OMPA Synthesis with a Stoichiometric Amount of Triamido Phosphate.—A mixture of 55 g. of tetramethyldiamidophosphoryl chloride, 38.5 g. of hexamethylphosphoramide, and 19.6 g. of triethyl phosphate in the mole ratio of 3:2:1 was heated with agitation at 155°. The released gas was absorbed in ethanol and identified as ethyl chloride. Its amount was determined by weighing the reaction mixture repeatedly as the reaction progressed. According to equation e a total of 20.8 g. of ethyl chloride should be formed. The amount actually released as a function of time was: 1 hr., 86.5%; 2 hr., 91.4%; 3.5 hr., 95.4%; 4.5 hr., 95.4%.

The reaction mixture was then heated to a temperature of 130° under a pressure of 15 mm. in order to remove volatile components still dissolved in the mixture. The clear, dark-brown oil obtained weighed 93.3 g. (theory 92.3 g.).

In a parallel run of equal size the molecular weight of the reaction mixture as a function of time was determined. It was: start, 189; 1 hr., 265; 2 hr., 272; 3.5 hr., 295; 4.5 hr., 296 (through 286.3). From the second run two additional samples were taken after a reaction time of 3.5 and 4.5 hours, respectively, and tested insecticidally. Their activity was found to be the same as that of a material prepared according to equation a.

The reaction mixture from the first run was then separated by molecular distillation (boiling range 75 to 120° under a pressure of 1.0 to 0.5 mm.). It left a residue of 34 g. of an amidopolyphosphate product which could not be identified. The distillate had a weight of 56 g. and was analyzed by infrared. It was found to consist of 77% OMPA and 22% hexamethylphosphoramide. The total amount of OMPA formed was, therefore, 43 g. and represented a yield of 46.7%. The triamidophosphate recovered amounted to 32.0% of the quantity originally used. This was due to the equilibrium character of the synthesis method.

OMPA Synthesis in the Presence of an Excess of Triamidophosphate.—A mixture of 24.5 g. of tetramethyldiamidophosphoryl chloride plus 26.0 g. of hexamethylphosphoramide plus 8.75 g. of triethyl phosphate was heated four hours with agitation at 155°. The reaction mixture contained the components of the mole ratio of 3:3:1. A total of 8.0 g. of ethyl chloride was released, representing only 87% of the theoretical quantity due to the solubility of C_2H_5Cl in the triamidophosphate.

The crude reaction mixture was then concentrated by heating to a pot temperature of 140° under a pressure of 20 mm. The distillate obtained weighed 13 g. and contained according to infrared analysis 90% triamidophosphate and 10% OMPA.

The clear, dark brown oil residue weighed 37 g.; its analytical data compared in the following way with pure OMPA:

	Reaction product	Pure OMPA
P, %	21.6	21.64
N, %	18.7	19.57
Mol. wt.	288	286.3
d^t_4	1.1632 (20°)	1.1360 (25°)
n^t_D	1.4655 (20°)	1.4620 (25°)

This material was now purified by molecular distillation, which yielded a distillate of 31 g. and 5 g. of a polyphosphate residue. Infrared analysis of the distillate showed the presence of 88% OMPA and 12% triamidophosphate.

The boiling point of the pure OMPA was found to be 119–120° (0.65 mm.).

The total yield of OMPA was, therefore, 1.3 g. in the first distillate (vacuum concentration) plus 27.3 g. in the second distillate (molecular distillation). This quantity represented 69.6% of the theoretical yield.

A mixture of tetramethyldiamidophosphoryl chloride with hexamethylphosphoramide, as necessary for the synthesis described, can be prepared from dimethylamine and phosphorus oxychloride.

Thus, the synthesis of OMPA from $POCl_3$, dimethylamine and ethyl phosphate is possible by a two-step process.

Acknowledgment.—The author is indebted to Drs. A. W. Baker, Ch. W. Young and L. E. Streeter for analyses and to E. E. Kenaga for insecticidal tests reported in this paper.

MIDLAND, MICHIGAN

[CONTRIBUTION FROM THE ROSS CHEMICAL LABORATORY, ALABAMA POLYTECHNIC INSTITUTE]

The Synthesis of Amino-substituted Phosphonic Acids. III[1]

BY MARY E. CHALMERS AND GENNADY M. KOSOLAPOFF

RECEIVED JUNE 1, 1953

The interaction of dialkyl phosphites, ammonia and aldehydes was employed for the synthesis of the following dialkyl phosphonates which contain an amino group on the first carbon atom: diethyl and dibutyl α-aminobenzylphosphonates, diethyl α-aminoethylphosphonate, diethyl α-aminopropylphosphonate, diethyl *p*-methoxybenzyl-α-aminophosphonate, diethyl *p*-hydroxybenzyl-α-aminophosphonate, diethyl *o*-hydroxybenzyl-α-aminophosphonate and diethyl β-phenylethyl-α-aminophosphonate. The esters were converted to the free aminophosphonic acids, which were characterized. Additional details concerning the preparation of aminomethylphosphonic acid were obtained.

In continuation of our work on the synthesis and the determination of properties of phosphonic acids that contain an amino group in the molecule we examined the Mannich-type reaction which takes place between dialkyl phosphites, carbonyl compounds and ammonia, a reaction which was reported recently by Kabachnik and Medved in several examples involving ketones as the carbonyl compounds. The reaction can be summarily represented by the equation

$$(RO)_2P(O)H + NH_3 + R'COR'' \longrightarrow (RO)_2P(O)CR'R''NH_2$$[2]

Kabachnik and Medved report rather low yields of the products, but the method has advantages over other possible procedures.[3] Of particular interest to us is the fact that the method produces derivatives that carry the amino group in position adjacent to the phosphono group, thus yielding a number of compounds that are structurally analogous to the common naturally occurring amino acids.

We applied the above reaction to several aliphatic and aromatic aldehydes with satisfactory results. The esters of the amino acids, that were formed in the primary reaction, were characterized either as such or as the hydrochlorides. The esters were then converted to the free amino acids (Kabachnik and Medved dealt primarily with the esters only), which were characterized in the usual way. Thus, seven aminophosphonic acids in the form of race-

(1) Paper II, THIS JOURNAL, **70**, 1283 (1948).

(2) M. I. Kabachnik and T. Ya. Medved, *Doklady Akad. Nauk S.S.S.R.*, **83**, No. 5, 689 (1952).

(3) G. M. Kosolapoff, THIS JOURNAL, **69**, 2112 (1947).

mic (DL) mixtures were obtained. The work on resolution of the racemates is in progress.

The rather low yields of the aminophosphonates can be fairly substantially improved over those reported by Kabachnik and Medved if anhydrous ammonia and the aldehyde are premixed in alcohol solution. Passage of ammonia into a mixture of the aldehyde and the dialkyl phosphite, in alcohol solution, generally gave lower yields.

Experimental Part

α-Aminobenzylphosphonic Acid.—Freshly distilled benzaldehyde (10.6 g.) and 19.4 g. of dibutyl phosphite were placed into a stainless steel autoclave. To this mixture was added a solution of dry ammonia in 100 ml. of absolute ethyl alcohol (saturated at 0°) and the autoclave was heated for 10 hr. at 100°. The cooled reaction mixture was evaporated to dryness, the residue was taken up in 1:1 mixture of absolute ethanol and diethyl ether, and dry hydrogen chloride was passed into the solution. The yellowish precipitate of the hydrochloride of the dibutyl ester of the desired acid was filtered off and recrystallized from dioxane, yielding 6.0 g. (18%) of di-*n*-butyl α-aminobenzylphosphonate hydrochloride, m.p. 147–148°. Kabachnik and Medved gave m.p. 149°.[2] If the product is crystallized from the least volume of water, a 28% yield of pure product is obtained.

Diethyl phosphite gave somewhat better results. The reaction of 13.8 g. of diethyl phosphite, 10.6 g. of benzaldehyde and 100 ml. of ethanol saturated with ammonia, carried out as above, gave 8.7 g. (31%) of diethyl α-aminobenzylphosphonate hydrochloride, which melted at 159–160°, after crystallization from water. Kabachnik and Medved gave m.p. 158–159°.[2]

Anal. Calcd. for $C_{11}H_{19}O_3NPCl$: N, 5.01; P, 10.47; Cl, 12.48. Found: N, 5.17; P, 10.64; Cl, 12.16.

The hydrochlorides of either ester (5–6 g.) were readily hydrolyzed by refluxing overnight with 100 ml. of concentrated hydrochloric acid. After evaporation to dryness, the residue was taken up in 100 ml. of water and the solution was treated, while hot, with lead oxide (PbO) which was added gradually until the solution became alkaline to litmus. The solids were filtered off and were washed with much hot water, until the filtrate was free of chlorides. The lead salt was suspended in water and the suspension was treated with hydrogen sulfide. The lead sulfide was removed by filtration and the filtrate evaporated. The residue of crude α-aminobenzylphosphonic acid was recrystallized from water, yielding 64–65% of the pure acid, which melted at 271–273°. Kabachnik and Medved[2] give m.p. 272°; Kosolapoff[1] gives m.p. 273°.

Anal. Calcd. for $C_7H_{10}O_3NP$: P, 16.84; N, 7.48. Found: P, 16.95; N, 7.61.

α-Aminopropylphosphonic Acid.—Propionaldehyde (29.0 g.) was placed into the stainless steel autoclave which was chilled to 0°. Absolute ethanol (100 ml.) was saturated with dry ammonia at 0° and the solution was added to the aldehyde. Diethyl phosphite (69.0 g.) was added to the mixture and the autoclave was heated for 8 hr. at 100°. The cooled reaction mixture was distilled *in vacuo*, yielding 35.2 g. (36%) of diethyl α-amino-*n*-propylphosphonate, b.p. 47–49° at 3.1 mm. Repetitions of the reaction gave 29% and 32% yields.

Modified procedure, mentioned in the Introduction, gave better results.

Propionaldehyde (5.8 g.) in 50 ml. of absolute ethanol was chilled to 0° and dry ammonia was passed into the solution until the latter was saturated. The resulting cold solution was added slowly to 13.8 g. of diethyl phosphite contained in a steel autoclave, precooled to approximately 0°. The mixture was then heated for 8 hr. at 100° and the reaction mixture yielded on distillation 10.9 g. (56%) of the desired ester, b.p. 45–47° at 2.6 mm., $n^{20}D$ 1.4080, d^{20}_4 0.9798.

Anal. Calcd. for $C_7H_{18}O_3NP$: P, 15.89; N, 7.18; *MR*, 49.34. Found: P, 16.0; N, 7.10; *MR*, 49.1.

The ester was hydrolyzed and the acid was isolated, as described above, in 74% yield. The acid forms colorless plates, m.p. above 350°. If the acid is obtained from its hydrochloride by precipitation with aniline from dry ethanol,[3] the yield of the acid rises to 87%.

Anal. Calcd. for $C_3H_{10}O_3NP$: P, 22.30; N, 10.07. Found: P, 22.52; N, 10.3.

α-Aminoethylphosphonic Acid.—Acetaldehyde (4.4 g.) and 13.8 g. of diethyl phosphite, placed in a chilled steel autoclave, were mixed with a saturated solution of dry ammonia in 100 ml. of absolute ethanol and the mixture was heated for 8 hr. at 100°. Distillation gave 6.3–7.8 g. (35–43%) of diethyl α-aminoethylphosphonate, b.p. 74° at 6 mm., b.p. 70–73° at 3 mm., $n^{20}D$ 1.4150, d^{20}_4 1.0224.

Anal. Calcd. for $C_6H_{16}O_3NP$: P, 17.13; N, 7.73; *MR*, 44.72. Found: P, 17.2; N, 7.82; *MR*, 44.3.

The ester was hydrolyzed as above and the free acid was isolated through the lead salt procedure. After recrystallization from water there was obtained a 72% yield of α-aminoethylphosphonic acid in the form of colorless plates, m.p. above 340°.

Anal. Calcd. for $C_2H_8O_3NP$: P, 24.80; N, 11.20. Found: P, 24.69; N, 11.31.

***p*-Methoxybenzyl-α-aminophosphonic Acid.**—*p*-Anisaldehyde, b.p. 245–248°, prepared by a modified Gattermann reaction[4] (13.6 g.), in 100 ml. of absolute ethanol was saturated with dry ammonia at 0° in a steel autoclave and the solution was mixed with 13.8 g. of diethyl phosphite. After heating for 8 hr. at 100° the reaction mixture was evaporated to dryness, the residue was taken up in 1:1 mixture of dry ether and ethanol, and treated with dry hydrogen chloride. The colorless precipitate of diethyl *p*-methoxybenzyl-α-aminophosphonate hydrochloride was recrystallized from water. The pure product, obtained in 10.4 g. (33%) yield, formed X-shaped crystals and melted at 205–208°.

Anal. Calcd. for $C_{12}H_{21}O_4NPCl$: P, 10.01; N, 4.52; Cl, 11.29. Found: P, 10.13; N, 4.11; Cl, 11.45.

The ester was hydrolyzed and the free acid was isolated by the aniline procedure. The acid, obtained in 89% yield, formed cross-shaped crystals which melted at 215–218°.

Anal. Calcd. for $C_8H_{12}O_4NP$: P, 14.28; N, 6.45. Found: P, 14.41; N, 6.51.

***p*-Hydroxybenzyl-α-aminophosphonic Acid.**—Duplication of the above reaction with 6.1 g. of *p*-hydroxybenzaldehyde and 6.9 g. of diethyl phosphite gave 0.52 g. (3.5%) of diethyl *p*-hydroxybenzyl-α-aminophosphonate hydrochloride, which resinified at 175°.

If the aldehyde (6.1 g.) in 100 ml. of absolute ethanol was saturated with dry ammonia at near 0° and the mixture treated with 6.9 g. of diethyl phosphite, the usual procedure gave 4.1 g. (28%) of the above product.

Anal. Calcd. for $C_{11}H_{19}O_4NPCl$: P, 10.60; N, 4.78; Cl, 11.81. Found: P, 10.62; N, 4.35; Cl, 11.69.

The ester was hydrolyzed and the free acid was isolated by the aniline procedure in 85% yield. The acid formed colorless cross-shaped crystals, m.p. 150–152°.

Anal. Calcd. for $C_7H_{10}O_4NP$: P, 15.69; N, 6.93. Found: P, 15.82; N, 6.98.

***o*-Hydroxybenzyl-α-aminophosphonic Acid.**—The second procedure, given above for the *p*-isomer, yielded 26% of diethyl *o*-hydroxybenzyl-α-aminophosphonate hydrochloride, which melted above 310° after crystallization from water.

Anal. Calcd. for $C_{11}H_{19}O_4NPCl$: P, 10.60; N, 4.78; Cl, 11.81. Found: P, 10.71; N, 4.62; Cl, 11.73.

The ester was hydrolyzed and the free acid was isolated by means of the aniline procedure. The product formed cross-shaped crystals after recrystallization from water; it resinified at 180°; yield 85%.

Anal. Calcd. for $C_7H_{10}O_4NP$: P, 15.69; N, 6.93. Found: P, 15.54; N, 6.89.

β-Phenylethyl-α-aminophosphonic Acid.—Phenylacetaldehyde was obtained in 73% yield by hydrogenation of phenylacetyl chloride.[5] The aldehyde (2.0 g.) in 50 ml. of absolute ethanol was saturated at nearly 0° with ammonia in a glass liner of an autoclave, the solution was mixed with

(4) A. I. Vogel, "A Textbook of Practical Organic Chemistry," Longmans, Green & Co., New York, N. Y., 1948, p. 671.

(5) "Organic Reactions," Vol. 4, John Wiley and Sons, Inc., New York, N. Y., 1948, p. 362; K. W. Rosemund and F. Zetzsche, *Ber.*, **54**, 425 (1921).

2.4 g. of diethyl phosphite and heated for 8 hr. at 100°. The reaction mixture yielded 1.4 g. (31%) of diethyl β-phenylethyl - α - aminophosphonate hydrochloride, which formed colorless needles, m.p. 230–232°, after crystallization from water.

Anal. Calcd. for $C_{12}H_{21}O_3NPCl$: P, 10.56; N, 4.77; Cl, 11.89. Found: P, 10.42; N, 4.46; Cl, 11.93.

The ester was hydrolyzed and the free amino acid was isolated by the aniline method. The acid, obtained in 83% yield, formed cross-shaped crystals which melted at 225–227°.

Anal. Calcd. for $C_8H_{12}O_3NP$: P, 15.42; N, 6.97. Found: P, 15.50; N, 7.06.

Aminomethylphosphonic Acid.—This compound was prepared according to Chavanne[6] in order that a more convenient method of isolation be explored.

Bromomethylphthalimide (100 g.) and 54.6 g. of triethyl phosphite were heated at 150–160° until the evolution of ethyl bromide ceased. The residue was refluxed for 12 hr. with 100 ml. of 48% hydrobromic acid and phthalic acid was filtered from the cooled solution. The filtrate was evaporated to dryness, taken up in 100 ml. of dry ethanol and the clear solution treated with aniline until it became slightly acid to congo red. The precipitated acid was taken up in water, neutralized with sodium hydroxide and steam-distilled to remove traces of aniline. The solution was acidified to litmus with hydrochloric acid and treated with a saturated solution of lead acetate. The precipitate was thoroughly washed with hot water and the suspension was treated with hydrogen sulfide. Evaporation of the filtrate and recrystallization of the resulting crude acid from water gave a 58% yield of pure aminomethylphosphonic acid, m.p. above 300°.

Anal. Calcd. for CH_6O_3NP: P, 27.92; N, 12.61. Found: P, 28.10; N, 12.74.

The Mannich reaction with dialkylamines and dialkyl phosphites has been also reported by Fields.[7] Two products of this reaction that were necessary for our studies were prepared in good yield by the procedure given by Fields. Since Fields does not cite any physical properties of his products other than boiling points, the following may be of interest: diethyl N,N-diethylaminomethylphosphonate, b.p. 128–130° at 15 mm., $n^{20}D$ 1.3848, d^{20}_4 0.8779; diethyl α-(N,N-diethylamino)-isopropylphosphonate, b.p. 94–95° at 15 mm., $n^{20}D$ 1.4190, d^{20}_4 0.9256.

(6) V. Chavanne, *Bull. soc. chim., France*, **15**, 774 (1948).

(7) E. K. Fields, THIS JOURNAL, **74**, 1528 (1952).

AUBURN, ALA.

[CONTRIBUTION FROM ABBOTT LABORATORIES]

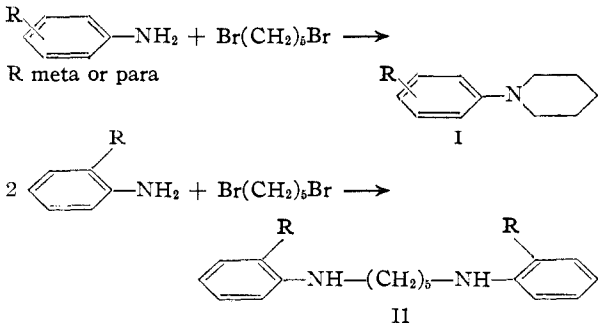
The Reaction of 1,5-Dibromopentane with *o*-Substituted Anilines. The Synthesis of 1-Arylpiperidines[1]

BY ARMIGER H. SOMMERS AND SHARON E. AALAND

RECEIVED JUNE 22, 1953

The reaction of *o*-toluidine, *o*-anisidine, *o*-chloroaniline or α-naphthylamine with 1,5-dibromopentane yielded an N-(*o*-substituted-phenyl)-piperidine (IV) as the principal product, although a small amount of an N,N'-diarylpentamethylenediamine (II) was sometimes isolated as by-product. 2,6-Dimethoxyaniline behaved similarly; however, the only product obtained with 2,6-dimethylaniline is N,N'-bis-(2,6-dimethylphenyl)-pentamethylenediamine (VII), a result which indicates greater steric hindrance by the two methyl groups. *m*-Anisidine gave N-*m*-methoxyphenylpiperidine from this reaction, and demethylation of the methoxyphenylpiperidines provided the corresponding aminophenols. Two of these were converted to dimethylcarbamyl esters, and quaternary salts were prepared and tested as anti-curare agents.

Soon after von Braun described a synthesis of 1,5-dibromopentane[2] this compound was used by Scholtz and Wassermann[3] for the synthesis of *m*- or *p*-substituted N-phenylpiperidines (I) from the corresponding substituted anilines. An *o*-substituent, they reported, prevented the formation of a piperidine ring and led to the formation of an N,N'-diarylpentamethylenediamine (II).



This conclusion was accepted by von Braun[4] and reference to it is made, without comment, in more recent publications,[5] but there seems to be no other experimental evidence to indicate that sufficient steric hindrance exists in *o*-substituted anilines to prevent N,N-disubstitution. To the contrary, two papers[6,7] take exception to physical data presented for N-tolylpiperidines prepared by this reaction, and other results have been reported which are not compatible with those of Scholtz and Wassermann.[3] Cerkovnikov and Prelog[8] obtained N-arylpiperidines by the action of 3-dimethylamino-1,5-dibromopentane upon *o*-toluidine and α-naphthylamine. This cannot be reconciled with the failure of 1,5-dibromopentane to undergo similar ring formation, unless the reactions are significantly different. A possible intermediate[9] in the former alkylation is 1,1-dimethyl-2-(β-bromoethyl)-azetidinium bromide, which was prepared by Cerkovnikov and Prelog,[8] and which yields a substituted piperidine upon treatment with aniline. These authors con-

(1) Presented before the Organic Division of the American Chemical Society, Chicago, Ill., September, 1953.

(2) J. von Braun, *Ber.*, **37**, 3210 (1904).

(3) M. Scholtz and E. Wassermaun, *ibid.*, **40**, 852 (1907).

(4) J. von Braun, *ibid.*, **41**, 2156 (1908).

(5) J. Houben, "Die Methoden der Organischen Chemie," Third Edition, Vol. 4, George Thieme, Leipzig, 1941, (Edwards Brothers, Inc., Ann Arbor, Mich., 1944), p. 580; A. A. Morton, "The Chemistry of Heterocyclic Compounds," McGraw-Hill Book Co., Inc., New York, N. Y., 1946, p. 232.

(6) A. N. Bourns, H. W. Embleton and M. K. Hansuld, *Can. J. Chem.*, **30**, 1 (1952).

(7) J. von Braun, *Ber.*, **40**, 3922 (1907).

(8) E. Cerkovnikov and V. Prelog, *ibid.*, **74**, 1648 (1941).

(9) R. C. Elderfield and C. Ressler, THIS JOURNAL, **72**, 4059 (1950).