Novel Regioselective Iodination of Estradiol, Estriol, and Estrone using Iodine–Copper(II) Acetate

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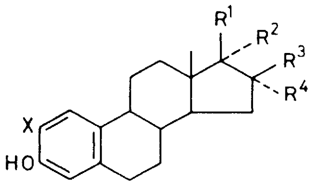
Direct iodination of estradiol, estriol, and estrone using iodine–copper(II) acetate in acetic acid afforded the 2-iodo-derivatives regioselectively in high yield.

2-Iodoestradiols are important as synthetic intermediates, and as possessors of biological activity, and also in making highly radioactive iodine isotopes. They are usually prepared from diazotization of the corresponding 3-methoxyaminoestrone derivative, reduction with sodium borohydride, and then demethylation using boron tribromide,[1] and from the reaction of estradiol (**1**) with mercury(II) acetate and iodine.[2] However, recently the synthesis of 2-iodoestradiol by reaction of (**1**) with mercury(II) acetate and iodine in acetic acid has been questioned.[1] More recently, Santaniello and Ferraboschi[3] reported that the reaction of 3-methoxy-17β-acetoxy-1,3,5(10)-estratriene with mercury(II) acetate in dry acetonitrile gave the

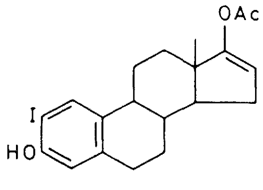


(**1**) $R^1 = OH, R^2 = R^3 = R^4 = X = H$
(**2**) $R^1 = R^4 = OH, R^2 = R^3 = X = H$
(**3**) $R^1, R^2 = O, R^3 = R^4 = X = H$
(**4**) $R^1 = OH, X = I, R^2 = R^3 = R^4 = H$
(**5**) $R^1 = R^4 = OH, X = I, R^2 = R^3 = H$

2-chloromercurio-derivative; treatment of this with iodine gave the 2-iodo-derivative. However, these methods involve many steps and demethylation gives low yield, and we wished to find a method for the direct iodination of estradiol (**1**). Recently, it was reported[4] that the reaction of phenol derivatives with iodine and thallium(I) acetate in either acetic acid or dichloromethane selectively gave phenols iodinated in the *ortho*-position. Moreover, we previously reported[5] that iodine–copper(II) acetate is a useful reagent for the α-iodination of ketones.

In the present communication, we report the direct iodination of estradiol, estriol, and estrone with iodine–copper(II) acetate in acetic acid.

The reaction of estradiol (**1**) (0.734 mmol) with copper(II) acetate monohydrate(1.5 mol. equiv.)–iodine(1.5 mol. equiv.) in acetic acid at 55 °C for 22 h yielded 2-iodoestradiol (**4**) (64%),† m.p. 186—189 °C (lit.,[1] m.p. 177—178 °C), δ ($CDCl_3$): 6.71 (1H, s), 7.52 (1H, s), and 3.70 (1H, t, J 8 Hz). In the case of estriol (**2**), 2-iodoestriol (**5**) (35%), m.p. 238—240 °C, δ (CD_3OH): 6.54 (1H, s) and 7.48 (1H, s) was obtained and in the case of estrone (**3**), 2-iodoestrone enol acetate (**6**) (90%), m.p. 105—107 °C, δ ($CDCl_3$): 2.17 (3H, s), *ca.* 5.40—6.00 (1H, m), 6.70 (1H, s), and 7.50 (1H, s) was produced. Reduction of the enol acetate (**6**) using sodium borohydride in methanol converted it into 2-iodoestradiol (**4**) in 95% yield.



(**6**)

Direct iodination of estrogen derivatives using iodine–copper(II) acetate in acetic acid thus occurs at the C-2 rather than the C-4 position. Moreover, this is the first time that direct iodination of these compounds has been successfully accomplished. It is particularly noteworthy that this reaction affords a new synthetic method for 2-iodoestradiol, more convenient than the method used heretofore.

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† After the usual work-up, the resultant oil was purified by preparative t.l.c. coated with silica gel (2 mm thick) (E. Merck). Elution with benzene–diethyl ether (2 : 1) gave the 2-iodoestrogen derivative from hexane–diethyl ether.

References

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