Regioselective Mercuriation of an Estradiol Derivative: A Facile Entry to 2-Substituted Estrogens

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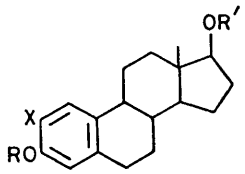
Summary 3-Methoxy-17β-acetoxy-1,3,5(10)-estratriene was regioselectively chloromercuriated at C-2 to afford (**1d**), which was converted into the 2-bromo- and 2-iodo-derivatives.

THERE exist conflicting reports on the reaction of estradiol (**1a**) with mercury(II) acetate, $Hg(OAc)_2$. In fact, a previous paper which reported the synthesis of 2-iodo-estradiol by reaction of (**1a**) with $Hg(OAc)_2$ and I_2 in acetic acid[1] has been very recently corrected.[2] Apparently, only a complex mixture of iodinated compounds has been obtained by the above reaction. Moreover, both reports seem to be in contrast with the preparation of 4-acetoxymercurio-estradiol by reaction of (**1a**) with $Hg(OAc)_2$ in acetic acid.[3] In any event, none of the described procedures seems to provide a clean preparation of 2-mercuriated estradiol. Because of the biological importance of 2-catecholestrogens (2-hydroxy-estrogens) and their derivatives,[4] we have attempted the preparation of a stable mercuriated estradiol of synthetic significance.

Since (**1a**) reacted sluggishly with $Hg(OAc)_2$ and (**1b**) was apparently unreactive, (**1c**) was chosen for the mercuriation reactions. Furthermore, it is known that *o*-hydroxyphenyl mercury chloride can be easily prepared from phenol and $Hg(OAc)_2$, followed by treatment with a saturated NaCl solution.[5]

We allowed (**1c**) to react with $Hg(OAc)_2$ in dry acetonitrile and treated this solution with aqueous NaCl solution. The 2-chloromercurio-derivative (**1d**) was obtained in 80% yield.† In order to confirm the position of mercuriation, we treated (**1d**) with a chloroform solution of I_2 and Br_2, and obtained the 2-iodo- and 2-bromo-derivatives (**1e**) and (**1f**)



(**1**)

a; R = R′ = X = H
b; R = R′ = Ac, X = H
c; R = Me, R′ = Ac, X = H
d; R = Me, R′ = Ac, X = HgCl
e; R = Me, R′ = Ac, X = I
f; R = Me, R′ = Ac, X = Br
g; R = Me, R′ = Ac, X = Cl

in quantitative yields (10 min, room temperature). For preparative purposes, the 2-chloro-derivative (**1g**) was prepared also using *N*-chlorosuccinimide in dichloromethane (2 h reflux and left overnight at room temperature, 90% yield). The above reactions both prove the regioselectivity of the mercuriation reaction and constitute proof that facile preparation of 2-halogeno-estrogens is possible by this route. In addition, hydrolysis of 3-methoxy-ethers in the estrogen series is possible by various methods[6] and organomercurio-derivatives are valuable intermediates in organic synthesis.[7] Thus, (**1d**) could constitute the starting material for the preparation of 2-substituted estrogens of various structures and of potential biological activity.

We thank C.N.R. (Rome) for financial support.

(*Received*, 3*rd December* 1980; *Com.* 1289.)

† The ^{1}H-n.m.r. spectra of the regioisomers were in accord with the proposed structures. Two singlets were found in the aromatic region with the following resonances: (**1d**) and all three halogeno-derivatives showed a singlet δ 6·6 (4-H), whereas 1-H resonated at δ 7·1 (**1d**), 7·3 (**1g**), 7·4 (**1f**), and 7·7 (**1e**).

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