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A Metal Catalyzed Phosphorylation with 8-Quinolyl Phosphates

Methods for the synthesis of phosphoric acid esters have been the subject of numerous investigations and a number of phosphorylating agents have so far been introduced.[1] Recently, Takaku, *et al.*[2] reported the formation of several alkyl phenyl hydrogen phosphates from the metal-catalytic alcoholysis of phenyl 8-quinolyl hydrogen phosphate. More recently, it has been demonstrated in this laboratory that benzyl 8-quinolyl hydrogen phosphate (I) reacts with cupric ion in moist pyridine to give, under the concurrent formation of 8-hydroxyquinoline-Cu(II) complex, an intermediary active species (III), from which benzyl dihydrogen phosphate (IV) and P^1,P^2-dibenzyl pyrophosphate (V) are fromed (Chart 1).

In this communication, we report the metal catalyzed reaction of I and its application for the preparation of phosphate and pyrophosphate esters.

I (NH_4 salt, mp 145—148°) was prepared in 76% yield by the condensation of 8-quinolyl dihydrogen phosphate (II) (free ester, mp 210—218°)[3] (4 mmoles) with benzyl alcohol (20 mmoles) in the presence of dicyclohexylcarbodiimide in pyridine. Process of the decomposition of I in moist pyridine was examined in the presence of 0—0.75 mol. eq. $CuCl_2$ at 100°.[4] As shown in Table I, Cu(II) obviously affects both the rate of decomposition and the direction of cleavage of I.

The amount of Cu (II) necessary for this reaction can be deduced as 0.5 mol. eq. from the result shown in Table I and the isolation of a stoichiometric amount of 8-hydroxyquinoline-Cu (II) (2:1) complex from the reaction mixture. The data shown in Table II indicate that water content in the pyridine used markedly affects both the rate of decomposition and the pattern of reaction products of I. Metal ions which can form a chelate with 8-hydroxyquinoline, Co (II), Ni (II), Mn (II), Zn (II), and Fe (III), displayed almost the same effect as Cu (II) did (data not shown). The reactivity of I in moist polar solvents other than pyridine was examined (Table III). It was noted that I was effectively alcoholyzed

Table I. Effect of Cu(II) Ion on the Decomposition of Benzyl 8-Quinolyl Hydrogen Phosphate in Pyridine containing Water (5%, v/v) at 100°

Cu(II) added (mol. eq.)	Reaction time (min)	Composition of reaction mixture (%)				
		I	II	IV	V	Pi
0	30	74.0	11.6	8.7	2.1	3.7
0.35	30	27.5	0	64.8	4.7	3.0
0.5	30	3.9	0	85.7	7.5	2.9
0.75	10	1.6	0	85.9	9.7	2.7

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2) H. Takaku, Y. Shimada, and K. Arai, The 8th United Meeting of Kagaku Kanren Shibu in Kyushu District, Fukuoka, July 1971.

3) Y. Murakami, J. Sunamoto, H. Sadamori, H. Kondo, and M. Takagi, *Bull. Chem. Soc. Japan*, 43, 2518 (1970).

4) Both quantitative and qualitative analyses were carried out on paper chromatography (Whatman No. 1) or thin-layer chromatography (Avicel SF) by the ascending technique using the solvent system of isopropanol–conc. ammonia–water (7:1:2, v/v).

Table II. Effect of Water Content in Pyridine on the Cu(II)-Catalyzed Decomposition of Benzyl 8-Quinolyl Hydrogen Phosphate[a)]

Water content (%, v/v)	Composition of reaction mixture (%)			
	I	IV	V	Pi
0[b)]	34.7	4.3	54.4	2.1
0.5	0	44.3	55.7	0
5	1.6	85.9	9.7	2.7
10	21.7	70.8	6.5	1.0
100	33.3	55.3	6.8	4.5

a) The reaction was carried out in the presence of 0.6 mol. eq. of $CuCl_2$ for 10min at 100°.
b) An unidentified phosphorus compound was formed in 4.5% yield.

Table III. Effect of Solvents on the Cu(II)-Catalyzed Decomposition of Benzyl 8-Quinolyl Hydrogen Phosphate[a)]

Solvent	Composition of reaction mixture (%)				
	I	IV	V	VI	Pi
Quinoline	22.7	19.8	57.4		0
Dioxane	12.9	12.9	70.2		3.9
Dimethylformamide	30.4	59.6	8.2		0.8
Dimethylsulfoxide	13.5	86.5	0		0
Morpholine	29.6	6.3	64.2		0
Ethanol	22.4	6.0	0	71.6	0

a) The reaction in a solvent containing water (0.5%, v/v) was carried out in the presence of 0.6 mol. eq. of $CuCl_2$ for 10 min at 100°.

with moist ethanol to yield benzyl ethyl hydrogen phosphate (VI) as a sole product. A distinct difference in the compositions among the reaction products obtained by dimethylsulfoxide or morpholine is also remarkable.

On the basis of the results obtained, a mechanism of the Cu (II)-catalyzed reaction of I is presented in Chart I.

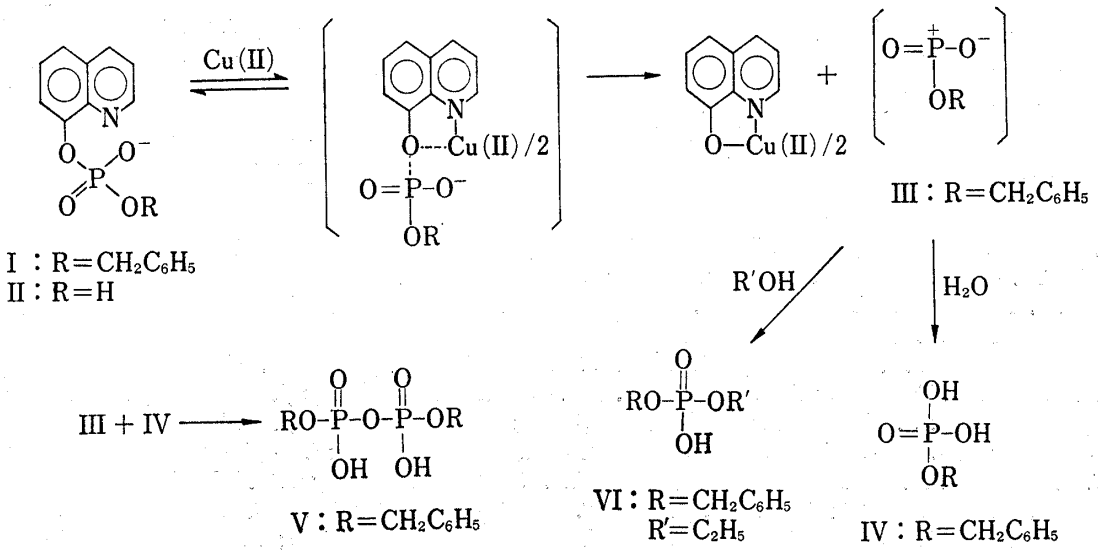

Chart 1

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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