[CONTRIBUTION FROM THE VENEREAL DISEASE EXPERIMENTAL LABORATORY, U. S. PUBLIC HEALTH SERVICE, SCHOOL OF PUBLIC HEALTH, UNIVERSITY OF NORTH CAROLINA]

Phosphanilic Acid and Related Compounds. II. Alkylamino-Substituted Phosphonic and Phosphinic Acids[1]

BY G. O. DOAK AND LEON D. FREEDMAN

RECEIVED JULY 17, 1952

The method of Limaye and Bhide for the synthesis of phosphanilic acid has been extended to the preparation of alkylamino-substituted phosphonic and phosphinic acids. The necessary bromo acids were prepared from the appropriate diazonium fluoborates and either phosphorus trichloride or tribromide. *p*-Methylamino- and *p*-hydrazinobenzenephosphonic acids were readily prepared and isolated by a procedure similar to that used for phosphanilic acid. *p*-*n*-Propylamino-, *m*-ethylamino-, *m*-*n*-butylamino- and *m*-hydrazinobenzenephosphonic acids were also obtained, but their properties were such as to require modification of the isolation technique. Many other alkylamino-substituted phosphonic and phosphinic acids, including those in which the amino group was in ortho position, could not be isolated, although it is believed that the reaction occurred. Reasons for this failure are discussed. With bis-(*m*-bromophenyl)-phosphinic acid and methylamine it was possible to isolate, depending upon the reaction conditions employed, either bis-(*m*-methylaminophenyl)-phosphinic acid or (*m*-bromophenyl)-(*m*-methylaminophenyl)-phosphinic acid. The reaction between bromo acids and dialkylamines was too slow to be satisfactory for synthetic purposes.

A previous paper from this Laboratory has described the synthesis of amino- and hydroxy-substituted phosphonic and phosphinic acids.[2] These compounds were prepared as part of a systematic investigation of the biological properties of organophosphorus compounds. The present paper describes an attempt to prepare a series of alkylamino-substituted arylphosphonic and diarylphosphinic acids.

Phosphanilic acid was first prepared by the reaction between *p*-chlorobenzenephosphonic acid and ammonia in a sealed tube.[3] This method was subsequently modified by Limaye and Bhide[4] who employed the more reactive *p*-bromobenzenephosphonic acid and thus avoided the use of a sealed tube. We anticipated that the latter reaction could be extended to the preparation of alkylamino-substituted phosphonic and phosphinic acids by the substitution of alkylamines for ammonia according to the equations

$$BrC_6H_4PO_3H_2 + 2RNH_2 \longrightarrow RNHC_6H_4PO_3H_2 + RNH_3Br$$

$$BrC_6H_4PO_3H_2 + 2R_2NH \longrightarrow R_2NC_6H_4PO_3H_2 + R_2NH_2Br$$

$$(BrC_6H_4)_2PO_2H + 4RNH_2 \longrightarrow (RNHC_6H_4)_2PO_2H + 2RNH_3Br$$

Unfortunately, unexpected difficulties were encountered and many of the desired acids have not been isolated.

The necessary bromobenzenephosphonic acids were prepared by means of the diazo reaction recently described in a paper from this Laboratory.[5] A variation of the reaction conditions was investigated, namely, the use of phosphorus tribromide in place of trichloride. This change usually resulted in an increased yield of the secondary acid and a decreased yield of the primary acid. In addition, the resulting phosphinic acids were purified more easily than those prepared from the trichloride. Although the preparation of *o*-bromobenzenephosphonic acid and bis-(*o*-bromophenyl)-phosphinic acids has been described previously,[2] we have been unable to obtain consistent yields with this synthesis. Further investigation has revealed that, in the presence of copper salts, *o*-bromobenzenephosphonic acid is unstable in alkaline solution. This instability is due presumably to replacement of bromine by a hydroxyl group. On several occasions, in which a low yield of bromobenzenephosphonic acid was obtained, the presence of a phenol in the reaction mixture was demonstrated by the ferric chloride test. We have also found that *o*-bromobenzenephosphonic acid differs from most of the other phosphonic acids in that the hemi-sodium salt is more soluble than the free acid. For these reasons the synthesis of the *o*-bromo acid was modified considerably. Details of the method used are described in the Experimental section.

p-Methylaminobenzenephosphonic acid was readily prepared, in satisfactory yield, from aqueous methylamine and *p*-bromobenzenephosphonic acid in the presence of cuprous oxide. *p*-Hydrazinobenzenephosphonic acid was similarly prepared, although in smaller yield. These two compounds were isolated in a manner similar to that used for phosphanilic acid.[4] The *n*-propylaminobenzenephosphonic acid could not be isolated by the same procedure. However, it was obtained as the hydrochloride through the magnesium ammonium salt. The reaction between ethanolamine and the *p*-bromo acid differed somewhat from the other reactions and is described in detail in the Experimental section.

When *p*-bromobenzenephosphonic acid was reacted with either ethylamine or *n*-butylamine, we were unable to isolate any phosphonic acid, either by the method used for phosphanilic acid or through the magnesium ammonium salt, or by the methods successfully used for isolating the corresponding meta compounds (*vide infra*). Similar failures were encountered with the following pairs of reactants: *o*-bromobenzenephosphonic acid–methylamine; bis-(*p*-bromophenyl)-phosphinic acid–methylamine; bis-(*o*-bromophenyl)-phosphinic acid–ammonia; and bis-(*o*-bromophenyl)-phosphinic acid–methylamine. In all these cases bromide ion analyses on aliquots from the reaction mixtures

(1) Presented before the Medicinal Division of the American Chemical Society in Milwaukee, Wis., March, 1952.

(2) G. O. Doak and L. D. Freedman, THIS JOURNAL, **74**, 753 (1952).

(3) H. Bauer, *ibid.*, **63**, 2137 (1941).

(4) N. S. Limaye and B. V. Bhide, *J. Indian Chem. Soc.*, **25**, 251 (1948).

(5) G. O. Doak and L. D. Freedman, THIS JOURNAL, **73**, 5658 (1951).

TABLE I

ANALYSES, YIELDS AND MELTING POINTS OF PHOSPHONIC AND PHOSPHINIC ACIDS

Compound	Isolation procedure	Yield, %	M.p.,[a] °C.	Phosphorus,[b] % Calcd.	Found	Neutral equivalent,[c] Calcd.	Found	Nitrogen, % Calcd.	Found
m-$BrC_6H_4PO_3H_2$[d]			149–151	13.07	12.73	118.5	119.3		
p-$BrC_6H_4PO_3H_2$[e]			201–202	13.07	12.84	118.5	118.5		
m-$CH_3NHC_6H_4PO_3H_2$[f]	II	46	226.5–228.5	16.55	16.34	93.6	94.3	7.49	7.40
p-$CH_3NHC_6H_4PO_3H_2$[g]	I	41	177.5–179.5	16.55	15.93	93.6	95.0	7.49	7.35
m-$C_2H_5NHC_6H_4PO_3H_2$	III	43	238–241	15.40	15.04	100.6	101.8	6.96	6.88
p-*n*-$C_3H_7NHC_6H_4PO_3H_2 \cdot HCl$[h]	IV	14	180.5–183.5	12.31	12.20	83.9	85.3	5.57	5.47
m-*n*-$C_4H_9NHC_6H_4PO_3H_2$	II	60	198–201	13.52	13.22	114.6	115.2	6.11	6.10
p-$HOCH_2CH_2N(NO)C_6H_4PO_3H_2$			Dec. > 140	12.59	12.35	123.1	124.7	11.38	[i]
p-$H_2NCH_2CH_2OC_6H_4OP_3H_2$[j]		7	>300	14.27	14.13	108.6	[k]	6.45	6.45
m-$H_2NHNC_6H_4PO_3H_2$[l]	II	10	Dec. >248	16.47	16.21	94.1	94.4	14.89	14.91
p-$H_2NHNC_6H_4PO_3H_2$[m]	I	26	Dec. >212	16.47	16.11	94.1	93.8	14.89	[i]
$(m\text{-}BrC_6H_4)_2PO_2H$			186.5–189	8.24	8.19	376.0	373.4		
$(p\text{-}BrC_6H_4)_2PO_2H$			170.5–172.5	8.24	8.06	376.0	375.4		
$(m\text{-}BrC_6H_4)(m\text{-}CH_3NHC_6H_4)PO_2H$	II	25	80–93[n]	9.50	9.26	326.1	320.2	4.30	4.26
$(m\text{-}CH_3NHC_6H_4)_2PO_2H$[l]	II	75	232.5–235.5	11.21	10.90	276.3	278.0	10.14	9.84

[a] Melting points were taken as previously described; *cf.* reference 5. [b] Phosphorus was determined by a modification of the method of Bachofer and Wagner, *Ind. Eng. Chem., Anal. Ed.*, 15, 601 (1943). [c] The indicator used for the primary acids was thymolphthalein; the indicator used for the secondary acids was phenolphthalein. [d] Previously prepared by G. M. Kosolapoff, THIS JOURNAL, **70**, 3465 (1948); m.p. 152–153°. [e] Previously prepared by G. M. Kosolapoff, ref. *d*, and other workers. Highest previously reported m.p. 202°. [f] This compound was recrystallized from aqueous alcohol and finally dried *in vacuo* at 100° to remove solvent of crystallization. [g] Although soluble in hot water, this compound does not crystallize from this solvent on cooling. Evaporation of the aqueous solution to a small volume gave a sirup in which phosphoric acid and methylaniline were identified. Purification of the crude *p*-methylaminobenzenephosphonic acid was accomplished by dissolving it in hot 6 *N* hydrochloric acid and treating this solution with charcoal. Adjusting the *p*H to 4 with sodium acetate caused the phosphonic acid to separate as white crystals. [h] This compound was isolated through the magnesium ammonium salt. In contrast to most phosphonic acids the salt precipitated in the cold. It was recrystallized several times from 6 *N* hydrochloric acid. [i] Nitrogen analysis on this compound by the Kjeldahl procedure was unsatisfactory. [j] Calcd.: C, 44.24; H, 5.57. Found: C, 44.08; H, 5.65. [k] Potentiometric titration of this compound by H. H. Jaffé showed that the last dissociation constant was too small (pK_a 9.5) to permit the use of thymolphthalein as the indicator. [l] These compounds were recrystallized from aqueous alcohol. [m] This compound has been reported previously, without analyses, by E. A. H. Friedheim, U. S. Patent 2,415,555. [n] Three recrystallizations from aqueous alcohol did not appreciably change the m.p. nor the analyses on this compound.

indicated that all of the bromine was split from the ring.[6]

The difficulties described above are believed to be due to two factors: (1) the solubility of these phosphonic acids in aqueous media, (2) the occurrence of side reactions which resulted in the formation of phosphoric acid. The apparent solubility of most alkylaminobenzenephosphonic acids is in marked contrast to the behavior of phosphanilic acid which is insoluble in water and can be recrystallized unchanged from 6 *N* hydrochloric acid.

Cleavage of phosphorus from the ring was demonstrated by the precipitate of magnesium ammonium phosphate obtained when magnesia mixture was added to the cold reaction mixture, after the copper had been removed. This cleavage undoubtedly is due to the influence of the electron-repelling alkylamino groups on the stability of the carbon–phosphorus bond. Dimethylaminobenzenephosphonic acid also is known to be relatively unstable.[7]

With the majority of the reactions discussed above, 10–25% of the phosphorus was converted to phosphoric acid. However, with *n*-butylamine, where the reaction mixture was heated for a much longer period, our results indicated that essentially all of the phosphonic acid was converted to the inorganic acid.

The reaction of *p*-bromobenzenephosphonic acid with dimethylamine, diethylamine and di-*n*-butylamine was also investigated. We were unable to isolate the desired compounds, and in each case most of the starting material was recovered.[8] Bromide ion analyses on aliquots of the reaction mixture at varying time intervals indicated that the reaction with dialkylamines proceeded at a very slow rate—less than 10% with dimethylamine in 8 hours.

The results obtained with *m*-bromobenzenephosphonic acid and bis-(*m*-bromophenyl)-phosphinic acid were somewhat better than with the ortho and para isomers. This difference was due in part to the increased stability of the carbon–phosphorus bond when the alkylamino group is in the meta position. Thus, even with the 43 hours heating used in the preparation of *m*-*n*-butylaminobenzenephosphonic acid, only a trace of phosphoric acid was formed. With bis-(*m*-bromophenyl)-phosphinic acid and methylamine it was found possible to isolate, depending upon the reaction conditions employed, either the symmetrical bis-(*m*-methylaminophenyl)-phosphinic acid or (*m*-bromophenyl)-(*m*-methylaminophenyl)-phosphinic acid.

The compounds prepared, together with their analyses and m.ps., are listed in Table I. Preliminary investigation indicates that none of these

(6) Bromide ion analyses were also used to follow the progress of these reactions; thus, the time for completion (in hours) of the reaction between *p*-bromobenzenephosphonic acid and various amines was as follows: methylamine, 1; ethylamine, 5; *n*-propylamine, 24; *n*-butylamine, >40. This order of reactivity is in contrast with uncatalyzed nucleophilic reactions involving amines and activated aromatic halogens; *cf.* J. F. Bunnett and R. E. Zahler, *Chem. Revs.*, **49**, 273 (1951).

(7) A. Schenk and A. Michaelis, *Ber.*, **21**, 1497 (1888).

(8) R. K. Robins and B. E. Christensen, *J. Org. Chem.*, **16**, 324 (1951), have reported that bis-(*p*-chlorophenyl)-phosphinic acid failed to react with dimethylamine.

compounds is markedly superior to phosphanilic acid in antibacterial properties.[9]

Experimental

o-Bromobenzenephosphonic Acid and Bis-(o-bromophenyl)-phosphinic Acid.—*o*-Bromobenzenediazonium fluoborate (54 g., 0.2 mole) was suspended in 250 ml. of ethyl acetate, and 17.4 ml. of phosphorus trichloride and 4 g. of cuprous bromide were added. The apparatus used has been described in a previous paper.[5] The nitrogen was evolved spontaneously after a short lag period. When the evolution of nitrogen was complete, 50 ml. of water was added and the mixture was steam distilled until 1 liter of distillate had been collected. The residual liquid in the flask was filtered hot. The crude bis-(*o*-bromophenyl)-phosphinic acid, which remained on the filter paper, was washed several times with hot water and purified by the procedure previously described for other phosphinic acids.[5] The filtrate was evaporated on the water-bath to incipient crystallization (approximately 25 ml.). When the solution was cooled, crude *o*-bromobenzenephosphonic acid separated. The phosphonic acid was dissolved in 20% sodium hydroxide solution and the precipitated copper hydroxide was removed by filtration. The filtrate was shaken with decolorizing charcoal for 10 minutes and again filtered. (The volume at this point should not exceed 100 ml.; otherwise it is necessary to evaporate the solution to this volume.) The *p*H of the solution was adjusted to 1.0 by the addition of concentrated hydrochloric acid. Crystallization was induced by scratching the sides of the beaker; the mixture was cooled and the *o*-bromobenzenephosphonic acid removed by filtration. It was recrystallized from 6 *N* hydrochloric acid.

m-Bromobenzenephosphonic Acid and Bis-(m-bromophenyl)-phosphinic Acid.—These compounds were prepared by the general method previously described.[5] The following slight modification was used to separate the two acids. After the reaction mixture was steam distilled, the residual liquid in the flask was transferred to a beaker and allowed to stand at room temperature overnight. The phosphinic acid, which separated out of the solution, was purified by the usual procedure.[5] The phosphonic acid was then isolated and purified by procedure A as previously described.[5]

p-Bromobenzenephosphonic Acid and Bis-(p-bromophenyl)-phosphinic Acid.—*p*-Bromobenzenephosphonic acid is much less soluble in aqueous media than the other phosphonic acids we have studied. Accordingly, its separation from bis-(*p*-bromophenyl)-phosphinic acid could not be accomplished by the procedure previously described. The following method proved satisfactory. After steam distillation the residual liquid was cooled. The crystals were removed by filtration and extracted with boiling water (approximately one liter for reactions on 0.5 mole scale) to dissolve the phosphonic acid. The insoluble phosphinic acid was purified by the usual procedure. The original filtrate was evaporated to 125 ml. The phosphonic acid which separated on cooling was combined with the main crop which had been obtained by evaporating the aqueous extract to 125 ml. The acid was then readily purified by procedure A.[5]

The yields obtained with the isomeric bromo acids under varying reaction conditions are given in Table II.

TABLE II

THE YIELDS OF THE ISOMERIC BROMOBENZENEPHOSPHONIC AND BIS-(BROMOPHENYL)-PHOSPHINIC ACIDS UNDER VARIOUS CONDITIONS

	EtOAc, PCl_3		EtOAc, PBr_3		*i*-PrOAc, PCl_3		*i*-PrOAc, PBr_3	
R	$RP(O)H_2$ yield, %	$R_2P(O)H$ yield, %	$RP(O)H_2$ yield, %	$R_2P(O)H$ yield, %	$RP(O)H_2$ yield, %	$R_2P(O)H$ yield, %	$RP(O)H_2$ yield, %	$R_2P(O)H$ yield, %
o-BrC_6H_4	37	13	35	14	31	13	17	17
m-BrC_6H_4	47	6	39	15	34	20	21	19
p-BrC_6H_5	61	1	45	8	49	5	21	11

The Preparation of Alkylaminobenzenephosphonic Acids.—All of these compounds were prepared by heating the corresponding bromobenzenephosphonic acid with an aqueous solution of the amine in the presence of cuprous oxide.[10] The apparatus consisted of a 3-necked flask equipped with sealed stirrer and reflux condenser and the mixture was heated on a steam-bath. The course of the reaction was followed by bromide ion determinations on aliquots removed at varying time intervals. When the reaction was complete, hydrogen sulfide was passed through the reaction mixture to remove the copper. Subsequent isolation of the phosphonic acids proved to be difficult and no satisfactory general procedure has been evolved.

Several compounds were successfully isolated by the procedure used for phosphanilic acid[4] (procedure I). Either acetic or hydrochloric acid was used for acidification; the most satisfactory *p*H range was 2.9 to 4.3. When no phosphonic acid separated on acidification, the acid solution was evaporated to a small volume and cooled. The crude acid crystallized slowly from solution (procedure II). In one case better results were obtained by the addition of an equal volume of alcohol and cooling in the deep-freeze at −25° (procedure III). In other cases, isolation was effected through the magnesium ammonium salt (procedure IV).

Aqueous alcohol was used successfully for recrystallization of several of the phosphonic acids. In one case 6 *N* hydrochloric acid was used. With other compounds no satisfactory solvent was found.

p-(β-Aminoethoxy)-benzenephosphonic Acid and p-[(N-Nitroso)-(N-β-hydroxyethylamino)]-benzenephosphonic Acid.—A 25% aqueous solution (130 ml.) of ethanolamine was heated for 17 hours with 8 g. of *p*-bromobenzenephosphonic acid and 6 g. of cuprous oxide. After removal of the copper with hydrogen sulfide the solution was acidified to congo red with hydrochloric acid and filtered from a trace of sulfur. The filtrate was adjusted to *p*H 4.4 with sodium acetate when crystals separated from solution. These were recrystallized from hot water. Although analysis indicated that this compound could be the desired hydroxy amine, the material gave a negative test for a secondary amine.[11] From this result it appears probable that the compound is the isomeric amino ether ($H_2NCH_2CH_2OC_6H_4PO_3H_2$).

After the crystalline acid had been removed the filtrate was made alkaline with ammonia and magnesia mixture was added. The precipitated magnesium ammonium phosphate (equivalent to 10% of the total phosphonic acid used) was removed and the filtrate boiled to precipitate the magnesium salt of the organic acid. From this salt the free acid was obtained as an uncrystallizable sirup. When an acid solution of this sirup was treated with sodium nitrite, a crystalline solid separated which was recrystallized from alcohol. Analysis indicated that this was the N-nitroso derivative of the desired β-hydroxyethylaminobenzenephosphonic acid.

Bis-(m-methylaminophenyl)-phosphinic Acid.—Bis-(*m*-bromophenyl)-phosphinic acid (6.34 g.), 133 ml. of 25% aqueous methylamine and 6 g. of cuprous oxide were refluxed for 7 hours. A Dry Ice condenser was used to prevent escape of the methylamine from the reaction mixture. After the copper was removed the filtrate was evaporated to 100 ml. The solution was treated with Darco and the *p*H was adjusted to 4.6. A crystalline precipitate separated on standing.

(m-Methylaminophenyl)-(m-bromophenyl)-phosphinic Acid.—When the reaction described above was run for one hour and a water condenser was used in place of the Dry Ice condenser, the unsymmetrical compound was the principal product. It was recovered from the reaction mixture, after removal of the copper, by evaporating the solution to a small volume and adjusting the *p*H to 2.0.

Acknowledgment.—The authors wish to thank Miss Sadie Herndon for performing the analyses necessary for this research and Mrs. Carolina Mockler for skilled technical assistance.

CHAPEL HILL, N. C.

(9) J. D. Thayer, H. J. Magnuson and M. S. Gravatt, paper presented before the Society of American Bacteriologists, Boston, Mass., April, 1952.

(10) Although previous investigators (ref. 3 and 4) specified freshly prepared cuprous oxide, we have found commercially available C.P. material to be equally satisfactory. No reaction occurred in the absence of cuprous oxide.

(11) R. L. Shriner and R. C. Fuson, "The Systematic Identification of Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1948, p. 111.