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Phosphorylation via the Oxidation of Phosphite. II. The Preparation of the Diesters of Phosphorous Acid by the Reaction of Alcohols with Ethyl *N*-Phenylimino Phosphite and Acids[*1]

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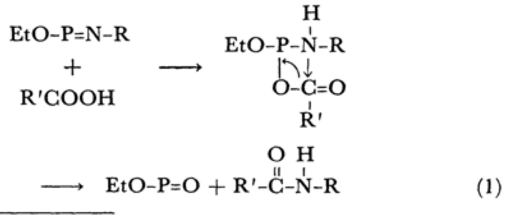
The diesters of phosphorous acid were prepared in good yields by the reaction of primary or secondary alcohols, such as methanol, ethanol, and *s*-butanol, or of phenols, such as phenol, *p*-chlorophenol and *p*-cresol, with ethyl *N*-phenylimino phosphite and *p*-toluenesulfonic acid monohydrate. Similarly, when carboxylic acids, such as acetic acid, benzoic acid, *p*-chlorobenzoic acid and trichloroacetic acid, were used in place of the acid monohydrate in the above experiment, the diesters of phosphorous acid were also obtained. Ethyl *N*-*n*-propylimino or ethyl *N*-isopropylimino phosphite could be successfully used in place of ethyl *N*-phenylimino phosphite in the above experiments. Further, various derivatives of methylphosphinic acid, such as ethyl dicyanomethyl-, ethyl cyanocarboethoxymethyl- and ethyl dicarboethoxymethylphosphinate, were obtained by the reaction of ethyl *N*-phenylimino phosphite, *p*-toluenesulfonic acid monohydrate and active methylene compounds, such as malononitrile, ethyl cyanoacetate and diethyl malonate.

Recently, it has been found that diesters of phosphorous acid are successfully oxidized under mild conditions to give dialkyl hydrogen phosphates in high yields by means of monobromocyanoacetamide and benzyl alcohol. Therefore, a new useful method for the synthesis of diesters of phosphoric acid can be expected to be offered by the phosphonylation of alcohols and the subsequent oxidation of the phosphites. In this connection, the preparation of diesters of phosphorous acid by the reaction of alcohols with ethyl *N*-phenylimino phosphite and benzaldehyde was reported in the preceding paper.[1]

In the present study, the preparation of diesters of phosphorous acid from alcohols and metaphosphite, formed by the reaction of ethyl *N*-phenylimino phosphite and either carboxylic acid or *p*-toluenesulfonic acid, was attempted. The possible formation of metaphosphite from the reaction of ethyl *N*-phenylimino phosphite and carboxylic acids (Eq. 1) was suggested by the fact that the reaction of phenyl isocyanate with acetic acid resulted in the formation of acetanilide and carbon dioxide by way of a mixed anhydride of phenylcarbamic acid and acetic acid.[2]



$$\mathrm{EtO\text{-}P{=}N\text{-}R} + \mathrm{R'COOH} \longrightarrow \mathrm{EtO\text{-}\underset{\displaystyle O\text{-}\underset{\displaystyle R'}{C}{=}O}{P}\text{-}\overset{H}{N}\text{-}R} \longrightarrow \mathrm{EtO\text{-}P{=}O} + \mathrm{R'\text{-}\overset{O}{\overset{\|}{C}}\text{-}\overset{H}{N}\text{-}R} \qquad (1)$$

Indeed, when acetic acid and ethyl *N*-phenylimino phosphite were refluxed in anhydrous benzene for an hour, acetanilide was obtained in a 59% yield, but the expected metaphosphite could not be detected and an orange-colored resinous product was formed.

The presence of the intermediate, i. e., metaphosphite, is demonstrated by the formation of the corresponding diesters of phosphorous acid, diethyl phosphite or ethyl butyl phosphite, along with acetanilide, when acetic acid reacts with ethyl *N*-phenylimino phosphite in the presence of such alcohols as ethyl alcohol or butyl alcohol. Similarly, dialkyl phosphites were obtained, along with the corresponding anilides, when benzoic acid, *p*-chlorobenzoic acid or trichloroacetic acid was used in place of acetic acid in the above experiment. In these cases, ethyl alkyl phosphite was contaminated with small amounts of triethyl phosphite, a compound containing a carbonyl group and aniline, the presences of which were confirmed by the infrared spectra.

On the other hand, when ethyl *N*-phenylimino phosphite was treated with a strong acid such as *p*-toluenesulfonic acid monohydrate in the presence of alcohols, an exothermic reaction soon took place and diesters of phosphorous acid were obtained in good yields, along with the anilinium salt of *p*-toluenesulfonic acid (see Table I).

Contrary to the results obtained in the case of the phosphonylation of alcohols by means of ethyl *N*-phenylimino phosphite and benzaldehyde, both

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[1] O. Mitsunobu and T. Mukaiyama, *J. Org. Chem.*, **29**, 3005 (1964).

[2] T. Hoshino, T. Mukaiyama and H. Hoshino, *J. Am. Chem. Soc.*, **74**, 3097 (1952).

Table I. Reactions of alcohols with ethyl *N*-phenylimino phosphite and *p*-toluenesulfonic acid monohydrate

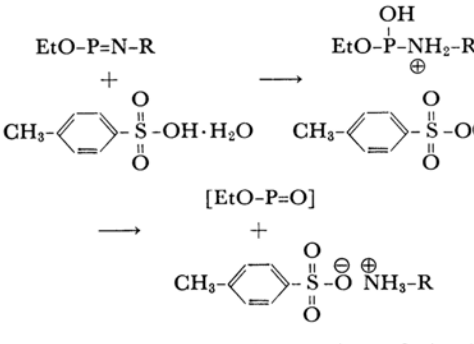
Alcohol	Reaction condition			Ethyl alkyl phosphite			Anilinium salt
	Solvent	Time hr.	Temp. °C	Yield %	b. p. °C/mmHg	$n_D^{\circ C}$	%
Methyl-	Benzene	2.0	65—78	61	59—61/14	?	93
Ethyl-	Benzene	2.0	80	59	70/14	n^{16} 1.4081	93
n-Propyl-	Benzene	2.0	80	54	52—53/4	n^{14} 1.4150	89
Isopropyl-	Benzene	2.1/3	80	63	38—39/3	n^{12} 1.4101	90
n-Butyl-	Benzene	2.0	80	64	55—72/3	n^{17} 1.4192	93
Isobutyl-	Benzene	1.2/3	80	61	52—62/3	n^{19} 1.4150	?
t-Butyl-	Benzene	2.0	80	—	—	—	95
Benzyl-	Benzene	2.0	80	54	113/3	n^{20} 1.4893	90

primary and secondary alcohols were similarly phosphonylated in good yields by the present method. However, in the case of the phosphonylation of such tertiary alcohols as *t*-butyl alcohol, the yield of phosphite decreased markedly.

Further, it was established, that phenols, such as phenol, *p*-chlorophenol and *p*-cresol, reacted with ethyl *N*-phenylimino phosphite and *p*-toluenesulfonic acid to give the corresponding ethyl aryl phosphites. Unfortunately, these phosphites could not be purified by distillation; a small amount of phenols always contaminated the phosphites.

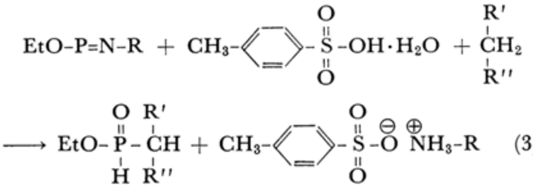
In a similar way, it was also found that ethyl *N*-isopropylimino phosphite or ethyl *N*-*n*-propylimino phosphite gave the corresponding dialkyl phosphite by reaction with ethyl alcohol and *p*-toluenesulfonic acid.

The reaction may proceed through the initial formation of an intermediate, formed by the addition of the water of crystallization of *p*-toluenesulfonic acid to ethyl *N*-phenylimino phosphite, which in trun decomposes to metaphosphite and the anilinium salt of *p*-toluenesulfonic acid, as is shown in the following scheme (Eq. 2). Alcohols then join with the metaphosphite to form diesters of phosphorous acid.



(2)

These results suggest that various derivatives of methylphosphinic acid can be prepared by the reaction of ethyl *N*-phenylimino phosphite, *p*-toluenesulfonic acid monohydrate and active methylene compounds. Indeed, when malononitrile, ethyl cyanoacetate or diethyl malonate was refluxed in benzene with ethyl *N*-phenylimino phosphite and *p*-toluenesulfonic acid monohydrate, the corresponding methylphosphinic acid derivatives, such as ethyl dicyanomethylphosphinate, were obtained (Eq. 3).



(3)

Experimental

All melting points and boiling points are uncorrected.

Solvents and Reagents.—The solvents and alcohols were dried and purified by ordinary procedures. Ethyl *N*-phenylimino phosphite was prepared from ethyl dichlorophosphite and aniline according to a method previously reported.[1)]

Ethyl *N*-*n*-propylimino phosphite, b. p. 80—110°C/0.5 mmHg, 41%, and ethyl isopropylimino phosphite, b. p. 72—85°C/0.5 mmHg, 29%, were prepared by a method analogous to that used for ethyl *N*-phenylimino phosphite. These compounds were also obtained when ethyl dichlorophosphite was treated with an equimolar amount of isopropylamine or *n*-propylamine in the presence of triethylamine.

The Reaction of Ethyl *N*-Phenylimino Phosphite with Carboxylic Acids.—When a solution of acetic acid (1.20 g., 0.02 mol.) and ethyl *N*-phenylimino phosphite (1.67 g., 0.01 mol.) in 40 ml. of benzene was refluxed for an hour, acetanilide (0.80 g., 59%) was obtained, along with a colorless oily product. Similarly, benzanilide (88%) and trichloroacetanilide (96%) were obtained when benzoic acid and trichloroacetic acid respectively were used in place of acetic acid in the above experiment.

The Reaction of Ethyl Alcohol with Ethyl *N*-Phenylimino Phosphite and Acetic Acid.—Into a solution of ethyl *N*-phenylimino phosphite (1.67 g., 0.01 mol.) in 10 ml. of benzene there were stirred, at room temperature and in one portion, both a solution of acetic acid (0.60 g., 0.01 mol.) in 5 ml. of benzene and a solution of ethyl alcohol (0.46 g., 0.01 mol.) in 5 ml. of benzene. After the solvent had been removed under reduced pressure, acetanilide was separated by

TABLE II. THE REACTIONS OF ETHYL ALCOHOL WITH ETHYL *N*-PHENYLIMINO PHOSPHITE AND CARBOXYLIC ACIDS

Carboxylic acid	Reaction condition*1	Yield of anilide, %	Yield of*2 diethyl phosphite, %
Acetic	Reflux 7.5 hr.	59	72
Benzoic	Reflux 5.0 hr.	33	86
p-Chlorobenzoic	Reflux 6.0 hr.	*3	14
Trichloroacetic	Reflux 1.0 hr.	26	33

*1 Each reaction was carried out in dry benzene on the scale of 0.01 mol.

*2 In each case, the phosphites were contaminated with small amounts of aniline, triethyl phosphite and a substance containing a carbonyl group.

*3 0.76 g. (46%) of *p*-chlorobenzoic acid was recovered.

the addition of petroleum ether to the residue. The acetanilide was then removed by filtration; 0.30 g. (22%); m. p. 113—114°C. The filtrate was fractionally distilled to give 1.00 g. (72%) of crude diethyl phosphite (b. p. 38—45°C/5 mmHg, n_D^{22} 1.4184), and the residue was solidified to give 0.50 g. (37%) of acetanilide.

Similarly, crude ethyl *n*-butyl phosphite (0.87 g., 52%; b. p. 45—77°C/4 mmHg, n_D^{19} 1.4320) was obtained by the reaction of *n*-butyl alcohol (0.74 g., 0.01 mol.) with ethyl *N*-phenylimino phosphite (1.67 g., 0.01 mol.) and acetic acid (0.60 g., 0.01 mol.). The reactions of ethyl alcohol with ethyl *N*-phenylimino phosphite and benzoic acid, *p*-chlorobenzoic acid or trichloroacetic acid gave the corresponding anilides and crude diethyl phosphite (see Table II).

The Reaction of Ethyl *N*-Phenylimino Phosphite with *p*-Toluenesulfonic Acid Monohydrate.—When ethyl *N*-phenylimino phosphite (0.42 g., 0.025 mol.) and *p*-toluenesulfonic acid monohydrate (0.43 g., 0.026 mol.) were mixed in one portion by stirring them at room temperature, white needles were soon separated. The crystalline compound, 0.50 g. (80%), m. p. 229—232°C, was filtered off and identified by a comparison of its infrared spectrum with an authentic anilinium salt of *p*-toluenesulfonic acid.

The Reaction of Ethyl Alcohol with Ethyl *N*-Phenylimino Phosphite and *p*-Toluenesulfonic Acid Monohydrate.—To a solution of ethyl *N*-phenylimino phosphite (1.67 g., 0.01 mol.) in 20 ml. of benzene there was added a mixture of *p*-toluenesulfonic acid monohydrate (1.90 g., 0.01 mol.) and ethyl alcohol (0.46 g., 0.01 mol.) in 40 ml. of benzene. After the reaction mixture had been stirred for two hours at 80°C, a separated anilinium salt of *p*-toluenesulfonic acid (2.45 g.; 93%), was filtered off; the filtrate was then concentrated under reduced pressure. The fractionation of the residual oil gave diethyl phosphite, 0.82 g. (60%); b. p. 70°C/14 mmHg, n_D^{16} 1.4081, which was identified by a comparison with both its retention time of the gas chromatography and the infrared spectrum with these of an authentic sample (see Table I).

Similarly, when 1.41 g. (0.015 mol.) of phenol was treated with 3.34 g. (0.020 mol.) of ethyl *N*-phenylimino phosphite and 3.80 g. (0.02 mol.) of *p*-toluenesulfonic acid monohydrate, crude ethyl phenyl phosphite, 1.52 g. (82%); b. p. 110—117°C/5 mmHg, was obtained. Redistillation gave 0.48 g. (26%) of pure ethyl phenyl phosphite, b. p. 105°C/5 mmHg.

Infrared spectrum: 2420 (P–H), 1270 (P=O), 1595, 1495, 760 and 690 cm^{-1} (mono-substituted benzene).

Found: C, 52.09; H, 5.86. Calcd. for $C_8H_{11}O_3P$: C, 51.69; H, 5.96%.

The Reaction of Ethyl Alcohol with Ethyl *N*-Isopropylimino Phosphite and *p*-Toluenesulfonic Acid Monohydrate.—A solution of ethyl alcohol (0.51 g., 0.011 mol.) and *p*-toluenesulfonic acid monohydrate (2.09 g., 0.011 mol.) in 5 ml. of benzene was added, drop by drop, to a solution of ethyl *N*-isopropylimino phosphite (1.44 g., 0.011 mol.) in 20 ml. of benzene. The solution was refluxed for an hour. A separated isopropylammonium salt of *p*-toluenesulfonic acid 2.47 g. (97%); m. p. 137—139°C, was filtered off. After the solvent had been removed, diethyl phosphite, 1.21 g. (80%); b. p. 45—50°C/3 mmHg, n_D^{19} 1.4070, was obtained by distillation. Similarly, ethyl *N*-*n*-propylimino phosphite gave diethyl phosphite (50%).

The Reaction of Malononitrile with Ethyl *N*-Phenylimino Phosphite and *p*-Toluenesulfonic Acid Monohydrate.—A solution of 0.66 g. (0.01 mol.) of malononitrile and 1.90 g. (0.01 mol.) of *p*-toluenesulfonic acid monohydrate in 40 ml. of benzene was added to a solution of 1.67 g. (0.01 mol.) of ethyl *N*-phenylimono phosphite in 20 ml. of benzene. After the reaction mixture had been stirred for 2.1/4 hr. under refluxing, the anilinium salt of *p*-toluenesulfonic acid, 2.40 g.; (91%), was obtained by filtration. The filtrate was fractionated to give crude ethyl dicyanomethylphosphinate, 0.92 g, (58%); b. p. 60—63°C/4 mmHg, n_D^{12} 1.4138. Redistillation gave an analytical sample, b. p. 60—64°C/4 mmHg, n_D^{15} 1.4091.

Infrared spectrum; 2440 (P–H), 2260 (CN), 1250 cm^{-1} (P=O).

Found: N, 17.93. Calcd. for $C_5H_7O_2N_2P$: N, 17.72%.

Summary

Diesters of phosphorous acid have been prepared by the reaction of alcohols or phenols with ethyl *N*-phenylimino phosphite and acids, such as acetic acid, benzoic acid and *p*-toluenesulfonic acid monohydrate. Further, methylphosphonic acid derivatives have been obtained using active methylene compounds in place of alcohols in the above reaction.

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