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Studies on Reactions of the *N*-Phosphonium Salts of Pyridines. I. A New Method for the Activation of Carboxylic Acids *via* the *N*-Phosphonium Salts by Means of the Oxidation of Tri- and Di-esters of Phosphorous Acid in the Presence of Tertiary Amines

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Carboxylic acids were found to be activated by an oxidation mixture prepared from tri- and di-esters of phosphorous acid and mercuric chloride in a pyridine solution; they yielded the corresponding anilides upon treatment with aniline, together with a nearly quantitative yield of metallic mercury. The yield of the anilides was affected by the alkyl groups in the esters and by the tertiary amines. Only a small effect of the steric factor of carboxylic acids upon the reaction was seen in the cases of the diesters, and none at all was observed in the triesters. The reaction was proposed to proceed *via* the *N*-phosphonium salts of pyridines, which were not purely isolated, but which were assumed on the basis of the IR spectra.

Though various methods[1] have been reported for the phosphorylation of alcohols by means of the esters of phosphorous acid, there are few which are effective for the phosphorylation of carboxylic acids.[2] Mukaiyama *et al.*[3] have reported obtaining diethyl acyl phosphates by means of the oxidation of triethyl phosphite and monobromocyanoacetamide in the presence of carboxylic acids. They have also shown that mercuric salts such as mercuric chloride are useful oxidizing agents for the oxidation of phosphorous acid in the course of the preparation of monoalkyl phosphates.[4] In the oxidation of trialkyl phosphite with *N*-chlorosuccinimide, an *N*-phosphonium salt[5] have been suggested to be involved.

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[1] G. M. Blackburn, "Topics in Phosphorus Chemistry," Vol. 6, Interscience Publishers Inc., New York (1969), p. 187.

[2] G. W. Anderson, J. Blodinger, and A. D. Welcher, *J. Amer. Chem. Soc.*, **74**, 5309 (1952).

[3] T. Mukaiyama, T. Hata, and O. Mitsunobu, *Yuki Gosei Kagaku Kyokai Shi*, **20**, 969 (1962).

[4] T. Obata and T. Mukaiyama, *J. Org. Chem.*, **32**, 1063 (1967).

[5] A. K. Tsolis, W. E. McEven, and C. A. Vanderwerf, *Tetrahedron Lett.*, **1964**, 3217.

In a previous paper,[6] we ourselves reported briefly a convenient method for the synthesis of carboxylic amides and esters *via* the *N*-phosphonium salts of pyridine prepared by the oxidation of phosphorous acid and its esters with mercuric chloride in pyridine, and showed that pyridine played an important role in this reaction.

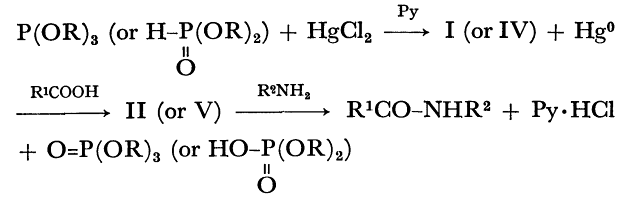
This paper will present the detailed results of the oxidation of various tri- and di-esters of phosphorous acid in tertiary amines, especially in pyridine, resulting in the *N*-phosphonium salts of pyridine, and of the activation of carboxylic acids to give the corresponding amides by means of the salts.

Results and Discussion

Through the studies of this series of reactions, aniline was chosen as the amine component of the amides, because anilides are readily isolated and the yield of the activated carboxylic acids can be estimated almost quantitatively from the amount of the anilides obtained.

When tri- and di-isopropyl esters of phosphorous acid were brought into reaction with mercuric chloride in refluxing pyridine, followed by treatment with an equimolar amount of acetic acid and then with aniline, acetanilide was obtained in 73 and 94% yields respectively, together with a nearly quantitative yield of metallic mercury. In a similar manner, various anilides were successfully synthesized from various phosphites (see Tables 1 and 2). However, no detectable amount of the anilide was obtained when a mixture of acetic acid and aniline was heated in pyridine under reflux in the absence of these phosphorous compounds.

The reaction may be summarized as follows:



$$\mathrm{P(OR)_3\ (or\ H\text{-}\underset{\underset{\displaystyle O}{\|}}{P}(OR)_2) + HgCl_2 \xrightarrow{Py} I\ (or\ IV) + Hg^0}$$

$$\mathrm{\xrightarrow{R^1COOH} II\ (or\ V) \xrightarrow{R^2NH_2} R^1CO\text{-}NHR^2 + Py\cdot HCl}$$

$$\mathrm{+\ O{=}P(OR)_3\ (or\ HO\text{-}\underset{\underset{\displaystyle O}{\|}}{P}(OR)_2)}$$

Compounds I, II, IV, and V have been assumed to be the *N*-phosphonium salts of pyridines.[6] The phosphorous compounds may be considered to participate not catalytically but stoichiometrically in this reaction from the fact that the yield of the anilide was reduced with a decrease in the amount of the phosphites in pyridine.

The effect of the alkyl group in the phosphites on this reaction was examined by using various phosphites under identical conditions. From the yield of acetanilide (Table 1), the reactivities of trialkyl phosphites are determined to be in the following order: trimethyl< tri-*n*-butyl≈triethyl<triisopropyl. In the cases of the diesters of phosphorous acid, the order of reactivities was similar to that of the triesters; dimethyl<di-*n*-butyl≈diethyl<diisopropyl. Triphenyl phosphite was not oxidized in this system, whereas diphenyl phosphite gave acetanilide in a 93% yield.

Table 1. The preparation of acetanilide using various phosphites and mercuric chloride in pyridine

Phosphite	Acetanilide, Yield, %
Trimethyl	0
Triethyl	53
Triisopropyl	73
Tri-*n*-butyl	50
Dimethyl	56
Diethyl	77
Diisopropyl	94
Di-*n*-butyl	74
Diphenyl	93

There was expected a side reaction in which alkyl groups of the phosphites were attacked by acids to afford the acid esters. Actually, a small amount of ethyl acetate was detected by the gas-chromatographic analysis of the reaction mixture from acetic acid and the oxidation product (I) of triethyl phosphite, besides a 53% yield of acetanilide. Since a separate experiment gave only a small amount of acetanilide upon the reaction of ethyl acetate with aniline under identical conditions, the amide by the present method was not formed through the reaction of the esters thus obtained with aniline.

The steric requirement of I and IV upon carboxylic acids was not observed in the cases of the triesters, whereas only a small effect was observed in the cases of the diesters, when the carboxylic residues were quite large (see Table 2). These results suggested that the reaction of I and IV with carboxylic acids was a replacement of the chlorine atom by the acyloxy groups instead of an addition of the acyloxy groups to the phosphorus-oxygen double bond in IV, as will be discussed in this paper.

Table 2. The preparation of various anilides using tri- and di-isopropyl phosphites and mercuric chloride in pyridine

Anilides	Triisopropyl phosphite, Yield, %	Diisopropyl phosphite, Yield, %
Acetanilide	73	94
n-Butyranilide	77	98
Isobutyranilide	74	97
Pivalanilide	61	70
Benzanilide	79	78

Tertiary amines influenced the yield of the anilide. Of the amines examined, pyridine was most effective for the reactions of phosphorous acid and its mono- and di-esters. In the case of triisopropyl phosphite, α-picoline among the pyridine derivatives gave the best results; even in 2,6-lutidine acetanilide was obtained in a 59% yield (Table 3). These results indicated that the basicity of the amine was rather more influential than its steric effect on the yield of the anilide. Triethylamine did not yield acetanilide. This may be caused by the instability of the I and/or II obtained from the amine. On the contrary, in the case of diisopropyl phosphite, pyridine gave a better result (a 94% yield of acetanilide) than α-picoline (77% yield).

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[6] N. Yamazaki and F. Higashi, *Tetrahedron Lett.*, **1972**, 415.

TABLE 3. THE PREPARATION OF ACETANILIDE IN VARIOUS TERTIARY AMINES USING TRIISOPROPYL PHOSPHITE

Amines	pK_a	Acetanilide[a], Yield, %
Pyridine	5.23	73
α-Picoline	5.97	83
2,6-Lutidine	6.99	59
Triethylamine	10.87	0

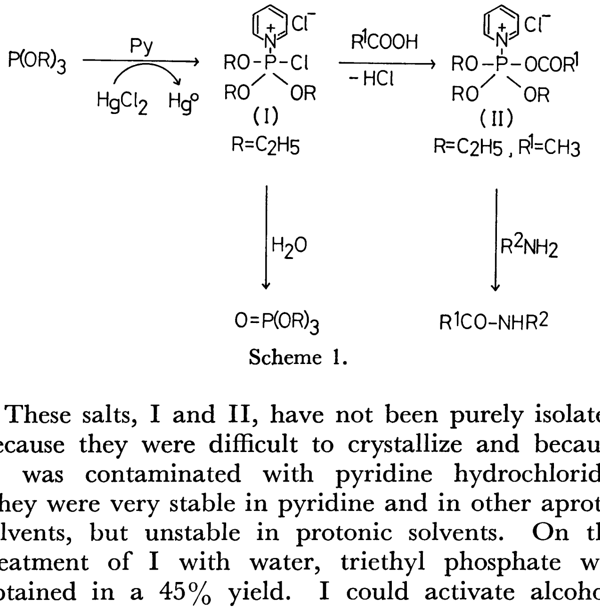
a) The reaction was carried out in refluxing pyridine or 115 °C in other pyridines. In the case of triethylamine refluxing acetonitrile was used as solvent.

The difference in the effect between tri- and di-isopropyl phosphites may be caused by the stability and reactivity of I and IV to carboxylic acids and/or amines like aniline.

In order to confirm the proposed mechanism described in a previous paper,[6] we have attempted to isolate the intermediate compounds, I and II, but with only limited success.

The N-phosphonium salt of pyridine (I) was separated as an ether-insoluble pale brown syrup from an oxidation mixture of triethyl phosphite. When I or the oxidation mixture, without the separation of I, was treated with carboxylic acids, the N-phosphonium salt of pyridine carrying acyloxy groups (II) was obtained. On further treatment of II with aniline, the anilides were obtained in good yields.

The over-all route of the reaction is summarized in Scheme 1:



Scheme 1.

These salts, I and II, have not been purely isolated because they were difficult to crystallize and because II was contaminated with pyridine hydrochloride. They were very stable in pyridine and in other aprotic solvents, but unstable in protonic solvents. On the treatment of I with water, triethyl phosphate was obtained in a 45% yield. I could activate alcohols and amines as well as carboxylic acids.[6] II carrying active acyloxy groups gave the corresponding carboxylic amides and esters by aminolysis and alcoholysis respectively.

Generally, trialkyl phosphites are dealkylated when oxidized with halogens. However, the fact that triethyl phosphate was obtained instead of diethyl phosphate when I was treated with water indicated that dealkylation seemed to be exclusive and that the phosphorus compound in I was in the form of a triester.

The IR spectrum of I showed strong absorption bands at 1630 and 1485 cm^{-1} and a weak band at 1580 cm^{-1}. These bands are assumed to be due to $\nu_{C=N^+}$ in the N-phosphonium salt of pyridine, judging from the fact that the N-phosphoryl pyridines[7] have characteristic bands near 1650 cm^{-1}. Although pyridinium halides and N-alkyl-pyridinium halides also have bands[8] around 1630 cm^{-1} which are also attributable to $\nu_{C=N^+}$, the absence of dealkylation on I as has been mentioned above, ruled out the possibility that I was the pyridinium salt. The band at 565 cm^{-1}, which disappeared upon the reaction of acetic acid with I may be due to ν_{P-Cl}.[9]

The UV spectrum of I exhibited the characteristic bands around 260 nm due to a pyridine moiety. The results of the quantitative analysis of chlorine in I by the use of silver nitrate; and of the acid-base titration of I showed that I contained one mole of pyridine and two chlorine atoms.

The proposed chemical structure of I is shown in Scheme 1; it will here be called the N-phosphonium salt of pyridine, taking into account its types of reactions, though it might also be named the pyridinium salt.

The band at 1710 cm^{-1} in the IR spectrum of II is due to $\nu_{C=O}$; it is quite similar to that of acetic acid and different from that of diethyl acetyl phosphate[10] at 1780 cm^{-1}. The characteristic bands at 1630, 1580, and 1485 cm^{-1} are due to the $\nu_{C=N^+}$ caused by the N-phosphonium salt of a pyridine like I. Though these bands overlapped with those of pyridine hydrochloride, the latter contribution to these bands was not very significant, judging from the weak intensity of the bands at 1535 and 1430 cm^{-1} due to the hydrochloride.

The result of the acid-base titration of II indicated that about equimolar amounts of acetic acid and pyridine were involved in II, assuming that II was contaminated with an equimolar amount of pyridine hydrochloride.

As has been described above, pyridine hydrochloride, which was not observed in I, appeared in this step of the formation of II. This shows that the chlorine atom (or chloride ion) on I may be replaced by the acetoxy group, resulting in II. This explanation is in good agreement with the aforementioned findings on the steric effect of carboxylic acids.

On the basis of these results, II is proposed to be the acyloxy N-phosphonium salt of pyridine (Scheme 1). The band due to $\nu_{C=O}$ in II, which was expected to shift to a higher wave number, had a relatively low wave number. This would account for the insufficient migration of electrons on the carbonyl carbon of the acyloxy groups to the phosphorus atom, as has been discussed by Cramer.[10]

In a similar manner, by using the diethyl ester of phosphorous acid, IV and V in Scheme 2 were obtained.

The IR spectrum of IV showed the bands due to $\nu_{C=N^+}$ caused by the N-phosphonium salt of pyridine;

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[7] M. Wakselman and E. Jampel, *Tetrahedron Lett.*, **1970**, 1521.

[8] B. Witkop, *Experimentia*, **10**, 420 (1954).

[9] R. A. Chittenden and L. C. Thomas, *Spectrochim. Acta*, **21**, 861 (1965).

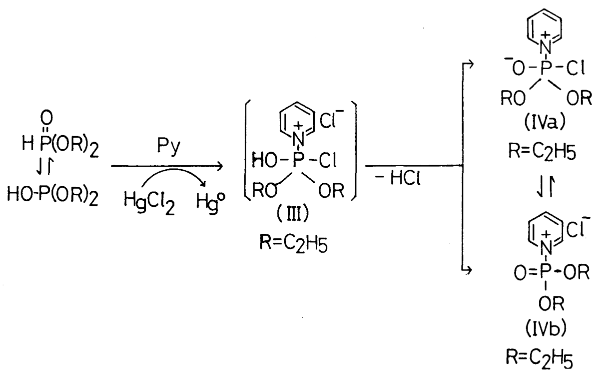
[10] F. Cramer and K. G. Gärtner, *Chem. Ber.*, **91**, 704 (1958).

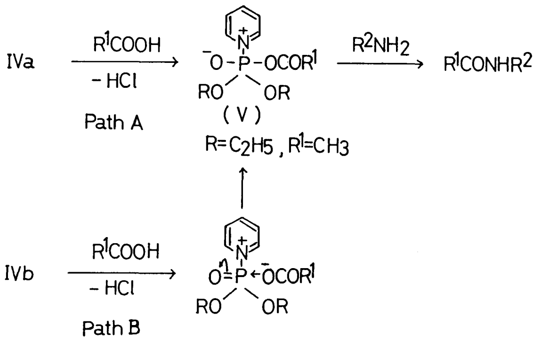
also those of pyridine hydrochloride were observed. Therefore, in the case of the diester, an intermediate similar to I was formed initially and then it was changed into IVa and IVb by releasing hydrogen chloride in two possible ways. The loss of the chloride anion from pyridinium salt (III) gave IVa, which included a phosphorus-chlorine bond. On the other hand, a phosphorus-oxygen double bond was formed by releasing the chlorine atom on the phosphorus, resulting in IVb. IVa seemed to be more plausible because there was no substantial change in the bands except for the $\nu_{C=O}$ band of acetic acid during the reaction of IV with acetic acid, and it is unlikely that V has the structure corresponding to IVb.

The steric requirement of IV upon carboxylic acids was observed, though it was not very large (see Table 2). This can not be expected from the structure of IVa alone because of the simple replacement of the chlorine atom of IVa by acyloxy groups in the reaction of IVa with the acids, such as was observed on I (Path A in Scheme 2). This fact may be accounted for by the minor participation of IVb, whose reaction with the acids would be a direct attack of the acyloxy anions on the phosphorus atom and would be affected by the steric effect (Path B).

From these results it may be considered that both structures, IVa and its isomer IVb, were involved in this system, and that the former appeared preferably to participate in this reaction.

In the spectrum of V, the bands due to the $\nu_{C=N^+}$ caused by the *N*-phosphonium salt (as in IV) and due to the $\nu_{C=O}$ of the acetoxy group as appeared in II were observed, indicating that V was an *N*-phosphonium salt, like IV (see Scheme 2).





Scheme 2.

Experimental

The infrared spectra were recorded on a Jasco IR-G spectrometer. The syrupy samples were placed between sodium chloride cells or between polyethylene films for low wave numbers (400 to 700 cm^{-1}). The ultraviolet spectrum was taken in ethanol on a Shimadzu RS-27 spectrometer.

The mercuric chloride, tertiary amines, and diphenyl phosphite were obtained from commercial sources. The trialkyl and dialkyl phosphites were prepared according to the literature.[11]

Separation of I and IV. A mixture of equivalent amounts of triethyl phosphite (2.1 g, 12.5 mmol) and mercuric chloride (3.5 g) was refluxed for 1 hr in 20 ml of pyridine. After cooling, the mixture was separated from the liberated metallic mercury and extracted with ether. The separated ether-insoluble syrup (I) was washed with ether to remove the unchanged phosphite and pyridine and was then evaporated under reduced pressure. I was obtained as a pale brown syrup. In the same way, IV was obtained by the reaction of diethyl phosphite (1.8 g, 12.5 mmol) and mercuric chloride (3.5 g) in 20 ml of pyridine.

Separation of II and V. A mixture of equivalent amounts of triethyl phosphite (2.1 g, 12.5 mmol) and mercuric chloride (3.5 g) was refluxed in 20 ml of pyridine. After 1 hr, acetic acid (0.8 g, 12.5 mmol) was added and the mixture was refluxed for an additional hour. By the same procedure as has been described above, II was obtained as a green syrup. Similarly, V was obtained by using diethyl phosphite, mercuric chloride, and acetic acid in pyridine.

Preparation of Anilides using Various Phosphites. The anilides were prepared by the method described in our previous paper.[6] These showed the IR spectra and melting points to be identical with those of authentic samples. Acetanilide was prepared in various tertiary amines in refluxing pyridine or at 115°C in other pyridine derivatives. In the case of triethylamine (4 equiv), the reaction was conducted for 2 hr under reflux in acetonitrile.

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[11] R. A. McIvor, G. D. MaCarthy, and G. A. Grant, *Can. J. Chem.*, **34**, 1819 (1956); H. McCombie, B. C. Saunders, and G. J. Stacey, *J. Chem. Soc.*, **1954**, 381; A. H. Ford-Moore, and B. J. Perry, "Organic Syntheses," Coll. Vol. 4, p. 955 (1963).