II could also react with Cu (II) in pyridine to afford the corresponding reaction products to those of I according to Chart 1, and nearly the same effect of the factors such as those involved in the reaction of I was observed in II (data not shown).

Both alcoholysis and phosphorolysis of 8-quinolyl phosphate derivatives were examined on a preparative scale. The results described below indicate that this metal-catalyzed reaction can offer a unique and effective method for the preparation of phosphate and pyrophosphate esters. II (1 mmole) was reacted with alcohols (ROH, 50 mmoles), and $CuCl_2$ (1 mmole) in anhydrous pyridine (15 ml) for 1 hr at 100°. Alkyl dihydrogen phosphates (R=ethyl, amyl, cyclohexyl, and benzyl) were isolated as their barium salts in 61, 66, 31, and 54% yield, respectively. Alkyl 8-quinolyl hydrogen phosphates (R=ethyl, cyclohexyl, and benzyl) were reacted with alcohols (R'OH) in a similar way, except heating for 5 hr at 70°. Dialkyl hydrogen phosphates (R-R'=ethyl-cyclohexyl, cyclohexyl-amyl, benzyl-cyclohexyl, and benzyl-ethyl) were isolated as their barium salts in 76, 80, 78, and 90% yield, respectively. Alkyl 8-quinolyl hydrogen phosphates (1 mmole each) were reacted in anhydrous pyridine (20 ml) in the presence of cupric acetate (1 mmole) for 1 hr at 100°. The phosphorolysis products, P^1,P^2-disubstituted pyrophosphates (R=ethyl, cyclohexyl, and benzyl) were isolated as their barium salts in 69, 71, and 73% yield, respectively.

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Simple Preparation of Catechol Estrogen and Its Derivatives

From a variety of studies, it appears to be established that aromatic 2-hydroxylation of estrogen is a characteristic metabolic alteration in estrogenic hormone.[1] By this biological conversion, catechol estrogens such as 2-hydroxyestrone or 2-hydroxyestradiol (III) are produced, some of which are metabolized further to their 2- and 3-methyl ethers by the similar pathway as observed in the case of catecholamines.[2] It becomes necessary, therefore, to obtain such 2-oxygenated estrogens in the course of biological or endocrinological research on this hormone. Since the discovery of 2-methoxyestrone as the *in vivo* metabolite of estradiol in human,[3] several synthetic procedures for the preparation of this catechol estrogen and its various derivatives have been proposed.[4] These methods hitherto proposed, however, are not necessarily satisfactory in respect of feasibility and/or yield.

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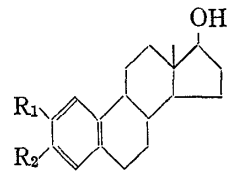
In the present communication, the authors describe the simple and direct preparation of catechol estrogen by using benzoyl peroxide as the reagent introducing oxygen function into *ortho* position of phenols as described by Walling, *et al.* and Denney, *et al.*[5]

Estradiol (I) was refluxed in benzene containing an equivalent mole of benzoyl peroxide under nitrogen stream for 4 hr. After cooling, the reaction mixture was washed with 10% aqueous Na_2CO_3 solution and then with water. Reaction product obtained by removal of the solvent was then submitted to preparative thick layer chromatography (1.25 mm thickness, Silica Gel B5-F) by using solvent system: acetic acid-chloroform (1: 9) to give mono-benzoate (II),[6] NMR (in $CDCl_3$) δ: 7.03 (aromatic C_1-H), 6.73 (aromatic C_4-H), in the yield of 60%. Since catechol estrogen is fairly unstable, especially in basic media, hydrolysis of II was carried out in 10% HCl in methanol with refluxing for 6 hr resulting to give 2-hydroxyestradiol (III) quantitatively. The catechol thus obtained was identified as the objective material by comparison with the authentic specimen in melting point or spectral determinations. Similarly, another starting material (IV) was converted to isomeric mono-benzoate (V),[6] NMR (in $CDCl_3$) δ: 6.85 (aromatic C_1-H), 6.74 (aromatic C_4-H), in the yield of 65%, which was also hydrolyzed to give catechol (III) quantitatively.



I : R_1=-H, R_2=-OH
II : R_1=-O-CO-C_6H_5, R_2=-OH
III : R_1=-OH, R_2=-OH
IV : R_1=-OH, R_2=-H
V : R_1=-OH, R_2=-O-CO-C_6H_5

Chart 1

When it is unnecessary to isolate such intermediates (II) or (V), the reaction mixture was directly afforded to acid hydrolysis as described and then submitted to column chromatography on silica gel by which catechol (III) was eluted with 40—60% ethylacetate in benzene while the starting material unreacted was with 100% benzene and 10% ethylacetate in benzene. The yield was 55—60% when estradiol was used as starting material.

As the abundant conveniences of this present synthetic procedure, the following significances should be pointed out:

(1) Estrogen catechol was easily obtained in satisfactory yield.

(2) Two mono-benzoates (II) and (V) were able to be isolated, those of which were further methylated with diazomethane in methanol, followed by hydrolysis with alkali to give 2- and 3-methyl ethers of catechol which are also important estrogen metabolites.[2b]

(3) Another catechol estrogen analogues, such as those of estrone and estriol, were also available by the present procedure.

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6) No recrystallization was carried out on these mono-benzoates (II) and (V), since the rearrangement of benzoyl group to adjacent hydroxyl was possible. The nuclear magnetic resonance (NMR) spectroscopy, therefore, was run with crude materials which were homogenous on thin layer chromatographic plate.