cm^{-1}.

^{1}H-N.M.R. [$(CD_3)_2CO/CD_3OD$ (1:1)]: δ = 0.77 (s, $\underline{H}_3C$—C-18), 6.81 (d, H—C-2, J = 9 Hz), 7.22 ppm (d, H—C-1, J = 9 Hz).

From the mother liquor the 2-bromoestradiol (**3**) was separated and crystallized from acetone/hexane; yield: 1.65 g (24%); m.p. 195.5–197.5°; Lit.[15] m.p. 195–196.5°.

$C_{18}H_{23}BrO_2$	calc.	C 61.54	H 6.60
(351.3)	found	61.88	6.59

I.R. (KBr): ν_{max} = 3600, 3580, 3260, 1605, 1560 cm^{-1}.

^{1}H-N.M.R. [$(CD_3)_2CO/CD_3OD$ (1:1)]: δ = 0.77 (s, H_3C—C-18), 6.71 (s, H—C-4), 7.38 ppm (s, H—C-1).

2-Methoxy-3,17β-dihydroxyestra-1,3,5(10)-triene (4):
Sodium (1.6 g) was dissolved in methanol (40 ml) and the cooled solution diluted with dimethylformamide (40 ml). Copper(I) iodide (250 mg) and 2-bromoestradiol (**3**; 2.6 g) were added and stirred under reflux. At the end of 22 h, an additional amount of copper(I) iodide (250 mg) was added and stirring continued for two more hours. The reaction mixture was cooled, the solvent evaporated, diluted with water, and acidified with hydrochloric acid. The reaction product was isolated with ethyl acetate. The ethyl acetate extract was washed with water, brine, dried over sodium sulfate, and the solvent evaporated. The residue so obtained was converted to the diacetate with acetic anhydride (7 ml) and pyridine (20 ml) and purified as the diacetate. Hydrolysis of the diacetate with potassium carbonate in methanol and crystallization from methanol gave 2-methoxyestradiol (**4**); yield: 1.0 g. The mother liquor was purified on a dry silica gel column[18] (2.5 × 62 cm) employing dichloromethane/ether (9:1) as the developing solvent. The column, between 18.5–34 cm from the origin, was cut and eluted with ethyl acetate, and the solid crystallized from methanol to give an additional amount of product; total yield: 1.23 g (55%); m.p. 183–185°; Lit.[2] m.p. 188–190°.

I.R. (KBr): ν_{max} = 3420, 3190, 1605 cm^{-1}.

^{1}H-N.M.R. ($CDCl_3$): δ = 0.78 (s, $\underline{H}_3C$—C-18), 3.87 (s, H_3CO—C-2), 6.65 (s, H—C-1 or H—C-4), 6.8 ppm (s, H—C-4 or H—C-1).

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