

# Studies on Reactions of the *N*-Phosphonium Salts of Pyridines. II. A New Method for the Activation of Carboxylic Acids *via* the *N*-Phosphonium Salts by Means of the Oxidation of Phosphorous Acid and Its Monoesters in the Presence of Tertiary Amines

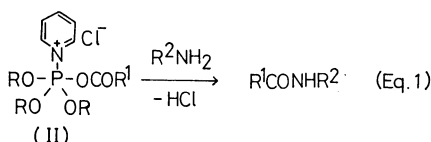
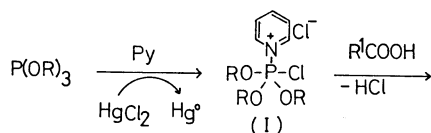
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The oxidation of phosphorous acid and its monoesters with mercuric chloride was carried out in pyridine; they were then treated with carboxylic acids and with aniline. The oxidation reaction was conducted also in the presence of carboxylic acids, after which the mixture was treated with aniline. By both procedures, the corresponding anilides were obtained in good yields. The influence of the steric factors of carboxylic acids, their acidity, and the tertiary amines were observed in the reaction. Phosphorous acid provided a better result than the monoesters. In addition, the chain length of carboxylic acids in the case of the esters influenced the yields of the anilides, which decreased with an increase in the chain length. The structural effect of tertiary amines was studied on pyridine derivatives. The ester residues also affected the yield, and of the esters examined the monophenyl ester was more favorable than the alkyl esters. Other mercuric halides and mercuric acetate were also found effective as oxidizing agents. The reaction was proposed to proceed *via* the *N*-phosphonium salts of pyridines.

In our previous papers,<sup>1,2)</sup> we have shown that carboxylic acids could be activated *via* the *N*-phosphonium salt (I) obtained by means of the oxidation of tri- and di-esters of phosphorous acid with mercuric chloride in tertiary amines like pyridine. Salt I is turned into II by the successive reaction with carboxylic acids. Salt II of the acids gives the corresponding amides upon further treatment with amines (Eq. (1)):



In this paper, we will describe a successful extension of this method to the reaction using phosphorous acid and its monoesters in the place of the tri- and di-esters.

## Results and Discussion

The oxidation of phosphorous acid and its monoesters (ammonium salt) with mercuric chloride was carried out in pyridine under reflux in two ways, in the absence and in the presence of carboxylic acids. In Method A, the oxidation was carried out in the absence of the acids in a way similar to those described in previous papers.<sup>1,2)</sup> A mixture of equimolar amounts of the ethyl ester and mercuric chloride was refluxed in pyridine for 1 hr and then treated with carboxylic acid for an additional hour of refluxing, followed by further

reaction with aniline for 2 hr. The corresponding anilides were obtained in good yields; the yields are listed in Table 1. In Method B, in the presence of carboxylic acids, *e.g.*, when a mixture of equimolar amounts of phosphorous acid or the monoesters, mercuric chloride and acetic acid was refluxed for 1 hr, and then treated with aniline for an additional 2 hr of refluxing, acetanilide was obtained in 92 and 80% yields respectively. In the same way, the anilides of various carboxylic acids were obtained in the yields shown in Tables 1 and 2.

TABLE 1. THE PREPARATION OF VARIOUS ANILIDES USING THE MONOETHYL ESTER OF PHOSPHOROUS ACID AND MERCURIC CHLORIDE IN PYRIDINE

| Acid              | p <i>K</i> <sub>a</sub> | Anilide                | Method A | Method B |
|-------------------|-------------------------|------------------------|----------|----------|
| Acetic            | 4.77                    | Acetanilide            | 92       | 80       |
| Propionic         | 4.87                    | Propionanilide         | 81       | 70       |
| <i>n</i> -Butyric | 4.82                    | <i>n</i> -Butyranilide | 71       | 59       |
| Isobutyric        | 4.86                    | Isobutyranilide        | 52       | 40       |
| Benzoic           | 4.13                    | Benzanilide            | —        | 39       |
| Phenylacetic      | 4.31                    | Phenylacetanilide      | —        | 64       |
| Trifluoroacetic   | 1.26                    | Trifluoroacetanilide   | —        | 86       |

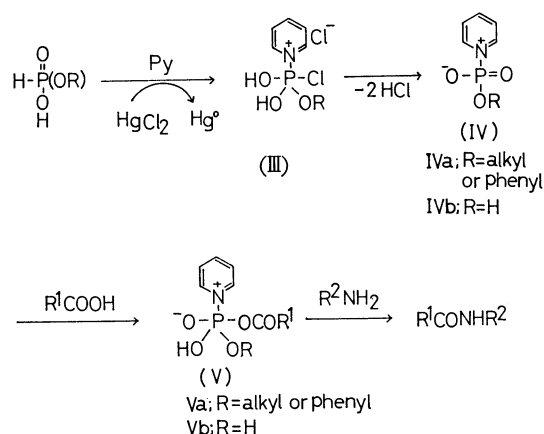
TABLE 2. THE PREPARATION OF VARIOUS ANILIDES USING PHOSPHOROUS ACID AND MERCURIC CHLORIDE IN PYRIDINE (Method B)

| Acid              | p <i>K</i> <sub>a</sub> | Mercuric Salt        | Anilide                | Yield (%) |
|-------------------|-------------------------|----------------------|------------------------|-----------|
| Acetic            | 4.77                    | HgCl <sub>2</sub>    | Acetanilide            | 92        |
| Acetic            | 4.77                    | HgBr <sub>2</sub>    | Acetanilide            | 92        |
| Acetic            | 4.77                    | HgI <sub>2</sub>     | Acetanilide            | 81        |
| Acetic            | 4.77                    | Hg(OAc) <sub>2</sub> | Acetanilide            | 91        |
| Propionic         | 4.87                    | HgCl <sub>2</sub>    | Propionanilide         | 90        |
| <i>n</i> -Butyric | 4.82                    | HgCl <sub>2</sub>    | <i>n</i> -Butyranilide | 92        |
| Isobutyric        | 4.86                    | HgCl <sub>2</sub>    | Isobutyranilide        | 79        |
| Pivalic           | 5.03                    | HgCl <sub>2</sub>    | Pivalanilide           | 23        |
| Benzoic           | 4.13                    | HgCl <sub>2</sub>    | Benzanilide            | 44        |

1) N. Yamazaki and F. Higashi, *Tetrahedron Lett.*, 415 (1972).

2) N. Yamazaki and F. Higashi, Part 1: This Bulletin, **46**, 1235 (1973).

The reaction can be explained in a manner similar to those in previous papers. In the first stage the *N*-phosphonium salt (III) was formed through the oxidation of phosphorous acid and its monoesters with mercuric chloride in pyridine. In this study, however, salt III was unstable in pyridine and was changed into IV by releasing hydrogen chloride. It is conceivable that IV does not contain any chlorine atoms and forms a zwitter-ion structure, since phosphorous acid and its monoesters have more than two hydrogen atoms capable of forming hydrogen chloride. Salt IV is then converted into V by the reaction with carboxylic acid. The aminolysis of V with aniline yielded the amides as is shown in Scheme 1.



Scheme 1

In order to confirm the proposed mechanism, IV and V were separated through the procedure described in the previous paper and were analyzed by the IR-spectroscopic method, though they were difficult to isolate in pure forms because of contamination with pyridine hydrochloride.

The IR spectra of IVa and IVb showed characteristic absorption bands at 1630 and 1485  $\text{cm}^{-1}$ . These bands, which were almost identical with those given by the *N*-phosphonium salts derived from the tri- and di-esters of phosphorous acid, were attributed to the  $\nu_{\text{C}=\text{N}^+}$  in the phosphonium salts of pyridine. Bands due to pyridine hydrochloride were also observed. Since phosphorous acid and its monoesters have two or three hydrogen atoms, they would afford two moles of the hydrochloride. From these results, the structure of IV was proposed, as is shown in Scheme 1.

The characteristic bands appearing at 1630, 1485, and 1710  $\text{cm}^{-1}$  in the spectra of Va and Vb were almost identical with those provided by the reaction products from the tri- and di-esters of phosphorous acid and acetic acid. The former two bands were attributed to the  $\nu_{\text{C}=\text{N}^+}$  of the *N*-phosphonium salt, and the latter, to the  $\nu_{\text{C}=\text{O}}$  of the acetoxy group. Therefore, the structure of V was proposed to be the *N*-phosphonium salt carrying the acetoxy group, as is shown in Scheme 1.

In the reaction of the monoethyl ester, it was found that the yield of acetanilide increased from the 80% of Method B to the 92% of Method A. Prolonged heating for an additional hour of aminolysis (from 2 to

3 hr) also improved the yield to 94%. For the improvement of the yield, three explanations are possible: the incomplete oxidation of the ester, the slow nucleophilic reaction with the carboxylate anions, and the insufficient aminolysis of Va. Since the aminolysis with aniline has proceeded almost completely within 2 hr, as will be discussed later, and since metallic mercury was obtained in a nearly quantitative yield within 1 hr under the conditions of Method B, however, insufficient oxidation and aminolysis can be excluded in elucidating the improvement. As a consequence, the rate-determining step in the reactions turned out to be the conversion of IVa to Va by the attack of the carboxylate anions.

On the contrary, these improvements were not observed in the reaction using phosphorous acid. This must be the result of an intramolecular hydrogen bonding in IVb, which will be discussed later in this paper.

The results presented above suggest that the reaction of IV with carboxylic acids to yield V involves a direct nucleophilic attack of the anions on IV. Hence, the reaction might be influenced by the acidity and the steric effect of the acids, and by the electrophilic nature of the phosphorus atom in IV. The electrophilicity would be governed by the electronic nature of the ester residues and by the basicity of the tertiary amines involved in the *N*-phosphonium salt (IV).

The effects of the acidity and the steric factor of carboxylic acids upon the yield of the anilides were studied by using the monoethyl ester (ammonium salt), various carboxylic acids, and mercuric chloride in pyridine (Method B); the results are summarized in Table 1. Sterically hindered carboxylic acids, such as isobutyric and benzoic acids, gave their anilides in yields only about a half of that of acetanilide. The reaction was also influenced by the acidity of the acids. This was evident from the fact that trifluoroacetic acid, with a high  $\text{p}K_a$  value of 1.26, gave trifluoroacetanilide in 87% yield, although less than a 50% yield would be expected from a consideration of its steric effect alone. Furthermore, the reaction was affected by the chain length of the acids. Among the acids with similar  $\text{p}K_a$  values, the yields of the corresponding anilides decreased with an increase in the chain length of the acids. For example, acetic, propionic, and *n*-butyric acids, which have their  $\text{p}K_a$  values in the range of 4.7 to 4.8, gave anilides in 80, 70, and 59% yields respectively. Analogous phenomena were observed in the reaction using the other monoalkyl esters as well (see Table 3).

As has been expected, the reaction would be in-

TABLE 3. THE PREPARATION OF ANILIDES USING VARIOUS MONOESTERS OF PHOSPHOROUS ACID AND MERCURIC CHLORIDE IN PYRIDINE (Method B)

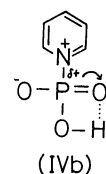
| Monoester | Anilide, yield, % |                        |
|-----------|-------------------|------------------------|
|           | Acetanilide       | <i>n</i> -Butyranilide |
| Methyl    | 74                | 54                     |
| Ethyl     | 80                | 59                     |
| Isopropyl | 74                | 59                     |
| Phenyl    | 94                | 87                     |

fluenced by the electrophilicity of the phosphorus atom in IV, which itself chiefly depends on the electronic character of the ester residues in the monoesters. The effect of the ester residues upon the reaction was studied in terms of the yield of the isolated anilides by using various monoesters (ammonium salt) by Method B (see Table 3). The facts that no effect of the bulkiness of the residues in the alkyl esters was observed, and that the monophenyl ester, in spite of having a more bulky group, gave better results than the monoalkyl esters, indicated that the reaction was not influenced by the bulkiness of the ester residues. In addition, no such substantial decrease in the yields was seen in the monophenyl ester with an increase in the chain length of carboxylic acids as was observed in the monoalkyl esters. These results led us to consider that the presence of electron-attracting groups like the phenyl group decreased the electron density on the phosphorus atom in IVa and facilitated the nucleophilic attack of the carboxylate anions on IVa, not causing a substantial decrease in the yields with an increase in the chain lengths of the acids. On the other hand, the electron-donating groups like the isopropyl group increased the electron density and slowed down the reaction, resulting in a decrease in the yields with an increase in the length.

In the reaction of phosphorous acid, a similar steric effect of the acids upon the yields was observed, though it was not so serious as that observed in the monoesters. The effect of the chain length of the acids was not seen in this case. This might be caused by the intramolecular hydrogen bonding involving in IVb, which facilitates the reaction of IVb with the acids.

In the reaction of IV with carboxylic acids, several differences were observed between IVa (monoesters) and IVb (phosphorous acid). The results of the steric effect, mentioned above, indicated that the nucleophilic attack of carboxylate anions on IVb (R=H) was preferable to that on IVa (R=alkyl or phenyl). As a rule, phenyl and alkyl groups are more electro-positive and electronegative respectively than the hydrogen atom. If the reactivity of IV to the anions is caused by the electron deficiency on the phosphorus atom in IV, which itself depends chiefly on the inductive effect of the ester residues, the relative reactivity of IV might be in the order of IVa (R=phenyl) > IVb (R=H) > IVa (R=alkyl). However, the order obtained in this study was, unexpectedly, IVb (R=H) > IVa (R=phenyl) > IVa (R=alkyl).

This conflict can be explained by considering an intramolecular hydrogen bonding in IVb, as is shown below. Because of this bonding, the phosphorus atom became electron-deficient through the migration of the electrons at the phosphorus-oxygen bond to the oxygen; consequently, the nucleophilic attack of the anions on IVb was facilitated. On the other hand, in the case of the monoesters such a hydrogen bonding was unlikely to be involved in IVa. Therefore, the reactivity of IVa was governed mainly by the inductive effect of the ester residues, since the relative reactivity obtained in this study was IVa (R=phenyl) > IVa (R=alkyl), compatible with the order of the effect.



Tertiary amines were expected to play an important role, through the phosphorus-nitrogen bond of IV and V, in affecting the electrophilic nature of the phosphorus atom. Using phosphorous acid, the effect of tertiary amines upon the reaction (the yield of acetanilide) was investigated by varying the substituents in the pyridine nucleus (Table 4). The effects were not in agreement with those obtained by using triesters. In the reaction using the triesters,  $\alpha$ -picoline gave a better result than pyridine, and even in 2,6-lutidine acetanilide was obtained in 59% yield. However, in this case pyridine was more favorable than  $\alpha$ -picoline, and in 2,6-lutidine the anilide was not formed. The yield in  $\gamma$ -picoline, which was nearly the same as in  $\alpha$ -picoline, was worse than that in  $\beta$ -picoline, indicating that the steric effect of the amines was not profound. Though the yield decreased with an increase in the basicity of amine among pyridine derivatives, the effect was inexplicable solely by the basicity, because triethylamine of a high  $pK_a$  value in acetonitrile gave acetanilide in 17% yield. The effect of amines appeared to be caused by the stability and reactivity of IV and/or V to carboxylic acids and aniline.

The aminolysis of V with aniline was investigated in reactions using phosphorous acid under various conditions (Table 5). The results showed that the acetoxy group carried by Vb was not so active, and that more than 2 hr of refluxing were required for the complete aminolysis of Vb with aniline. This fact provided additional evidence that V was not in the form of active acetyl phosphates.

TABLE 4. THE PREPARATION OF ACETANILIDE IN VARIOUS TERTIARY AMINES

| Amine                | $pK_a$ | Acetanilide, yield, % <sup>a)</sup> |
|----------------------|--------|-------------------------------------|
| Pyridine             | 5.23   | 92                                  |
| 2-Methylpyridine     | 5.97   | 64                                  |
| 3-Methylpyridine     | 5.52   | 90                                  |
| 4-Methylpyridine     | 6.02   | 67                                  |
| 2,6-Dimethylpyridine | 6.99   | 0                                   |
| Triethylamine        | 10.87  | 17 <sup>b)</sup>                    |

a) Aminolysis with aniline at 115°C for 2 hr.

b) Under reflux in acetonitrile.

TABLE 5. THE PREPARATION OF ACETANILIDE IN PYRIDINE UNDER VARIOUS CONDITIONS

| Conditions |                        | Acetanilide, yield (%) |
|------------|------------------------|------------------------|
| Temp., °C  | Time, hr <sup>a)</sup> |                        |
| 80         | 2                      | 40                     |
| 90         | 4                      | 70                     |
| Reflux     | 1                      | 79                     |
| Reflux     | 2                      | 92                     |
| Reflux     | 3                      | 95                     |

a) After aniline was added.

All of the oxidizing agents used in this study, such as mercuric halides and its acetate, were found to be effective for this reaction (see Table 2).

### Experimental

The mercuric chloride, tertiary amines, and phosphorous acid were obtained from commercial sources. The monoesters of phosphorous acid were prepared according to the literature.<sup>3)</sup>

*Separation of IVa (R=Et) and IVb.* A mixture of equivalent amounts of the monoethyl ester (ammonium salt) of phosphorous acid (1.60 g, 12.5 mmol) and mercuric chloride (3.5 g) was refluxed for 1 hr in 20 ml of pyridine. After the separation of the liberated metallic mercury and ammonium chloride, IVa was obtained by the procedure described in the previous paper. Similarly, IVb was obtained by the reaction of phosphorous acid (1.03 g, 12.5 mmol) and mercuric chloride (3.5 g) in 20 ml of pyridine.

*Separation of Va (R=Et) and Vb.* A mixture of equivalent amounts of the monoethyl ester (ammonium salt) of phosphorous acid (1.60 g, 12.5 mmol) or phosphorous acid

(1.03 g, 12.5 mmol) and mercuric chloride (3.5 g) was refluxed for 1 hr in 20 ml of pyridine. The reaction mixture was then treated with acetic acid (0.8 g, 12.5 mmol) under reflux for an additional hour. By the aforementioned procedures, Va and Vb were obtained. They were also obtained by the reaction of the monoethyl ester (ammonium salt) or phosphorous acid and mercuric chloride in the presence of acetic acid under reflux for 1 hr in pyridine.

*Preparation of Anilides using Phosphorous Acid and Its Monoesters.* The anilides were prepared by two methods.

*Method A:* The oxidation was carried out in the way described above. The reaction mixture was treated with an equivalent carboxylic acid under reflux for 1 hr, and then with a 10% excess of aniline for an additional 2 hr.

*Method B:* The oxidation was carried out under reflux for 1 hr in the presence of a carboxylic acid, and then treated with aniline for 2 hr under reflux. The product was isolated according to the procedure described in a previous paper.<sup>1)</sup> The anilides thus obtained showed IR spectra and melting points identical with those of authentic samples.

*Preparation of Acetanilide in Various Tertiary Amines.*

The reactions were carried out by Method B using phosphorous acid in refluxing pyridine or at 115°C in other pyridine derivatives. In the case of triethylamine (4 equiv.), the reaction was conducted in refluxing acetonitrile.

3) P. R. Hammond, *J. Chem. Soc.*, **1962**, 2521.