

A New Phosphorylating Reagent. III.¹⁾ Preparation of Mixed Diesters of Phosphoric Acid by the Use of an Activatable Protecting Group

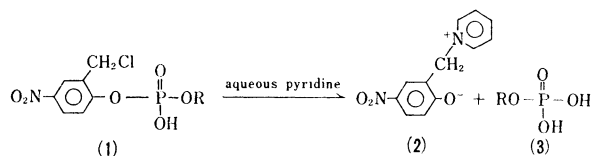
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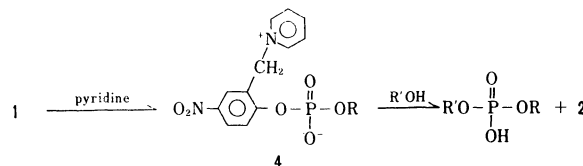
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A novel method for the preparation of mixed diesters of phosphoric acid has been investigated. It was found that mixed diesters of phosphoric acid were prepared by the reaction of alkyl 2-chloromethyl-4-nitrophenyl hydrogen phosphates with alcohols in dry pyridine. On the other hand, these diesters were also obtained from dialkyl 2-chloromethyl-4-nitrophenyl phosphates on hydrolysis under mild conditions. By using both of these methods, analytically pure samples of mixed diesters of phosphoric acid could be obtained in high yields.

In a previous paper,²⁾ it has been reported that highly pure samples of alkyl dihydrogen phosphates (**3**) were prepared in high yields under mild conditions by treating alkyl 2-chloromethyl-4-nitrophenyl hydrogen phosphates (**1**) with aqueous pyridine.



This result shows that 2-chloromethyl-4-nitrophenyl group functions to facilitate the elimination of this group through an intermediate, inner salt of 1-(2-alkyl hydrogen phosphoroxo 5-nitrobenzyl)pyridinium hydroxide (**4**), formed by an attack of pyridine on the chloromethyl group of **1** as sketched below. Therefore, it can be expected that mixed diesters of phosphoric acid would be successfully synthesized when **1** is treated with alcohols in dry pyridine.



When a mixture of one equiv. of **1** and two equiv. of *n*-pentyl alcohol in five equiv. of pyridine was allowed to stand at room temperature for two days and then was heated at 90°C for 6 hr, ethyl *n*-pentyl hydrogen phosphate (**5a**) was obtained in 81% yield along with inner salt of 1-(2-hydroxy-5-nitrobenzyl)pyridinium hydroxide (**2**).

In a similar manner, various mixed diesters of phosphoric acid were obtained in high yields as shown in Table 1.

In the cases of *n*-hexadecyl derivatives (**5b**, **5i**, **5j**, **5k**, and **5l**), it is necessary to carry out the reaction by using ten equiv. of pyridine because *n*-hexadecyl derivatives are less soluble in pyridine than the other

TABLE 1. PREPARATION OF DIALKYL HYDROGEN PHOSPHATES (**5**)

Compd.	R	R'	Yield ^{a)} (%)	Mp (°C)	<i>n</i> _D ²⁰	<i>R_f</i> ^{b)}	Formula	Calcd		Found	
								C	H	C	H
5a	Ethyl	<i>n</i> -Pentyl	81		1.4250 ²⁶	0.83	C ₇ H ₁₇ O ₄ P	42.85	8.73	42.91	8.90
5b		<i>n</i> -Hexadecyl	74	54—55		0.90	C ₁₈ H ₃₉ O ₄ P	61.69	11.22	62.31	11.21
5c		Cyclohexyl	58		1.4552 ²⁶	0.83	C ₈ H ₁₇ O ₄ P	46.15	8.23	46.50	8.51
5d		Bornyl	69		1.4717 ²⁵	0.87	C ₁₂ H ₂₃ O ₄ P	54.95	8.84	54.50	8.78
5e		Benzyl	60		^{c)}	0.81	C ₉ H ₁₃ O ₄ P	50.00	6.06	50.64	5.84
5f	<i>n</i> -Pentyl	<i>p</i> -Tolyl	57		1.4891 ²⁵	0.91	C ₁₂ H ₁₉ O ₄ P	55.81	7.42	55.62	7.17
5g		<i>p</i> -Chlorophenyl	61		1.4933 ²⁵	0.91	C ₁₁ H ₁₆ ClO ₄ P	47.41	5.79	47.27	5.62
5h		<i>p</i> -Nitrophenyl	55	61—62		0.91	C ₁₁ H ₁₆ NO ₆ P	45.68	5.58	46.30	5.62
								(N=4.84)		(N=4.69)	
5b	<i>n</i> -Hexadecyl	Ethyl	97	54—55		0.90					
5i		<i>n</i> -Pentyl	92	45—47		0.94	C ₂₁ H ₄₅ O ₄ P	64.25	11.55	63.95	11.90
5j		Cyclohexyl	87		1.4717 ²⁵	0.92	C ₂₂ H ₄₅ O ₄ P	65.31	11.21	65.73	10.96
5k		Bornyl	89		1.4782 ²⁴	0.94	C ₂₆ H ₅₁ O ₄ P	68.09	11.21	68.37	11.60
5l		Benzyl	86	58—60		0.94	C ₂₃ H ₄₁ O ₄ P	66.96	10.02	66.99	10.36
5f	<i>p</i> -Tolyl	<i>n</i> -Pentyl	72		1.4893 ²⁵	0.91					

a) Yields are based on the phosphate **1**.

b) Paper chromatography was carried out by ascending technique using Toyo Roshi No. 50 paper. Solvent system used was: isopropyl alcohol, conc. ammonium hydroxide, water (7 : 1 : 2 v/v).

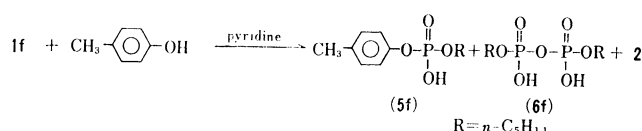
c) The compound **5e** is pale yellowish oil.

1) Paper II: T. Hata, Y. Mushika, and T. Mukaiyama, *Tetrahedron Lett.*, **1970**, 3505.

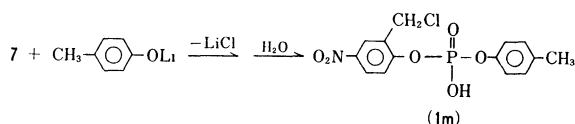
2) T. Hata, Y. Mushika, and T. Mukaiyama, *J. Amer. Chem. Soc.*, **91**, 4532 (1969).

derivatives.

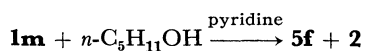
It was also found that phenols are successfully phosphorylated to give the corresponding alkyl aryl hydrogen phosphates. When *n*-pentyl 2-chloromethyl-4-nitrophenyl hydrogen phosphate (**1f**) was treated with *p*-cresol, *n*-pentyl *p*-tolyl hydrogen phosphate (**5f**) was obtained in 57% yield as a major product and a small amount of *P*¹,*P*²-di-*n*-pentyl pyrophosphate (**6f**) was detected as a by-product.



The formation of **6f** would be explained by considering the competitive reaction of **1f** with **4f** (R = *n*-C₅H₁₁). In order to avoid the undesirable formation of **6f**, *p*-tolyl 2-chloromethyl-4-nitrophenyl hydrogen phosphate (**1m**), prepared from lithium phenoxide and 2-chloromethyl-4-nitrophenyl phosphorodichloridate (**7**), was chosen with the consideration that **5f** would be exclusively produced because alcohols can react with **1m** much faster than phenols.



When the phosphate **1m** was treated with *n*-pentyl alcohol in dry pyridine, *n*-pentyl *p*-tolyl hydrogen phosphate (**5f**) was isolated in 72% yield without accompanying the formation of the pyrophosphate.



The reaction of thiols with **1** proceeded very sluggishly even when they were refluxed in dry pyridine. Similar to the cases of phenols mentioned above, *O,S*-di-*n*-pentyl hydrogen phosphorothioate (**8**) could be prepared in 42% yield starting from *S*-*n*-pentyl *O*-2-chloromethyl-4-nitrophenyl hydrogen phosphorothioate (**9**) by the treatment with *n*-pentyl alcohol in dry pyridine as shown in the following equation.

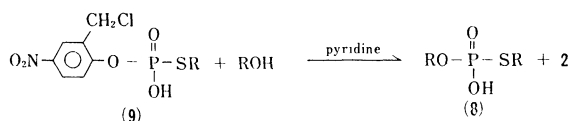


TABLE 2. PREPARATION OF DIALKYL 2-CHLOROMETHYL-4-NITROPHENYL PHOSPHATES (**11**)

Compd.	R ^{a)}	R' ^{a)}	R'OH (mol ratio)	Yield ^{b)} (%)	R _f ^{c)}	Formula	Calcd			Found		
							C	H	N	C	H	N
11p	Ethyl	Ethyl	1/1	64	0.94	C ₁₁ H ₁₅ ClNO ₆ P	40.82	4.67	4.35	41.02	4.98	4.64
11a	<i>n</i> -Pentyl	Ethyl	1/1	57	0.96	C ₁₄ H ₂₁ ClNO ₆ P	45.97	5.79	3.83	46.07	5.89	3.92
			5/1	93								
11b	<i>n</i> -Hexadecyl	Ethyl	2/1	81	0.96	C ₂₅ H ₄₃ ClNO ₆ P	57.74	8.33	2.69	57.99	8.08	2.78
11c	Cyclohexyl	Ethyl	2/1	91	0.95	C ₁₅ H ₂₁ ClNO ₆ P	47.69	5.60	3.71	48.01	5.82	3.88
11d	<i>n</i> -Pentyl	Cyclohexyl	1/1	46	0.96	C ₁₈ H ₂₇ ClNO ₆ P	51.49	6.48	3.34	51.26	6.31	3.56

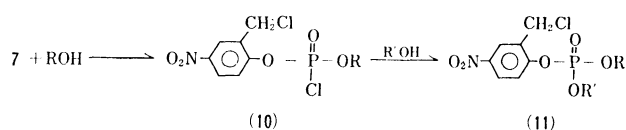
a) The phosphorodichloridate **7** was allowed to react with ROH and then with R'OH.

b) Yields are based on the phosphorodichloridate **7**.

c) Paper chromatography was carried out by ascending technique using Toyo Roshi No. 50 paper. Solvent system used was: isopropyl alcohol, conc. ammonium hydroxide, water (7 : 1 : 2 v/v).

In the next place, the preparation of mixed diesters of phosphoric acid from 2-chloromethyl-4-nitrophenyl phosphorodichloridate (**7**) and two different kinds of alcohols was investigated.

It was established that one of the two chlorine atoms of **7** reacts selectively with one equiv. of an alcohol in the presence of exactly one equiv. of pyridine to afford the corresponding alkyl 2-chloromethyl-4-nitrophenyl phosphorochloridate (**10**). The phosphorochloridate **10** was further, without isolating, treated with one equiv. of another alcohol in the presence of one equiv. of pyridine. The triester, dialkyl 2-chloromethyl-4-nitrophenyl phosphate (**11**) was obtained in high yield and it was purified by silica-gel column chromatography in order to remove **1**, formed by hydrolysis of **10**.



The structure of **11** was confirmed by elemental analysis as well as infrared and ultraviolet spectra. Several triesters **11** were obtained by this method as shown in Table 2.

TABLE 3. PREPARATION OF DIALKYL HYDROGEN PHOSPHATES (**5**) FROM DIALKYL 2-CHLOROMETHYL-4-NITROPHENYL PHOSPHATES (**11**)

Compd. ^{a)}	R	R'	Yield ^{b)} (%)	Appearance
5p	Ethyl	Ethyl	81	colorless oil
5a	Ethyl	<i>n</i> -Pentyl	85	colorless oil
5b	Ethyl	<i>n</i> -Hexadecyl	79	white powder (mp 54—55°C)
5c	Ethyl	Cyclohexyl	56	colorless oil
5n	<i>n</i> -Pentyl	Cyclohexyl	86	colorless oil

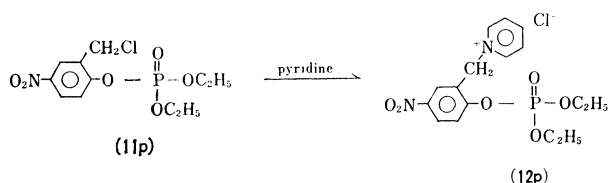
a) The compounds were identified with authentic samples listed in Table 1.

b) Yields are based on the phosphates **11**.

The triester **11** was smoothly hydrolyzed in aqueous pyridine to the corresponding dialkyl hydrogen phosphate (**5**). These results are summarized in Table 3.

The assumed intermediate, a pyridinium derivative (**12p**) could be isolated when diethyl 2-chloromethyl-

4-nitrophenyl phosphate (**11p**) was treated with one equiv. of pyridine in the absence of alcohol. The compound **12p** was very hygroscopic pale yellow prisms and melted at 191°C.



Experimental

Reagents. Alcohols, mercaptans, phenols and pyridine were purified and dried by ordinary procedures. 2-Chloromethyl-4-nitrophenyl phosphorodichloridate (**7**) and alkyl 2-chloromethyl-4-nitrophenyl hydrogen phosphates (**1**) were prepared as described in a previous publication.²⁾

Paper Chromatography. Paper chromatography was carried out by ascending technique using Toyo Roshi No. 50 paper. Solvent system used was: isopropyl alcohol, concentrated ammonium hydroxide, water (7 : 1 : 2 v/v).

Preparation of Dialkyl Hydrogen Phosphates (5) from Alkyl 2-Chloromethyl-4-nitrophenyl Hydrogen Phosphates (1). *General Procedure:*

Alkyl 2-chloromethyl-4-nitrophenyl hydrogen phosphate (**1**) (0.01 mol) and an alcohol (0.02 mol) were dissolved in 4–8 ml of dry pyridine. The mixture was allowed to stand at room temperature for 2 days and then heated at 90°C for 6 hr. After addition of 30 ml of ethanol, a pale yellowish precipitate, inner salt of 1-(2-hydroxy-5-nitrobenzyl)pyridinium hydroxide separated. It was removed by filtration and washed with 30 ml of ethanol. The combined filtrate and washings were concentrated to dryness. Dialkyl hydrogen phosphate was isolated from the oily residue by means of either *Method A* or *Method B*. The compounds (see Table 1), **5d**, **5f**, and **5g** were prepared by *Method A-1*. The compounds, **5a**, **5b**, **5c**, **5e**, and **5h** were obtained by *Method A-2*. The other compounds, **5i**, **5j**, **5k**, and **5l** were isolated by *Method B*.

The results are summarized in Table 1.

Method A: The oily residue was dissolved in 50 ml of water containing 1.7 g (0.02 mol) of sodium hydrogencarbonate and the solution was washed with ether. The aqueous layer was acidified with hydrochloric acid and extracted with three 30 ml portions of petroleum ether (*Method A-1*) or ether (*Method A-2*). The combined extracts were washed with three 10 ml portions of water and dried over anhydrous sodium sulfate. After removal of the solvent, pure sample of dialkyl hydrogen phosphate (**5**) was obtained without further purification.

Method B: After complete removal of the solvent under high vacuum, the residue was dissolved in 100 ml of petroleum ether (bp 45–60°C). The solution was washed with dilute hydrochloric acid and then three 10 ml portions of water. After drying the solution over anhydrous sodium sulfate, petroleum ether was removed by evaporation. Highly pure sample of dialkyl hydrogen phosphate (**5**) was obtained as white powder (**5i** and **5l**) or colorless oil (**5j** and **5k**).

S-n-Pentyl O-2-Chloromethyl-4-nitrophenyl Hydrogen Phosphorothioate (9). A suspension of lithium *n*-pentyl mercaptide, which was prepared from 2.42 ml (0.02 mol) of *n*-pentyl mercaptan in 20 ml of tetrahydrofuran (THF) and

12 ml (0.02 mol) of 10% solution of *n*-butyllithium in *n*-hexane, was slowly added at –20°C to a solution of 6.08 g (0.02 mol) of 2-chloromethyl-4-nitrophenyl phosphorodichloridate (**7**) in 30 ml of tetrahydrofuran. The stirring was continued at –20––10°C for 3 hr and further at room temperature for 2 hr. The mixture was poured into 50 ml of water containing 1.6 ml (0.02 mol) of pyridine at a temperature below 20°C and then stirred for 30 min. THF was removed and the solution was extracted with three 50 ml portions of benzene. The extract was washed with three 10 ml portions of water and dried over anhydrous sodium sulfate. After removal of benzene, *S-n*-pentyl O-2-chloromethyl-4-nitrophenyl hydrogen phosphorothioate (**9**) (3.30 g, 49%) was obtained as reddish oil; R_f : 0.92; $\lambda_{\text{max}}^{\text{H}_2\text{O}}$ 290 m μ (ϵ : 8400).

Found: C, 39.89; H, 4.77; N, 4.22%. Calcd for $\text{C}_{12}\text{H}_{17}\text{ClNO}_5\text{PS}$: C, 40.74; H, 4.84; N, 3.96%.

O,S-di-n-Pentyl Hydrogen Phosphorothioate (8). A solution of 3.40 g (0.01 mol) of *S-n*-pentyl O-2-chloromethyl-4-nitrophenyl hydrogen phosphorothioate (**9**) and 2.16 ml (0.02 mol) of *n*-pentyl alcohol in 4 ml (0.05 mol) of dry pyridine was allowed to stand at room temperature for 2 days and further heated at 90°C for 6 hr. Thirty ml of ethanol was added and pale yellowish precipitate, inner salt of 1-(2-hydroxy-5-nitrobenzyl)pyridinium hydroxide (1.76 g, 66%) separated and was filtered off. The filtrate was concentrated and the residue was dissolved in 30 ml of water containing 1.7 g of sodium hydrogencarbonate. The aqueous solution was washed with ether and acidified with hydrochloric acid and then extracted with three 30 ml portions of petroleum ether. The combined extracts were washed with three 10 ml portions of water and dried over anhydrous sodium sulfate. After decolorizing with charcoal, the solvent was removed by evaporation. *O,S*-di-*n*-pentyl hydrogen phosphorothioate (**8**) (1.19 g, 47%) was obtained as yellowish oil; R_f 0.92; n_D^{20} 1.4762.

Found: C, 47.67; H, 8.91, S, 13.50%. Calcd for $\text{C}_{10}\text{H}_{23}\text{O}_3\text{PS}$: C, 47.22; H, 9.12; S, 12.61%.

Formation of P^1, P^2 -di-*n*-Pentyl Pyrophosphate (6f). A solution of *n*-pentyl 2-chloromethyl-4-nitrophenyl hydrogen phosphate (**1f**) (3.38 g, 0.01 mol) in 4 ml (0.05 mol) of pyridine was allowed to stand at room temperature for 2 days and further heated at 90°C for 6 hr. Ethanol (30 ml) was added to the solution. Pale yellowish precipitate, inner salt of 1-(2-hydroxy-5-nitrobenzyl)pyridinium hydroxide (2.25 g, 84%) separated and was filtered off. The filtrate was evaporated and the residue was dissolved in 30 ml of water. The solution was acidified with hydrochloric acid and extracted with four 30 ml portions of ether. The extracts were combined and dried over anhydrous sodium sulfate. After removal of ether, the residual oil was dissolved in 20 ml of ether and then 3.0 g of aniline was added. The mixture was kept standing in a refrigerator overnight. A white precipitate separated and was collected by filtration. The precipitate was recrystallized from a mixture of ethanol and acetone. Di-anilinium salt of P^1, P^2 -di-*n*-pentyl pyrophosphate (**6f**) (0.93 g, 37%) was obtained as white prisms; mp 134°C; R_f 0.78.

Found: C, 51.78; H, 7.67; N, 5.57%. Calcd for $\text{C}_{22}\text{H}_{35}\text{N}_2\text{O}_7\text{P}_2$: C, 52.38; H, 7.59; N, 5.55%.

Preparation of Dialkyl 2-Chloromethyl-4-nitrophenyl Phosphates (11). *A Typical Procedure:* To a solution of 6.01 g (0.02 mol) of 2-chloromethyl-4-nitrophenyl phosphorodichloridate (**7**) in 30 ml of THF was added slowly a solution of cyclohexanol (2.00 g, 0.02 mol) and pyridine (1.60 g, 0.02 mol) in 20 ml of THF with stirring at a temperature below –10°C. The mixture was stirred for 4 hr and further at room tem-

perature for 2 hr. A solution of ethanol (2.33 ml, 0.04 mol) and pyridine (1.6 ml, 0.02 mol) in THF (20 ml) was then added under cooling. Stirring was continued for 2 hr and further at room temperature for 5 hr. After concentrating the mixture, the residue was poured into water (30 ml) and extracted with benzene (80 ml). The benzene was washed with water and dried over anhydrous sodium sulfate. After removal of the solvent, the syrupy residue was passed through a column of Wakogel C-200 (100—200 mesh) (20 mm \times 500 mm) by using benzene for elution. The eluent was concentrated to dryness. Ethyl cyclohexyl 2-chloromethyl-4-nitrophenyl phosphate (**11d**) (6.9 g, 91%) was obtained as a pale yellowish syrup. In a similar manner, the triesters (**11**), such as **11p**, **11b**, **11c**, and **11e** were obtained in high yields as shown in Table 2.

Preparation of Dialkyl Hydrogen Phosphates (5) from Dialkyl 2-Chloromethyl-4-nitrophenyl Phosphates (11). A Typical Procedure: A solution of *n*-pentyl cyclohexyl 2-chloromethyl-4-nitrophenyl phosphate (**11e**) (4.20 g, 0.01 mol) in 12 ml of aqueous pyridine (30% solution) was allowed to stand at room temperature for 2 days and then heated at 90°C for 3 hr. The reaction mixture was concentrated to dryness. Ethanol (30 ml) was added and pale yellowish precipitate, inner salt of 1-(2-hydroxy-5-nitrobenzyl)pyridinium hydroxide (2.35 g, 88%) separated and was filtered off. The filtrate was concentrated and the residue was dissolved in 30 ml of water. The aqueous solution was acidified with hydrochloric acid

and extracted with three 30 ml portions of petroleum ether (bp 45—60°C). The extracts were combined and washed with three 10 ml portions of water and dried over anhydrous sodium sulfate. After removal of petroleum ether, *n*-pentyl cyclohexyl hydrogen phosphate (**5n**) (2.15 g, 86%) was obtained as colorless oil, R_f 0.85; n_D^{25} 1.4552.

Found: C, 53.30, H, 8.61%. Calcd for $C_{11}H_{23}O_4P$: C, 52.79; H, 9.26%.

In a similar manner, the other dialkyl hydrogen phosphate (**5**), such as **5p**, **5a**, **5b**, and **5c** were prepared as shown in Table 3.

Isolation of an Intermediate 1-(2-Diethyl Phosphoroxo 5-Nitrobenzyl)pyridinium Chloride (12p). A solution of diethyl 2-chloromethyl-4-nitrophenyl phosphate (**11p**) (3.24 g, 0.01 mol) in 8.0 ml of dry pyridine was allowed to stand at room temperature for 3 days. After addition of acetone (40 ml), yellowish precipitate, **12p** was separated and was collected by filtration. It was recrystallized from a mixture of ethanol (4 ml) and acetone (15 ml) to afford a pure sample (1.65 g, 43%) as pale yellowish prisms; mp 191°C dec., $\lambda_{max}^{H_2O}$ 262 m μ (ϵ : 10700), 267 m μ (ϵ : 10700), 289 m μ (ϵ : 10500); R_f 0.61.

Found: C, 50.03; H, 5.65; N, 7.46%. Calcd for $C_{16}H_{21}N_2O_7P$: C, 50.00; H, 5.51; N, 7.29%.

We wish to thank Mr. Masaru Koezuka for his help with elemental analysis.