[Chem. Pharm. Bull.
21(11)2438—2443(1973)]

UDC 547.831.04 : 547.559.057

Preparation of Phosphate and Pyrophosphate Esters by the Metal-catalyzed Reaction of 8-Quinolyl Phosphates[1]

KINZO NAGASAWA and HISAE YOSHIDOME

School of Pharmaceutical Sciences, Kitasato University[2]

(Received February 21, 1973)

In the presence of Cu(II) ion, alkyl 8-quinolyl hydrogen phosphates (alkyl=ethyl, cyclohexyl, and benzyl) converted into the corresponding P^1,P^2-disubstituted pyrophosphates with formation of 8-hydroxyquinoline-Cu(II) chelate in anhydrous pyridine. When this reaction was carried out in pyridine containing alcohols (R'=ethyl, amyl, cyclohexyl, and benzyl), corresponding dialkyl hydrogen phosphates (R–R'=ethyl-cyclohexyl, amyl-cyclohexyl, cyclohexyl-benzyl, and ethyl–benzyl) were formed as a sole product.

The factors (water content, solvent, metal ion) which affect this metal-catalyzed reaction were examined, and a possible mechanism for the reaction was presented.

In 1966, Jakubuke and Voigt reported an effective method for peptide synthesis with aminoacyl and peptidyl esters of 8-hydroxyquinoline.[3] They did not mention the participation of metal ions in this reaction. In 1967, Hay and Edmonds reported a kinetic study of the hydrolysis of 8-quinolyl sulfate catalyzed by copper(II),[4] and in 1966, Barca and Freiser reported a similar observation on 8-acetoxyquinoline.[5] Murakami and Sunamoto also reported the solvolysis of 8-quinolyl phosphate in the presence of some bivalent metal ions.[6] All these investigators suggested that a chelate forming interaction of 8-quinolyl moiety with the metal ions accelerates these reactions of 8-quinolyl derivatives.

Recently, Takaku, *et al.*[7] reported the formation of several alkyl phenyl hydrogen phosphates from the metal-catalyzed alcoholysis of phenyl 8-quinolyl hydrogen phosphate. We have also examined in more detail the metal-catalyzed transformation of 8-quinolyl phosphate esters in polar organic solvents. This paper describes the metal catalyzed reaction of benzyl 8-quinolyl hydrogen phosphate (I: R=benzyl) and its application for the preparation of phosphate and pyrophosphate esters.

Decomposition of I, which has a favorable solubility in the solvents used and chromatographic behaviors, was examined in moist pyridine with 0—0.75 molar equivalent $CuCl_2$ at 100°. As shown in Table I, Cu(II) obviously affects both the rate of decomposition and the direction of cleavage of I. The data indicate that the hydrolysis in the absence of Cu(II) proceeds evenly in both sides of the phosphodiester linkage of I bacause the amount of 8-quinolyl dihydrogen phosphate (II) was almost equal to the total amount of benzyl dihydrogen phosphate (IV) and P^1,P^2-dibenzyl pyrophosphate (V), while the hydrolysis in the presence of Cu(II) occurrs exclusively in the 8-quinolyl-O-P linkage of I. The data also suggest that the amount of Cu(II) more than 0.5 molar equivalent is effective to a rapid decomposition of I. In this case, a stoichiometrical amount of 8-hydroxyquinoline–Cu(II) (2:1) complex to I was always recovered from the reaction mixture.

---

[1] This work was reported as preliminary communications: K. Nagasawa and H. Yoshidome, *Chem. Pharm. Bull.* (Tokyo), **20**, 1840 (1972).

[2] Location: *9–1 Shirokane 5 chome, Minato-ku, Tokyo, 108, Japan.*

[3] H.-D. Jakubuke and A. Voigt, *Chem. Ber.*, **99**, 2419 (1966).

[4] R.W. Hay and J.A.G. Edmonds, *Chem. Commun.*, **1967**, 969.

[5] R.H. Barca and H. Freiser, *J. Am. Chem. Soc.*, **88**, 3744 (1966).

[6] Y. Murakami and J. Sunamoto, *Bull. Chem. Soc. Japan*, **44**, 1827 (1971).

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

NII-Electronic Library Service

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

Cu(II) added (mol. eq.)	Reaction time (min)	Composition of reaction mixture (P%)				
		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

a) The reaction in pyridine containing water (5%, v/v) was carried out in the presence of the indicated amount of $CuCl_2$ at 100°.

The data shown in Table II indicate that water content in the pyridine used markedly affects both the rate of decomposition and the composition of reaction products of I. Metals other than Cu(II) 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, except Cd(II) (Table III). The acetate anion appears to affect either formation or degradation of P^1,P^2-dibenzyl pyrophosphate.[8)] The reactivity of I in moist polar solvents other than pyridine was examined (Table IV). It was noted that I was effectively alcoholyzed with moist ethanol to yield benzyl ethyl hydrogen phosphate (VI) and no formation of V was occurred.

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 (P%)			
	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 10 min at 100°.
b) An unidentified phosphorus compound was formed in 4.5% yield.

Table III. Effect of Metal Ions on the Metal-Catalyzed Decomposition of Benzyl 8-Quinolyl Hydrogen Phosphate[a)]

Metal ion	Composition of reaction mixture (P%)			
	I	IV	V	Pi
Cu^{2+}	0	44.3	55.7	0
Cu^{2+}[b)]	3.3	19.2	73.7	3.8
Ni^{2+}	0	36.7	63.3	0
Co^{2+}	4.5	44.9	52.8	2.3
Zn^{2+}	4.1	30.0	67.4	2.6
Cd^{2+}	45.2	36.0	18.0	0.9
Mn^{2+}	2.3	30.5	66.7	0.6
Fe^{3+}	0	38.8	51.9	0.3

a) The reaction was carried out in pyridine containing water (0.5%, v/v) with 0.6 mol. eq. of metal chloride for 10 min at 100°.
b) Cupric acetate was used in place of cupric chloride.

[8)] P^1,P^2-Dibenzyl pyrophosphate formed decomposes gradually into benzyl dihydrogen phosphate.

NII-Electronic Library Service

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

Solvent	Composition of reaction mixture (P%)				
	I	IV	V	VI	Pi
Pyridine	0	44.3	55.7		0
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
Water	33.3	55.3	6.8		4.5

[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°.

On the basis of the results obtained, a possible mechanism of the Cu(II)-catalyzed reaction of I is presented in Chart 1. I reacts with cupric ions through a transition state to form 8-hydroxyquinoline-copper complex and a reactive species, (supposedly, benzyl metaphosphate ion) (III). When an appropriate nucleophile exists, III reacts rapidly with it to afford a corresponding product. For example, III will react with a small amount of water existed in the reaction medium to form benzyl dihydrogen phosphate anion (IV), and the latter instantly combines with another molecule of III to form in P^1,P^2-dibenzyl pyrophosphate (V). Similarly, an alkoxide anion, $R'O^-$, reacts with III to give the corresponding phosphodiester, the compound VI.

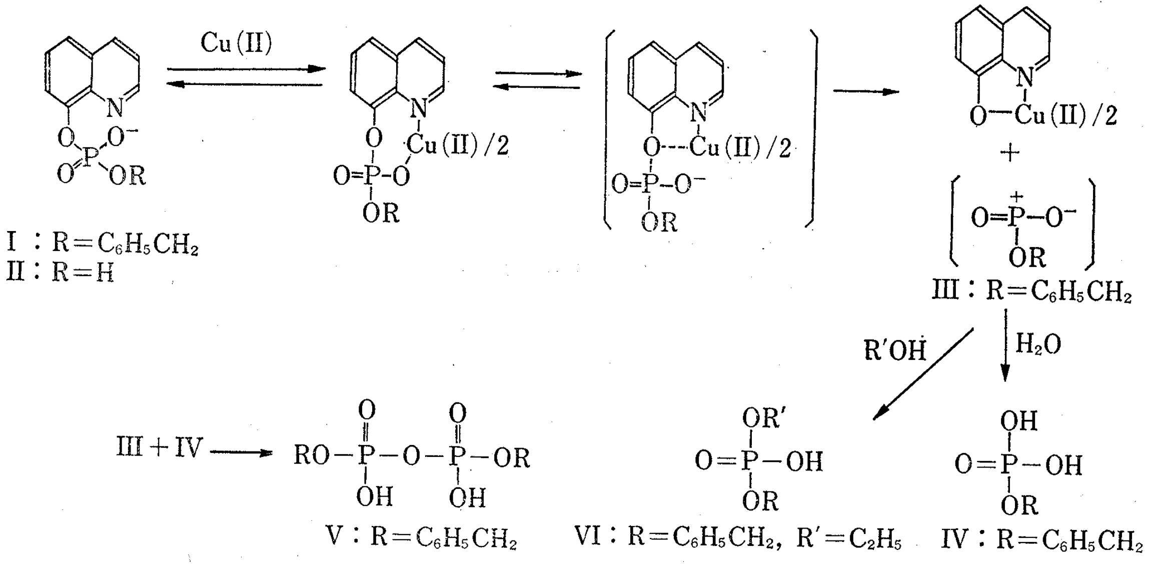
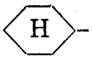


Chart 1

8-Quinolyl dihydrogen phosphate (II) can also react with cupric ions in pyridine to form reaction products corresponding to those of I according to this scheme, and nearly the same effect of the factors such as those involved in the reaction of compound I was observed in the reaction of II, although the data obtained are not shown.

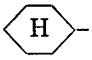
The approach involving the use of 8-quinolyl phosphate esters was applied successfully for the preparation of simple phosphate and pyrophosphate esters as can be seen from the following data. The results of cupric ion-catalyzed alcoholysis of 8-quinolyl dihydrogen phosphate (II) and alkyl 8-quinolyl hydrogen phosphates (I: R=ethyl, cyclohexyl, and benzyl)

Table V. Preparation of Alkyl Dihydrogen Phosphates through the Cu(II)-Catalyzed Alcoholysis of 8-Quinolyl Dihydrogen Phosphate

ROH	Alkyl dihydrogen phosphate $(RO)PO_3Ba$	Yield (%)	Analysis (%) Calcd. (Found) C	H	P
	R				
C_2H_5OH	C_2H_5-	61(80)[a]	9.19(9.36)	1.93(2.16)	11.85(12.17)
n-$C_5H_{11}OH$	n-C_5H_{11}-	66(75)	19.79(19.69)	3.65(4.00)	10.21(10.42)
-OH	-	33(44)	22.84(22.64)	3.52(4.04)	9.82(9.55)
$C_6H_5CH_2OH$	$C_6H_5CH_2$-	54(63)	25.99(26.16)	2.18(2.48)	9.58(9.79)

[a] The figures in parentheses are the yields of phosphates which were directly determined on paper strips.

Table VI. Preparation of Dialkyl Hydrogen Phosphates through the Cu(II)-Catalyzed Alcoholysis of Alkyl 8-Quinolyl Hydrogen Phosphates

R'OH	Dialkyl hydrogen phosphate $(RO)(R'O)PO_2Ba/_2$		Yield (%)	Analysis (%) Calcd. (Found) C	H	P
	R	R'				
-OH	C_2H_5-	-	76(88)[a]	34.88(34.85)	5.86(5.88)	11.24(10.85)
n-$C_5H_{11}OH$	-	n-C_5H_{11}-	80(94)	41.61(41.46)	6.98(7.32)	9.75(9.57)
C_2H_5OH	$C_6H_5CH_2$-	C_2H_5-	90(—)	38.14(38.15)	4.27(4.57)	10.93(10.58)
-OH	$C_6H_5CH_2$-	-	78(—)	46.26(46.43)	5.37(5.71)	9.18(9.18)

[a] The figures in parentheses are the yields of phosphates which were directly determined on paper strips.

with various alcohols were shown in Tables V and VI. I or II (1 mmole each) was reacted with alcohols (ROH, 50 mmoles), and $CuCl_2$ (1 mmole) in anhydrous pyridine (15 ml) for 1 hr at 100°. The yields of phosphodiesters are generally higher than that of phosphomonoesters.

The result on the transformation of I to the corresponding P^1,P^2-dialkyl pyrophosphates (V) was shown in Table VII. I (1 mmole) was reacted in anhydrous pyridine (20 ml) at 100°. To prevent decomposition of the pyrophosphates formed, the reaction time was reduced to 20 min, and cupric chloride was replaced by the acetate which is favorable for the pyrophosphate formation.

Table VII. Preparation of P^1,P^2-Dialkyl Pyrophosphates through the Cu(II)-Catalyzed Phosphorolysis of Alkyl 8-Quinolyl Hydrogen Phosphates

P^1,P^2-Dialkyl pyrophosphate (Ba salt) R	Yield (%)	Analysis (%) Calcd. (Found) C	H	P
C_2H_5-	69(79)	13.00(13.18)	2.73(2.96)	16.77(16.18)
-	71(85)	30.18(29.51)	4.64(4.98)	12.97(12.76)
$C_6H_5CH_2$-	73(85)	34.07(33.98)	2.86(3.18)	12.55(12.62)

[a] The figures in parentheses are the yields of pyrophosphates which were directly determined on paper strips.

If another phosphate anion exists in this system, unsymmetrically substituted pyrophosphate may be obtained. Ethyl 8-quinolyl hydrogen phosphate was reacted with an equimolar amount of phenyl dihydrogen phosphate according to the analogous conditions, and P^1-ethyl, P^2-phenyl pyrophosphate was formed in a satisfactory yield of 69%, as expected.

NII-Electronic Library Service

Experimental

Materials——8-Quinolyl dihydrogen phosphate (free esters, mp 210—218°) (II) was prepared by the method reported by Murakami, *et al.*9) Alkyl 8-quinolyl hydrogen phosphates were prepared by condensing II with alcohols by means of dicyclohexylcarbodiimide in pyridine. A solution of II (4 mmoles) in anhydrous pyridine (50 ml) was reacted with anhydrous alcohols (ROH, 2 ml) in the presence of dicyclohexylcarbodiimide (2 g). The reaction was continued for two days at room temperature with stirring. After filtration, the reaction mixture was evaporated *in vacuo* at 40° and the residue was dissolved in water, then washed twice with ether. The aqueous solution obtained was passed through a column of Dowex 50×8 (H^+) (1×10 cm) and eluted with 2% ammonia. The eluate was evaporated to dryness *in vacuo* and the residue was recrystallized from EtOH and ethyl acetate. Analytical data and yields of the alkyl 8-quinolyl hydrogen phosphates prepared were summarized in Table VIII.

TABLE VIII. Preparation of Alkyl 8-Quinolyl Hydrogen Phosphates

R (NH_4 salt)	Yield (%)	Analysis (%) Calcd. (Found)				mp (C°)	Appearance
		C	H	N	P		
C_2H_5-	54	48.71(48.90)	5.57(5.72)	10.33(10.35)	11.42(11.23)	145—148	needles
	53	55.37(54.82)	6.82(6.96)	8.61(8.56)	9.52(9.53)	178—180	needles
$C_6H_5CH_2$-	76	57.48(58.03)	5.13(5.30)	8.38(8.46)	9.27(9.54)	152—154	needles

Other reagents which were all special reagent grade, were used without further purification. Organic solvents were dehydrated and redistilled by conventional methods.

Chromatography——Qualitative analysis was carried out on thin-layer plates (Avicel SF layer, 0.25 mm thick) by the ascending technique using the solvent system: (A) isopropanol–conc. ammonia–water (7:1:2) or (B) EtOH–conc. ammonia–water (6:1:3). All the compounds having 8-quinolyl phosphoryl group were detectable as a white or blue fluorescent spot with UV irradiation. Phosphates and pyrophosphates were visualized as a blue or violet spot with the Hanes–Isherwood reagent.10) *Rf* data of the phosphates and pyrophosphates concenred were summarized in Table IX. For quantitative analysis, paper chromatography was carried out on Whatman No. 1 filter paper by the ascending technique using the solvent system (A) or (B). The spots resolved were cut out and analyzed for phosphorus.11)

Examination of the Effect of Various Factors on the Metal-Catalyzed Decomposition of I——(a) Effect of Cu(II) Ion Concentration: The solution of I (R=benzyl, NH_4 salt) (0.1 mmole) in 5 ml of pyridine containing water (5%, v/v) was reacted in the presence of $CuCl_2$ (0—0.075 mmole) at 100° with stirring. After

TABLE IX. *Rf* Data of Phosphates and Pyrophosphates

Compound	Solvent		Compound	Solvent	
	A	B		A	B
Orthophosphate	0.04	0.24	Benzyl ethyl hydrogen phosphate	0.84	0.89
Ethyl dihydrogen phosphate	0.14	0.49	Ethyl 8-quinolyl hydrogen phosphate	0.81	0.89
n-Amyl dihydrogen phosphate	0.41	0.68	Cyclohexyl 8-quinolyl hydrogen phosphate	0.91	0.93
Cyclohexyl dihydrogen phosphate	0.30	0.61	Benzyl 8-quinolyl hydrogen phosphate	0.87	0.91
Phenyl dihydrogen phosphate	0.23	0.54	Pyrophosphate	0.00	0.13
Benzyl dihydrogen phosphate	0.27	0.60	P^1,P^2-Diethyl pyrophosphate	0.49	0.74
8-Quinolyl dihydrogen phosphate	0.21	0.56	P^1,P^2-Dicyclohexyl pyrophosphate	0.79	0.86
Ethyl cyclohexyl hydrogen phosphate	0.86	0.91	P^1,P^2-Dibenzyl pyrophosphate	0.73	0.84
Cyclohexyl *n*-amyl hydrogen phosphate	0.94	0.94	P^1-Ethyl,P^2-phenyl pyrophosphate	0.57	0.79
Benzyl cyclohexyl hydrogen phosphate	0.91	0.92			

---

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

10) C.S. Hanes and F.A. Isherwood, *Nature*, **164**, 1107 (1949); R.S. Bandurski and B. Axelrod, *J. Biol. Chem.*, **193**, 405 (1951).

11) G.W. Kenner and J. Mater, *J. Chem. Soc.*, **1956**, 3524.

NII-Electronic Library Service

reacted for the indicated period, the reaction mixture was evaporated *in vacuo* and the residue was dissolved in 5 ml of water. The solution was filtered and passed through a column of Dowex 50×8 (H^+) (0.5×5 cm). The eluate was neutralized with 10% ammonia, then concentrated to *ca.* 0.5 ml *in vacuo*. Composition of the phosphorus compounds formed from I was analyzed on this concentrate by the quantitative paper chromatography using the solvent systems A and B.

(b) Effect of Water Content in Pyridine: The solution of I (0.1 mmole) in 5 ml of pyridine containing the indicated amount of water was reacted in the presence of $CuCl_2$ (0.06 mmole) for 10 min at 100° with stirring. After the reaction, the mixture was treated by the same procedure as described in the section (a) and analyzed on the phosphorus compounds formed from I using the solvent systems A and B.

(c) Effect of Metal Ions: The solution of I (0.1 mmole) in 5 ml of pyridine containing water (0.5%, v/v) was reacted in the presence of the metal chloride indicated (0.06 mmole) for 10 min at 100° with stirring. After the reaction, the mixture was followed by the same treatment as described above.

(d) Effect of Solvents: The solution of I (0.1 mmole) in 5 ml of the indicated solvent containing water (0.5%, v/v) was reacted in the presence of $CuCl_2$ (0.06 mmole) for 10 min at 100° with stirring. The reaction mixture was followed by the same treatment as described above.

Preparation of Alkyl Dihydrogen Phosphates through the Cu(II)-Catalyzed Alcoholysis of 8-Quinolyl Dihydrogen Phosphate——8-Quinolyl dihydrogen phosphate (II) (1 mmole) was reacted with alcohols (ROH, 50 mmoles) in anhydrous pyridine (15 ml) in the presence of $CuCl_2$ (1 mmole) for 1 hr at 100°. The reaction mixture was evaporated *in vacuo*, and the residue was dissolved in water. After removal of the insoluble material (oxine-copper complex), the solution was decationized by Dowex 50×8 (H^+) resin, then neutralized with 10% ammonia. The solution was concentrated to a small volume and applied to a column of Avicel (2×10 cm) using the elution system of isopropanol–conc. ammonia–water (7: 1: 2, v/v). The fractions which were monitored by thin-layer chromatography (TLC) were combined and concentrated almost to dryness. The residue was redissolved in a small volume of water and decationized with Dowex 50×8 (H^+) resin, then neutralized with barium hydroxide. The aqueous solution was concentrated to *ca.* 1 ml *in vacuo*, and filtered to remove a small amount of impurities. The clear concentrate was added dropwise with EtOH to crystallize out. The crystals formed were collected and dried over P_2O_5 *in vacuo* for 2 hr at 80°. Analytical data and yields of the alkyl dihydrogen phosphates prepared were summarized in Table V.

Preparation of Dialkyl Hydrogen Phosphotes through the Cu(II)-Catalyzed Alcoholysis of Alkyl 8-Quinolyl Hydrogen Phosphates——Alkyl 8-quinolyl hydrogen phosphate (R=ethyl, cyclohexyl, and benzyl) (1 mmole each) was reacted with alcohols (R'OH, 50 mmoles) and $CuCl_2$ (1 mmole) in anhydrous pyridine (15 ml) for 5 hr at 70° with stirring. The reaction mixture was treated as the same way described in the preceding section. Analytical data and yields were summarized in Table VI.

Preparation of P^1,P^2-Dialkyl Pyrophosphates through the Cu(II)-Catalyzed Phosphorolysis of Alkyl 8-Quinolyl Hydrogen Phosphates——Alkyl 8-Quinolyl hydrogen phosphate (R=ethyl, cyclohexyl, and benzyl) (1 mmole each) was reacted in anhydrous pyridine (20 ml) in the presence of cupric acetate (1 mmole) for 20 min at 100° with stirring. The reaction mixture was treated as the same way described in the preceding two sections. Each barium salt of P^1,P^2-dialkyl pyrophosphates was isolated and analyzed. Analytical data and yields were summarized in Table VII.

Formation of P^1-Ethyl, P^2-Phenyl Pyrophosphate by the Cu(II)-Catalyzed Phosphorolysis of Ethyl 8-Quinolyl Hydrogen Phosphate in the Presence of Phenyl Dihydrogen Phosphate——A mixture of ethyl 8-quinolyl hydrogen phosphate (NH_4 salt, 0.1 mmole) and phenyl dihydrogen phosphate (NH_4 salt, 0.1 mmole) in anhydrous pyridine (2 ml) was reacted in the presence of cupric acetate (0.06 mmole) for 10 min at 100°. The reaction mixture was treated by the same procedure as described in the preceding section and the aqueous solution of ammonium salts of reaction products was prepared. Qualitative and quantitative analyses of this solution on paper chromatography revealed the formation of P^1-ethyl, P^2-phenyl pyrophosphate in 69.3 % yield besides P^1,P^2-diethyl pyrophosphate (7.0%, yield). The residual solution was concentrated to *ca.* 0.5 ml *in vacuo* and chromatographed on an Avicel column (1×10 cm) using the solvent system of isopropanol–conc. ammonia–water (7: 1: 2). The fractions containing only the aimed pyrophosphate were combined and evaporated to dryness *in vacuo*. A part of the residue obtained was dissolved in water to an appropriate concentration and analyzed for phosphorus. Another part of the residue was dissolved in 0.1M phosphate buffer (pH 7.0) to an appropriate concentration and the absorbancy at λ 267 nm of this solution was determined. The molar concentration of P^1-ethyl, P^2-phenyl pyrophosphate was calculated from the absorbancy at λ 267 nm obtained above using ε 267 of phenyl dihydrogen phosphate$=0.631\times10^3$ (0.1M phosphate buffer, pH 7.0). A molar ratio of phenyl phosphoryl group to phosphorus was 1: 2.02.

Analysis of 8-Hydroxyquinoline-Cu(II) Complex formed in the Cu(II)-Catalyzed Decomposition of Ethyl 8-Quinolyl Hydrogen Phosphate——The water insoluble precipitate formed in the Cu(II)-catalyzed phosphorolysis of ethyl 8-quinolyl hydrogen phosphate in anhydrous pyridine (see Experimental) was collected and washed with water on a glass filter. The precipitate which was dried over P_2O_5 *in vacuo* at room temperature, was weighed and analyzed for copper. Yield 155 mg (88%). *Anal.* Calcd. for $C_{18}H_{12}O_2N_2Cu$: Cu, 18.06%. Found: Cu, 18.27%.

NII-Electronic Library Service