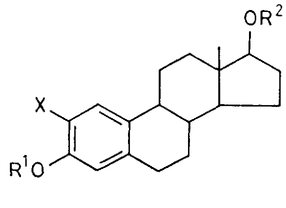
New Routes for the Synthesis of Estra-1,3,5(10)-triene-2,3,17β-triols-(Catechol Estrogens)

Enzo Santaniello,*[a] Alberto Fiecchi,[a] and Patrizia Ferraboschi[b]

[a] *Istituto di Chimica, Facoltà di Medicina, Università di Milano, Via Saldini, 50 I–20133 Milano, Italy*
[b] *Istituto di Endocrinologia, Facoltà di Farmacia, Università di Milano, Via A. Del Sarto, 21 I–20133 Milano, Italy*

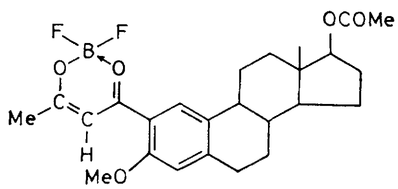
2,3,17β-Triacetoxyestra-1,3,5(10)-triene has been prepared in good yields either from 2-chloromercurio-3-methoxy-17β-acetoxyestra-1,3,5(10)-triene by a novel hydroboration–oxidation route or by oxidation of a previously unknown 2-organoboron substituted estradiol.

It is now well established that 2- and 4-hydroxyestrogens play a most important role in the oxidative metabolism of estrogens in man.[1] We have already reported the regioselective mercuriation at C-2 of 3-methoxy-17β-acetoxyestra-1,3,5(10)-triene (**1a**), which affords the 2-chloromercurio-derivative (**1b**) in 80% yield.[2] Direct replacement of the mercuriated function by a hydroxy-group proved unsuccessful in contrast with the successful oxygen substitution at C-4 in the 4-acetoxymercurio-analogue.[3] We therefore considered the reaction of (**1b**) with diborane and oxidation



(1)

a; X = H, R^1 = Me, R^2 = Ac
b; X = HgCl, R^1 = Me, R^2 = Ac
c; X = OAc, R^1 = Me, R^2 = Ac
d; X = OAc, R^1 = R^2 = Ac
e; X = OH, R^1 = R^2 = H



(2)

of the intermediate organoborane, a process which works satisfactorily on simple aromatic substrates.[4]

Hydroboration of (**1b**) proved to be successful and oxidation of the intermediate organoborane with 30% hydrogen peroxide,† followed by treatment with acetic anhydride and pyridine afforded 2,17β-diacetoxy-3-methoxyestra-1,3,5(10)-triene (**1c**),‡ after chromatography on an ascorbic acid impregnated silica gel column,[5] in 45% yield from (**1a**).

An alternative route for the preparation of (**1c**) arose from the consideration that acid anhydrides form bulky adducts with boron trifluoride.[6] These complexes may act as regioselective Friedel–Crafts reagents and therefore attack the less hindered 2-position of (**1a**).

From the reaction of (**1a**) with acetic anhydride and boron trifluoride at 0 °C we isolated the expected compound (**2**)§ in 80% yield.[7] The absence of the 4-isomer shows that the reaction is regiospecific. The ketonic nature of (**2**) and the presence of a Lewis acid moiety in the molecule suggests that (**2**) may be oxidized by neutral 30% hydrogen peroxide. The product of this oxidation (2 days, room temp.) was directly acetylated and after chromatography gave (**1c**).

Reaction of (**1c**) with pyridine hydrochloride[8] followed by acetylation afforded, in 75% yield, the 2,3,17β-triacetoxyestra-1,3,5(10)-triene (**1d**).

The preparation of (**2**) leads to a practical and simple synthesis of the triacetate (**1d**), from which 2,3,17β-trihydroxyestra-1,3,5(10)-triene (**1e**) can be easily prepared.[5]

We thank Dr. M. Chiari for experimental assistance and C.N.R. (Rome) for financial support.

Received, 5th July 1982; Com. 766

References

1 P. Ball and R. Knuppen, *Acta Endocrinol. (Copenhagen)*, 1980, Suppl. 32, **93**, 1.
2 E. Santaniello and P. Ferraboschi, *J. Chem. Soc., Chem. Commun.*, 1981, 217.
3 D. N. Kirk and C. J. Slade, *J. Chem. Soc., Chem. Commun.*, 1982, 563.
4 S. W. Breuer, M. J. Leatham, and F. G. Thorpe, *Chem. Commun.*, 1971, 1475.
5 H. P. Gelbke and R. Knuppen, *J. Chromatogr.*, 1972, **71**, 465. On using normal silica gel the recovery of the products was dramatically lowered.
6 K. Figge, *Fette, Seifen, Anstrichm.*, 1972, **74**, 9.
7 For an analogous boron difluoride complex with benzoylacetone see: C. L. Mao, F. C. Frostick, Jr., E. H. Man, R. M. Manyick, R. L. Wells, and C. R. Hansen, *J. Org. Chem.*, 1969, **34**, 1425.
8 J. Fishman, M. Tomasz, and R. Lehman, *J. Org. Chem.*, 1960, **25**, 585.

† Alkaline hydrogen peroxide was not used, owing to the instability of the catechol system; see ref. 1, p. 12.

‡ All compounds have ^{1}H n.m.r., i.r., and mass spectra in complete agreement with the assigned structures. All new compounds gave correct microanalyses.

§ Compound (**2**): m.p. 173—175 °C (from di-isopropyl ether); u.v. λ_{max} 320 (ϵ 19 000) and 380 nm (ϵ 12 800); i.r. ν_{max} 1 720 and 1 610 cm^{-1}; ^{1}H n.m.r. ($CDCl_3$, from Me_4Si) δ 0.90 (s, 3H, 18-H_3), 2.10 (s, 3H, –COMe), 2.40 (s, 3H, –COMe), 4.00 (s, 3H, –OMe), 4.75 (m, 1H, 17-H), 6.80 (s, 1H, aromatic), 7.10 (s, 1H, –CH=), and 8.10 (s, 1H, aromatic); ^{13}C n.m.r. ($CDCl_3$, p.p.m. from Me_4Si) δ 12.1 (q), 21.1 (q), 23.2 (t), 24.7 (q), 26.1 (t), 26.8 (t), 27.6 (t), 30.3 (t), 36.6 (t), 38.3 (d), 42.8 (s), 43.5 (d), 49.8 (d), 55.8 (q), 82.5 (d), 101.9 (d), 112.1 (d), 117.7 (s), 129.0 (d), 133.7 (s), 147.6 (s), 158.9 (s), 171.0 (s), 180.6 (s), and 190.7 (s).