salt could be obtained as an amorphous white solid. The solution was treated with 1 M sulfuric acid to give the free acid ester without isolating the barium salt. Lyophilization yielded an oil which crystallized on the addition of a small amount of water, to yield 3.7 g. (41%) (51% based on recovered Chloromycetin) of the phosphate ester. On recrystallization it had the same melting point, mixed melting point and monobasic neutralization equivalent as the product from phosphorus oxychloride. A residual phosphorus containing oil could not be crystallized and contained a small amount of Chloromycetin free base sulfate of m.p. 218–221° (uncor.).

Use of Orthophosphoric Acid.—Crystalline orthophosphoric acid[20] was used in attempts to phosphorylate L(+)-

Chloromycetin under the following conditions: 30 min. at 50°; 60 min. at 50°; three weeks at room temperature. A large excess of the acid was used to obtain homogeneous solutions. The isolation procedure was essentially the same as that employed using tetraphosphoric acid.

The short run; 30 min. at 50°, duplicated Poggi's[16] conditions and gave an almost complete recovery of unchanged Chloromycetin. Other experiments using 85%, "97%" and "100%" phosphoric acid prepared by mixing phosphorus pentoxide with sirupy phosphoric acid and varying the time and temperature, were unsuccessful. Longer reaction times gave considerable Chloromycetin free base (hydrolyzed amide group) which sometimes crystallized from the final lyophilized oils as the free base sulfate.

(20) W. H. Ross and R. M. Jones, THIS JOURNAL, 47, 2165 (1925).

STANFORD, CALIF.

Synthesis of Aromatic Phosphonic Acids and their Derivatives. III. Some Amino and Hydroxy Substituted Acids[1]

BY VERNON L. BELL, JR., AND GENNADY M. KOSOLAPOFF

The diazonium fluoborate method for synthesis of aromatic phosphonic acids with functional substituents was examined for possible improvements in the operating techniques. As a result, improved yields of several compounds were obtained. Typical organic substitutions of functional groups in such compounds were examined.

One finds little information in the literature on the possibilities of functional group replacements in organic compounds of phosphorus in general and in phosphonic acids, specifically. The purpose of the present investigation was to examine some of these replacements as a method of synthesis of aromatic phosphonic acids with hydroxy and amino substitution. The recent development of the diazonium fluoborate method for phosphonation reactions was selected as the starting point inasmuch as this method affords definite isomers of the desired starting materials.[2]

There are three rather obvious methods for preparation of hydroxy-substituted aromatic phosphonic acids. The first of these, diazo-replacement of an amino group, has been used with moderate success by Doak and Freedman.[3] A second method is that involving an alkaline hydrolysis of halogen-substituted aromatic phosphonic acids. Replacement of chlorine by the hydroxy group in compounds bearing a nitro group in o-position in respect to the chlorine was reported some time ago by Arnold and Hamilton,[4] but one is unable to find in the literature any data on reactions of this type involving otherwise unsubstituted halophosphonic acids. The third possible method involves the ether cleavage in ether-substituted phosphonic acids, such as anisolephosphonic acids. No data on such reactions can be found in the literature.

All three methods were examined as to possible utility with the several specific examples described in the Experimental section. It was readily found that any method which involves drastic high temperature treatment results in formation of phenol as the consequence of the cleavage of the phosphorus-to-carbon link. In contrast to the

ready ammonolysis of halobenzenephosphonic acids, the hydrolytic reaction appears to be applicable only to "activated" halogen derivatives of the type studied by Arnold and Hamilton. In fact, the thermal stability of the hydroxybenzene- and methoxybenzenephosphonic acids was found to be rather low. It appears that the first method of their synthesis, mentioned above, appears to be the only practicable one at this time.

The stability of the carbon-to-phosphorus bond in o-aminobenzenephosphonic acid is known to be of low order, as shown by rapid dephosphonation in bromine water.[5] We have found that p-aminobenzenephosphonic acid also shows this low order of stability of the carbon-to-phosphorus link. Thus, o- or p-substitution with strongly o–p-directing groups renders the carbon-to-phosphorus bond very susceptible to cleavage, a situation which is rather unusual in the family of substances noted for the high order of stability of the phosphonate group. The ease of dephosphonation shown by p-hydroxybenzenephosphonic acid is illustrated by formation of tribromophenol at room temperature with bromine water and by formation of phenol on heating the acid not only with dilute hydrochloric acid but even with water alone.

Experimental Part

The Phosphonation by the Diazonium Fluoborate Method.—The fluoborates used as the starting materials in the various syntheses were obtained through the sodium fluoborate procedure.[6]

Preparation of p-bromobenzenephosphonic acid by the procedure outlined by Doak and Freedman gave a 61% yield of the product,[7] which agreed with the previous work. In the preparation of the o-isomer, we obtained a consistent

(1) For part II see THIS JOURNAL, 70, 3465 (1948).

(2) G. O. Doak and L. D. Freedman, ibid., 73, 5658 (1951).

(3) G. O. Doak and L. D. Freedman, ibid., 74, 753 (1952).

(4) G. B. Arnold and C. S. Hamilton, ibid., 63, 2637 (1941).

(5) G. M. Kosolapoff, ibid., 71, 4021 (1949); G. O. Doak and L. D. Freedman, ref. 3.

(6) A. Roe, "Organic Reactions," Vol. 5, John Wiley and Sons, Inc., New York, N. Y., 1949, p. 217.

(7) G. O. Doak and L. D. Freedman, THIS JOURNAL, 75, 683 (1953).

53% yield, somewhat higher than the variable yields in the vicinity of 40% as reported by Doak and Freedman. This yield improvement possibly resulted from the removal of copper from the reaction mixture by means of hydrogen sulfide treatment immediately after isolation of the phosphinic acid. The shorter contact time of the o-bromo derivative with copper salts appears to be the only explanation.

In the preparation of o- and p-methoxybenzenephosphonic acids it was found that the use of an ester solvent (ethyl acetate), prescribed by Doak and Freedman, gave unsatisfactory results and low yields. Substitution of 1,4-dioxane for ethyl acetate resulted in a 61% yield of p-methoxybenzenephosphonic acid, m.p. 179°, and 14% yield of the corresponding phosphinic acid, m.p. 186–187°.[8] In this case the diazophosphonation reaction is best run at 50–55° for 5–6 hours and the phosphonic acid is readily isolated as the monosodium salt, by conventional method. For conversion to the free acid the monosodium salt is dissolved in hot 6 N hydrochloric acid and cooled. Exposure to hot acids must be kept to a minimum if dephosphonation is to be avoided.

The preparation of o-methoxybenzenephosphonic acid was run similarly in dioxane with the same catalyst (cuprous chloride), yielding 2% phosphinic acid and 41% phosphonic acid. The latter, after crystallization from 6 N hydrochloric acid, formed needles, m.p. 215° with some decomposition. After the experimental work was completed, there appeared two descriptions of the preparation of this acid, reporting its m.p. as 202–203° and 201–202°, with indication of variation of the melting point with rate of heating.[9] Since our preparation showed a rather higher melting point, it was subjected to analysis.

Anal. Calcd.: P, 16.47; neut. equiv., 94.1. Found: P, 16.15; neut. equiv., 93.4.

In the isolation of this acid it was found that the precipitation as the monosodium salt results in low yields. The acid was best purified by solution of the crude acid, obtained on cooling the concentrate after the removal of the phosphinic acid, in water, treatment of this with charcoal, evaporation of the clarified solution under reduced pressure, and crystallization of the residue from 6 N hydrochloric acid.

2-Bromo-4-nitroaniline was prepared in 79% yield according to Rowe, *et al.*[10] This readily yielded a 71% yield of the diazonium fluoborate, which decomposed at 148–152°. The latter reacted with phosphorus trichloride (cuprous chloride catalyst) noticeably more vigorously than the other fluoborates listed above. Gas evolution commenced within a few minutes of addition and the reaction of 0.1 mole of the salt was complete within one hour. The phosphonic acid was isolated as tan granular crystals, m.p. 217–220° (from 6 N hydrochloric acid), in 41% yield.

Anal. Calcd.: P, 10.99; neut. equiv., 141.0. Found: P, 10.87; neut. equiv., 141.8.

Several attempts to prepare 2-methoxy-4-nitrobenzenephosphonic acid from the corresponding fluoborate by the previously described procedure[2] were fruitless. A very vigorous reaction began immediately upon addition of phosphorus trichloride; its vigor was further increased by the subsequent addition of the catalyst. No organophosphorus compounds could be isolated from the reaction mixture.[11]

Replacement Reactions. 4-Bromo-3-nitrobenzenephosphonic Acid.—p-Bromobenzenephosphonic acid (58 g.) was added to an excess of fuming nitric acid (d. 1.51). The resulting solution was evaporated, sufficient fuming nitric

(8) Previous reports give for the phosphonic acid a m.p. 158° (A. Michaelis, *Ann.,* **293**, 193 (1896)), and 166° (G. M. Kosolapoff and S. Powell, *J. Chem. Soc.*, 3535 (1950)). The phosphinic acid was previously reported with m.p. 179–180° (G. M. Kosolapoff, THIS JOURNAL, **71**, 369 (1949)).

(9) L. D. Freedman, H. Tauber, G. O. Doak and H. J. Magnuson, *ibid.*, **75**, 1379 (1953), and N. D. Dawson and A. Burger, *J. Org. Chem.*, **18**, 207 (1953).

(10) F. M. Rowe, G. B. Jambuserwala and H. W. Partridge, *J. Chem. Soc.*, 1134 (1935).

(11) After our experimental work was completed, the preparation of this acid was reported by Freedman, *et al.*[9] In a private communication Dr. Freedman informed these writers that in this preparation the addition of phosphorus trichloride and cuprous bromide catalyst should be essentially simultaneous for satisfactory results.

acid was added to bring the material back into solution, which was again evaporated to near dryness. The precipitated acid was separated on a glass filter and was dried under reduced pressure over calcium chloride and sodium hydroxide. After recrystallization from 6 N hydrochloric acid, the product, m.p. 188–190°, was obtained in 96% yield. A previous report (Michaelis, ref. 8) gave m.p. 185°.

4-Hydroxy-3-nitrobenzenephosphonic Acid.—The above acid (20 g.) was refluxed for three hours with 4 N sodium hydroxide solution. The cooled mixture was acidified to congo red with concentrated hydrochloric acid and yielded 69% of 4-hydroxy-3-nitrobenzenephosphonic acid, which was recrystallized from water and melted with decomposition at 216–218°; previously reported m.p. 214–216°.[4]

3-Amino-4-hydroxybenzenephosphonic Acid.—The hydroxynitrobenzenephosphonic acid (10 g.) was dissolved in sodium hydroxide solution (pH 8.0) and was hydrogenated in the presence of 3 g. of 5% palladium-on-charcoal catalyst at room temperature and normal pressure. Addition of the catalyst in several portions served to eliminate the usually found difficulty of catalyst poisoning. Acidification of the filtrate, after removal of the catalyst, to congo red with concentrated hydrochloric acid and purification of the crude acid, which precipitated in the process, by another reprecipitation from dilute hydrochloric acid, gave the pure substance, m.p. 249–250°. Previous report merely stated that the melting point was above 200°.[4]

3-Amino-4-bromobenzenephosphonic Acid.—Hydrogenation of the 3-nitro analog under the conditions described above gave the amino acid, which decomposed without a definite melting point above 280°.

Anal. Calcd.: P, 12.29. Found: P, 12.02.

4-Methoxy-3-nitrobenzenephosphonic Acid.—Several attempts to nitrate p-methoxybenzenephosphonic acid at 100° (Michaelis, ref. 8) gave much 2,4-dinitroanisole. However, good results were obtained under milder conditions. p-Methoxybenzenephosphonic acid (12 g.) was added over a 30-minute period to 50 ml. of fuming nitric acid at 0°. The resulting solution was poured onto 100 g. of ice, and the resulting solution was evaporated to dryness in a stream of nitrogen, under water-pump vacuum, at a temperature below 60°. The crude acid was dried *in vacuo* over calcium chloride and sodium hydroxide, and the product was purified by precipitation with concentrated hydrochloric acid from sodium hydroxide solution. Final crystallization from 6 N hydrochloric acid gave 81% of 4-methoxy-3-nitrobenzenephosphonic acid, fine colorless needles, m.p. 208–210°. Michaelis[8] previously reported m.p. 187°.

Anal. Calcd.: P, 13.2; neut. equiv., 116.6. Found: P, 12.9; neut. equiv., 118.7.

4-Aminobenzenephosphonic Acid.—p-Bromobenzenephosphonic acid was heated in the presence of fresh cuprous oxide in concentrated ammonium hydroxide for six hours at 100°, yielding 80% of phosphanilic acid, in accord with previous work[12]; m.p. 245°, with rapid heating.

4-Hydroxybenzenephosphonic Acid. From 4-Aminobenzenephosphonic Acid.—Since it was found early in this work that the hydroxybenzenephosphonic acid is rather unstable in hot acid solutions, all efforts were directed to minimize contact under these conditions. As a result, the procedure of Doak and Freedman[3] was modified and the yield substantially improved.

Phosphanilic acid (12 g.) suspended in 50 ml. of water was treated with 17.5 ml. of concentrated hydrochloric acid, and ethyl nitrate was passed into the stirred suspension until the starch-iodide test remained positive for five minutes. The mixture was gently warmed until the evolution of nitrogen ceased and the solution was evaporated under water-pump vacuum at a temperature below 60° in a slow stream of nitrogen. The crude acid was recrystallized rapidly from 6 N hydrochloric acid, yielding 71% of p-hydroxybenzenephosphonic acid, m.p. 178°. The previous report[3] gave m.p. 177°. As reported previously,[3] attempts to obtain the neutralization equivalent of this acid with thymolphthalein indicator gave unsatisfactory results. Electrometric titration solved this difficulty: found equivalent 86.2, calcd. 87.0.

From **4-Bromobenzenephosphonic Acid.**—When p-bromobenzenephosphonic acid (8 g.) was refluxed in nitrogen at-

(12) H. Bauer, THIS JOURNAL, **63**, 2137 (1941), and N. S. Limaye and B. V. Bhide, *J. Indian Chem. Soc.*, **25**, 251 (1948).

mosphere in 60 ml. of 10% sodium hydroxide in the presence of 4 g. of cuprous oxide for eight hours, no reaction was evident, and on acidification 7.7 g. of the bromo acid was recovered. Repetition of the reaction in a glass liner within a steel autoclave at 140° for six hours also gave negative results. Extension of the reaction period to 48 hours, however, resulted in isolation of phenol as the only product. Intermediate reaction periods gave similar results, and no significant traces of the hydroxy acid were isolated.

From 4-Methoxybenzenephosphonic Acid.—*p*-Methoxybenzenephosphonic acid (10 g.) was refluxed in nitrogen atmosphere with 15 ml. of 57% hydriodic acid, while methyl iodide was being collected in a suitable cooled trap. In no case was it possible to secure over 65% of the theoretical amount of methyl iodide. After 2–3 hours the solution was evaporated to dryness at 50° in nitrogen atmosphere under reduced pressure. The residue contained considerable amounts of phenol, which was removed as much as possible by repeated evaporation, as described above. Its complete removal was impossible owing to continuous generation of this substance. Repetition of the ether cleavage under various conditions with acetic acid diluent gave only phenol and progressively smaller amounts of unchanged methoxy acid. Replacement of the hydriodic acid by 47% hydrobromic acid, and heating the mixture to 125–130° for three hours, followed by evaporation as described above, gave a very water-soluble acidic product, which melted at 171–174° after recrystallization. It gave only a minor melting point

depression on being mixed with an authentic specimen of the *p*-hydroxy derivative, indicating that it was substantially pure *p*-hydroxybenzenephosphonic acid. The yield, however, was very poor, amounting to some 1.5 g. Admixture of 25% of *p*-methoxybenzenephosphonic acid to the authentic *p*-hydroxy acid gave a melting point depression of over 30 degrees; only a very minor contamination gave a depression of 1–2 degrees. However, despite the rather considerable difference in solubilities of the individual hydroxy and methoxy acids in water, it was not possible to separate completely the contaminant (*p*-methoxy acid) from the above product. This was in full accord with the concept of association of acids of phosphorus in solutions (Kosolapoff and Powell, ref. 8), according to which the phosphonic acids exist in polymeric chains which can have links of the various acids present in a mixture; in such hydrogen-bonded aggregates the physical properties of the individual acids are no longer in normal evidence.

The relatively low order of hydrolytic stability of the *p*-methoxy acid is also shown by the fact that upon refluxing in concentrated hydrochloric acid for one to two hours, the substance began to evolve gradually increasing amounts of phenol. No *p*-hydroxybenzenephosphonic acid could be isolated from water washings of the residual material, obtained by evaporation of the aqueous filtrate from unchanged *p*-methoxy acid.

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The Chemistry of Phosphonic Acids with Aromatic Nuclei. II. The Isomeric Tolylphosphonic Acids

BY EUGENE C. ASHBY AND GENNADY M. KOSOLAPOFF

The apparent dissociation constants of the three isomeric tolylphosphonic acids were determined; these, in ascending order, are in series of: ortho, meta, para. The apparent molecular weights of the isomeric acids were determined in various solvents. The para isomer shows a consistently higher degree of association, followed in order by the meta and the ortho isomers. The differences of solubilities of the three isomers are interpreted in terms of these data.

It has been known for a long time that considerable differences in physical constants are found in the group of isomeric tolylphosphonic acids. These differences are expressed particularly strikingly in the solubilities of these acids. Whereas the *p*-tolylphosphonic acid is moderately soluble in water, the other two isomers are extremely soluble. The para isomer is essentially insoluble in various hydrocarbon solvents, while the other two isomers are appreciably soluble in benzene and other hydrocarbons. The melting points of the three isomers are unusual, in that the meta isomer has the lowest one.

In order to find some tenable explanation of these facts we examined the dissociation constants and the association tendencies of the three isomers.

The determination of dissociation constants, performed as described previously,[1] yielded results that are given below.

Acid: $CH_3C_6H_4PO(OH)_2$	pK_1'	pK_2'
Para isomer	1.84	7.33
Meta isomer	1.88	7.44
Ortho isomer	2.10	7.68

It is apparent that the values for the para and the meta isomers are very close to each other, while the

ortho isomer shows a very appreciable departure in the direction of weaker acidity. The latter isomer is the only one in this group in which steric hindrance exists between the side chain and the phosphono group, thus prohibiting the free rotation of the PO_3 unit. The results are in accord with the expected consequences of orientation of an electron-repelling group (methyl) in respect to an acidic group.[2]

As stated above, the meta and the ortho isomers, in addition to being very soluble in water, are also soluble in solvents such as benzene. The process of such solution is peculiar, however. These two acids dissolve in hot benzene very slowly to form even a 5% solution, but only part of the dissolved material separates on cooling to nearly the freezing point of the solvent. Details for the best recrystallization procedure are given in the experimental section.

On the basis of studies of association of various phosphorus-bearing organic acids, it has been suggested[3] recently that aliphatic phosphonic acids, $RPO(OH)_2$, are probably linear hydrogen-bonded aggregates, or polymers. The average size of such aggregates, as well as their shapes, can be expected to have a considerable bearing on their solubility.

(1) P. C. Crofts and G. M. Kosolapoff, THIS JOURNAL, 75, 3379 (1953).

(2) R. L. Herbst and M. E. Jacox, ibid., 74, 3004 (1952).

(3) G. M. Kosolapoff and J. S. Powell, J. Chem. Soc., 3535 (1950).