Amino Phosphonic Acids. II. Aminoalkylphosphonic Acids[1]

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Nine amino phosphonic acids have been synthesized from phosphonoalkanoate esters by the Curtius reaction. Five are new: 1-aminobutylphosphonic acid, 1-amino-2-methylpropylphosphonic acid, 1-aminopentylphosphonic acid, 1-aminoheptylphosphonic acid, and 1-aminohendecylphosphonic acid. Improvements in the synthesis and isolation of the amino phosphonic acids are described and the approximate pK values for seven of them are given.

The synthesis of amino phosphonic acids by the Curtius reaction[4] has been extended to the following compounds.

$$\underset{\text{Br}}{\underset{|}{\text{RR'C}}}(\text{CH}_2)_x\text{CO}_2\text{Et} + \text{P(OEt)}_3 \longrightarrow \underset{\text{PO(OEt)}_2}{\underset{|}{\text{RR'C}}}(\text{CH}_2)_x\text{CO}_2\text{Et} \quad (1)$$

1 2

$$2 \xrightarrow[\text{reaction}]{\text{Curtius}} \underset{\text{NH}_2}{\underset{|}{\text{RR'C}}}(\text{CH}_2)_x\text{PO(OH)}_2 \quad (2)$$

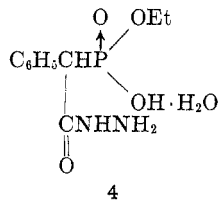
3

Compd	R	R'	x
a	C_2H_5	H	0
b	n-C_3H_7	H	0
c	i-C_3H_7	H	0
d	n-C_4H_9	H	0
e	n-C_6H_{13}	H	0
f	n-$C_{10}H_{21}$	H	0
g	H	H	2
h	CH_3	CH_3	0
i	C_6H_5	H	0

Attempts to prepare triethyl 2-methyl-2-phosphonopropionate (**2h**) by the methylation of triethyl phosphonoacetate[5] gave a mixture of the original ester and the monomethyl and the dimethyl derivatives, which could not be separated by fractional distillation; repeated methylation of triethyl 2-phosphonopropionate gave pure **2h**.

The Curtius reaction was carried out under a variety of conditions and ratios of reactants; the most satisfactory procedure is given in the Experimental Section.

Triethyl 2-phenyl-2-phosphonoacetate (**2i**) not only gave an easily crystallized hydrazide but the remainder of the Curtius reaction was surprising. Two crystalline intermediates were isolated and were found to correspond to structures **4** and **5**.



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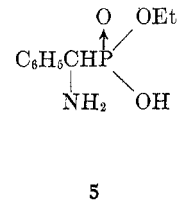

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(4) J. R. Chambers and A. F. Isbell, *J. Org. Chem.*, **29**, 832 (1964). Credit for the synthesis of 2-amino-4-phosphonobutyric acid (glutamic acid analog), as described earlier by P. Masterlerz, *Acta Biochim. Pol.*, **4**, 19 (1957), was inadvertently omitted.

(5) G. M. Kosolapoff and J. S. Powell, *J. Amer. Chem. Soc.*, **72**, 4198 (1950).

Experimental Section[6]

Ethyl 2-Bromoalkanoates (1).—These were prepared by a modified Schwenk and Papa[7] procedure. To 1 mol of the organic acid, held at 30°, 1.1–1.2 mol of thionyl chloride was added dropwise and the mixture was stirred at 60–80° until the gas evolution essentially stopped. At 80° 1.05 mol of Br_2 was added dropwise at approximately the rate that the Br_2 was consumed. Stirring was continued for several hours until the evolution of HBr nearly stopped. Absolute ethanol (100 ml) was added slowly to the crude acid chloride at 20–30°. After standing overnight, the mixture was washed with 100 ml of water, dilute $NaHSO_3$, and water. The organic layer was dried over anhydrous $MgSO_4$ and the dried ester was distilled slowly through a 24-in. Vigreux column to give the products in Table I.

Ethyl 4-Bromobutyrate (1g).—A mixture of 500 ml of absolute ethanol, 81 g of dry HBr, and 42 g of 4-butyrolactone was heated under reflux for 7 hr.[8] Distillation glve 57.0 g (58%) of ethyl 4-bromobutyrate, bp 104–107° (33 mm), $n^{25}D$ 1.4537 [lit.[8] bp 76–78° (7 mm)].

Triethyl Phosphonoalkanoates (2).[9]—The reaction flask was equipped with a stirrer, thermometer, dropping funnel and a steam-jacketed condenser, causing ethyl bromide to pass through while the higher boiling reaction components condensed. The bromo ester 1 (1 mol) was heated to 160° and 1.2 mol of triethyl phosphite was added dropwise over a period of 2 hr. The reaction temperature was increased to 190° and held there until the evolution of ethyl bromide ceased. The mixture was distilled rapidly the first time below 3 mm, primarily to remove some nonvolatile residue that often seemed to catalyze the decomposition of 2. The second distillation was carried out with a 24-in. Fenske or spinning band column. Lower boiling fractions were unchanged triethyl phosphite and a small amount of diethyl ethylphosphonate. The relatively unreactive ethyl 2-bromo-3-methylbutyrate (**2c**) gave the best results when equal quantities of triethyl phosphite were added once an hour at 160° over a period of 60 hr. Ester **2c** was also prepared by condensing the K derivative of triethyl phosphonoacetate with isopropyl bromide;[5] the esters prepared by the two routes were identical in all respects.

Triethyl 2-methyl-2-phosphonopropionate (**2h**) was prepared by methylating triethyl 2-phosphonopropionate (1 mol) as the K derivative in 1040 ml of toluene with 1.1 mol of methyl iodide.[5] To avoid the problem of separating a mixture of methylated products, the product from 3.5 mol of triethyl 2-phosphonopropionate was added to a slurry of 0.884 g-atom of K in 750 ml of toluene. The K dissolved slowly over a period of 2 hr. Methyl iodide (1 mol) was added and this second methylation reaction was carried out at 80° for 2 hr and at 100–112° for 8 hr. Solids were removed by filtering and the filtrate was distilled. Some

(6) All melting points were determined with a Hershberg apparatus and with a thermometer, calibrated with a set of thermometers having Bureau of Standards calibrations; boiling points are uncorrected. Triethyl phosphite was redistilled after kindly being supplied by the Hooker Chemical Co. Anhydrous hydrazine (95+%) was obtained from Matheson Coleman and Bell. Dowex 50W-X8 and Dowex 21K resins and propylene oxide were kindly supplied by the Dow Chemical Co. All other reagents were the best grade available and were used without further purification. Index of refraction measurements were taken with a Bausch and Lomb Abbe 3-L refractometer and the potentiometric titrations were carried out with a Sargent Model D recording titrator. Benzoyl derivatives were prepared with a Labline "Stir-O-Vac" high-speed stirrer. Analyses were made by Galbraith Laboratories, Knoxville, Tenn.

(7) E. Schwenk and D. Papa, *J. Amer. Chem. Soc.*, **70**, 3626 (1948).

(8) W. A. Reckhow and D. S. Tarbell, *ibid.*, **74**, 4960 (1952).

(9) B. Ackerman, R. M. Chladek, and D. Swern, *ibid.*, **79**, 6524 (1957).

TABLE I
BROMO ESTERS

Ester	Bp, °C (mm)	$n^{25}D$	Yield, %
Ethyl 2-bromobutyrate (1a)	67–69 (12)[a]		85
Ethyl 2-bromovalerate (1b)	93–96 (26)[b]	1.4462	86
Ethyl 2-bromoisovalerate (1c)	49–49.5 (1.6)[c]	1.4480	82
Ethyl 2-bromocaproate (1d)	53 (1)[d]	1.4488[d]	87
Ethyl 2-bromocaprylate (1e)	72–74 (0.7)[e]	1.4514	81
Ethyl 2-bromolaurate (1f)	119–121 (0.2)[f]	1.4550[f]	69
Ethyl 4-bromobutyrate (1g)	104–107 (33)[g]	1.4537[g]	58
Ethyl 2-bromo-2-phenylacetate (1i)	103–105 (1.4)[h]	1.5374	81

[a] Reference 9 gave bp 65° (10 mm). [b] N. A. Preobrazhenskii, M. E. Maurit, G. I. Bazilevskaya, G. V. Smiranova, M. M. El'manovich, A. I. Valakhanovich, and E. Persiyanova, *Zh. Obshch. Khim.*, **30**, 2250 (1960), gave bp 84–85° (10 mm). [c] B. Schleicher, *Justus Liebigs Ann. Chem.*, **267**, 114 (1892), gave bp 110–115° (40 mm). [d] Reference 9 gave bp 75° (4 mm), $n^{30}D$ 1.4456. [e] K. Bernhard and H. Lincke, *Helv. Chim. Acta*, **29**, 1457 (1946), gave bp 137–140° (25 mm). [f] Reference 9 gave bp 101° (0.1 mm), $n^{30}D$ 1.4531. [g] E. A. Prill and S. M. McElvain, *J. Amer. Chem. Soc.*, **55**, 1233 (1933), gave bp 104–105° (28 mm), $n^{25}D$ 1.4539. [h] H. Alexander, *Justus Liebigs Ann. Chem.*, **258**, 67 (1890), gave bp 143–145° (10 mm).

TABLE II
PHOSPHONOALKANOATE ESTERS

R	R′	x	Bp, °C (mm)	$n^{25}D$	d^{25}_4	Yield, %
C_2H_5	H	0	117–118 (0.6)[a]	1.4310[a]		87
n-C_3H_7[b]	H	0	98–100 (2.5)	1.4327	1.0579	70
i-C_3H_7[c]	H	0	85–85.5 (0.1)	1.4344	1.0543	67
n-C_4H_9	H	0	117.5–118 (0.85)[d]	1.4337[d]	1.0346[d]	87
n-C_6H_{13}	H	0	136–137 (0.75)[e]	1.4365	1.0178	72
n-$C_{10}H_{21}$	H	0	168–172 (0.25–0.35)[f]	1.4424[f]		58
H	H	2	120–122 (0.45)[g]	1.4355[g]		82
CH_3	CH_3	0	76–80 (0.25)[h]	1.4298[h]		53
C_6H_5	H	0	152–162 (1.0)[i]	1.4914[i]		75

[a] B. Fiszer and J. Michalski, *Rocz. Chem.*, **28**, 185 (1954), gave bp 152–154° (14 mm), $n^{20}D$ 1.4296. [b] *Anal.* Calcd for $C_{11}H_{23}O_5P$: C, 49.62; H, 8.71; P, 11.63. Found: C, 49.58, 49.64; H, 8.73, 8.82; P, 11.64, 11.60. [c] *Anal.* Calcd for $C_{11}H_{23}O_5P$: C, 49.62; H, 8.71; P, 11.63. Found: C, 49.51, 49.80; H, 8.65, 8.94; P, 11.60, 11.83. [d] Reference 9 gave bp 141° (4 mm), $n^{30}D$ 1.4300, d^{30}_4 1.0337. [e] V. Chavane, *Ann. Chim. (Paris)*, **4**, 352 (1949), gave bp 155–157° (1.5 mm). [f] Reference 9 gave bp 153–156° (0.1 mm), $n^{30}D$ 1.4398. [g] R. L. McConnell and H. W. Coover, Jr., *J. Amer. Chem. Soc.*, **78**, 4453 (1956), gave bp 127–129° (2.3 mm), $n^{20}D$ 1.4334. [h] Also $n^{30}D$ 1.4278. B. A. Arbuzov and V. S. Vinogradova, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 54 (1957), gave bp 103–103.5° (1 mm), $n^{20}D$ 1.4310, and ref 7 gave bp 74° (0.2 mm), $n^{30}D$ 1.4286. [i] V. S. Abramov and S. Pall, *Tr. Kazansk. Khim. Tekhnol. Inst.*, **23**, 105 (1957), gave bp 180–181° (3 mm), $n^{20}D$ 1.4952.

additional solid separated during the distillation and an additional quantity was left as a residue (hygroscopic). Data for phosphonoalkanoate esters are given in Table II.

$$RR'C(CH_2)_xCO_2Et$$
$$|$$
$$PO(OEt)_2$$

Amino Phosphonic Acids (3).—The Curtius reaction was carried out similarly to what has been described earlier.[4] In the production of the C hydrazides, the best reaction temperature seemed to be 25–40° with 100% excess hydrazine; no advantage was found in using a greater excess. The only esters that reacted exothermically with hydrazine under these conditions were triethyl 2-phenyl-2-phosphonoacetate (2i) and triethyl 4-phosphonobutyrate (2g). The remaining esters were not immediately miscible with hydrazine and were much less reactive, 2c and 2h being the slowest to react. These slower reacting esters were added to the hydrazine at 25° at a rate which maintained a homogeneous reaction mixture. After all of the 2 was added, the homogeneous solution was allowed to stand for 16 hr. Longer reaction times caused the yields to decrease, probably because the hydrazine seems to react slowly with the phosphonate ester group to give N-alkylated hydrazine salts of the phosphonic acids. Most of the crude hydrazides were viscous oils, but some (from 2i, 2e, and 2f) crystallized after standing for several days or after stirring with ether. The excess hydrazine was removed by heating the crude hydrazide to 45° at 1 mm for a few minutes.

Varying amounts of hydrochloric acid and sodium nitrite in the acyl azide forming step were also investigated, indicating that more than 2 mol of these per mole of hydrazide offered no advantages. Usually the crude acyl azide was extracted in the ether layer at about − 10° and was added to absolute ethanol (200 ml/mol of starting 2). This solution was allowed to stand overnight at 25° to decompose the acyl azide.

After the ether and ethanol were removed, the crude urethane was hydrolyzed by heating under reflux with 100% excess HCl, HBr, or HI. (Each mole of urethane theoretically requires 3 mol of acid.) Constant-boiling HCl required 48-hr hydrolysis for maximum yield and HBr and HI caused complete hydrolysis in about 8 hr. The dark solution was evaporated to dryness under vacuum, the residue was dissolved in 1 l. of water/mol of 2, and the solution was decolorized with Norit A.

The propylene oxide procedure[4] gave the amino acid in fair purity but the following procedure gave a higher yield of amino acid and the purity was excellent. The decolorized solution was passed through a column of Dowex 50W-X8 (H^+) resin (having at least 1 equivalent weight capacity/mol of 2) and the column was washed with deionized water. The first eluate was strongly acidic but ninhydrin negative and was discarded. Continued washing with water eluted the amino acid as a slightly acidic, ninhydrin-positive solution. (The best ninhydrin reagent was prepared by dissolving 200 mg of ninhydrin in 80 ml of ethyl alcohol, 15 ml of glacial acetic acid, and 5 ml of collidine. This solution keeps well in a closed bottle in a refrigerator.) All of the amino acids except 1-amino-1-methylethylphosphonic acid (3h) gave deep violet colors with this reagent. No color was produced with 3h but, if this compound was added to a mixture of 1–2 drops of 0.2 M $CuSO_4$ and 1–2 drops of saturated aqueous $NaHCO_3$ in 1 ml of water, a clear, deep blue solution resulted. Another excellent continuous detecting scheme involved monitoring the eluate with a Nester-Faust refractive index monitor. Evaporating the amino acid eluate to dryness left a white solid that was recrystallized from water–ethyl alcohol.

The low solubility of 1-aminoheptylphosphonic acid (3e) in water necessitated the utilization of large volumes of water to elute 3e from Dowex 50 resin and to recrystallize it. Even this procedure failed with 1-aminohendecylphosphonic acid (3f). It was recovered by evaporating the urethane hydrolysate on a steam bath under an air jet. (Evaporation under vacuum resulted in violent foaming.) Purification of 3f was accomplished by digesting it with hot ethyl alcohol and with boiling water. The amino acid remained undissolved and is insoluble in all

TABLE III
AMINO PHOSPHONIC ACIDS

Registry no.	R	R′	x	Mp, °C, dec	Yield, %	Neut equiv Calcd	Neut equiv Found	pK1	pK2	pK3	Calcd, % C	Calcd, % H	Calcd, % P	Found, % C	Found, % H	Found, % P
14047-23-5	C_2H_5	H	0	285–286[a]	16–63	139	141	1.95	5.75	10.28	25.90	7.25	22.27	26.16	7.18	22.14
														25.98	7.17	22.44
13138-36-8	n-C_3H_7	H	0	298–299	13–46	153	154	1.95	5.83	10.32	31.37	7.90	20.23	31.13	7.85	20.36
														31.18	7.79	20.11
18108-24-2	*iso*-C_3H_7	H	0	280–281	6.5–14	153	155	2.04	6.00	10.45	31.37	7.90	20.23	30.91	7.75	20.58
														31.12	7.69	20.48
13138-37-9	n-C_4H_9	H	0	284–285	46–52	167	169	1.83	5.82	10.35	35.93	8.44	18.53	35.99	8.29	18.89
														36.16	8.38	18.92
35045-86-4	n-C_6H_{13}	H	0	289–290	16–62	*b*	*b*	*b*	*b*	*b*	43.07	9.29	15.87	43.17	9.23	15.89
														42.98	9.15	16.09
14581-07-8	n-$C_{10}H_{21}$	H	0	286–287	36–72	*b*	*b*	*b*	*b*	*b*	52.57	10.43	12.33	52.23	10.35	12.44
														52.19	10.28	12.28
13138-33-5	H	H	2	294–296[c]	36–49	139	140	2.11	6.97	11.01	25.90	7.25	22.27	25.71	7.15	22.66
														25.81	7.29	22.48
5035-79-0	CH_3	CH_3	0	274–275[d]	7–41	157[e]	157	2.09	6.05	10.43	22.93[e]	7.64[e]	19.72[e]	22.71	7.88	20.09
														22.65	7.63	19.92
18108-22-0	C_6H_5	H	0	299.5[f]	43[g]	187	189	1.80	5.60	9.50						

[a] M. E. Chalmers and G. M. Kosolapoff, *J. Amer. Chem. Soc.*, **75**, 5278 (1953), gave mp >350°. [b] Not sufficiently soluble in water to make accurate measurements. [c] G. M. Kosolapoff, *J. Amer. Chem. Soc.*, **69**, 2112 (1947), gave mp 274°; N. Kreutzkamp and H. Schindler, *Arch. Pharm. (Weinheim)*, **295**, 28 (1962), gave mp 274°. [d] T. Ya. Medved and M. I. Kabachnik, *Dokl. Akad. Nauk SSSR*, **84**, 717 (1952), reported mp 258° for the monohydrate. [e] Values for the monohydrate. Heating the compound to 120° (30–40 mm) for 24 hr caused no loss of weight. [f] Reference *a* gave mp 271–273° and M. I. Kabachnik and T. Ya. Medved, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 868 (1953), gave mp 272–273°. [g] The result of only one run.

TABLE IV
N-BENZOYL DERIVATIVES

Registry no.	R	R′	x	Mp, °C	Yield, %	Neut equiv Calcd	Neut equiv Found	Calcd, % C	Calcd, % H	Calcd, % P	Found, % C	Found, % H	Found, % P
35045-90-0	C_2H_5	H	0	183–185	60	243	243	49.39	5.80	12.74	49.37	5.83	12.63
											49.34	5.84	12.50
35045-91-1	n-C_3H_7	H	0	186–187	75	257	256	51.36	6.27	12.04	51.28	6.37	12.17
											51.49	6.37	12.06
35045-92-2	i-C_3H_7	H	0	153–154	40	257	256	51.36	6.27	12.04	51.29	6.38	12.25
											51.40	6.43	12.07
35045-93-3	n-C_4H_9	H	0	106–107	51	289[a]	288	49.82[a]	6.97[a]	10.71[a]	49.86	7.05	10.78
											49.54	6.90	10.63
35045-94-4	n-C_6H_{13}	H	0	130–131	58	299	297	56.18	7.41	10.35	55.90	7.48	10.35
											55.83	7.35	10.43
35045-95-5	n-$C_{10}H_{21}$	H	0	83–85	45	355	355	60.83	8.50	8.72	61.09	8.57	8.92
											60.97	8.52	8.77
35045-96-6	H	H	2	145–147	50	243	241	49.39	5.80	12.74	49.36	5.90	12.65
											49.35	5.92	12.87
35045-97-7	CH_3	CH_3	0	207–208	43	243	241	49.39	5.80	12.74	49.21	5.71	12.83
											49.04	5.75	13.01
35045-98-8	C_6H_5	H	0	103.5[b]–129[c]	72	291[c]	295[c]						

[a] For the monohydrate. [b] The monohydrate; neut equiv 309 (calcd, 309), mp 103.5–105.5° from water. T. Ya. Medved and M. I. Kabachnik, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 1043 (1955), gave mp 105–107° for the monohydrate. [c] Anhydrous compound produced by heating the hydrate at 90° (30 mm). When the anhydrous compound was exposed to the air of the laboratory for 1 hr, the melting point changed to 103.5–105.5°.

common organic solvents and in dilute HCl. Significant amounts will dissolve in concentrated HCl and in dilute base, producing solutions that foam copiously. Data on the various amino acids are found in Table III.

$$RR'C(CH_2)_xPO(OH)_2$$
$$|$$
$$NH_2$$

A special case was the Curtius reaction of triethyl 1-phenyl-1-phosphonoacetate (**2i**). When this ester and hydrazine were condensed in a 1:2 molar ratio, the solution deposited crystals of the hydrazide after 2 days. The solid hydrazide (106.0 g) was slurried with ether and treated with HCl and $NaNO_2$ by the usual procedure. However, the two-phase mixture contained 10.0 g of a solid, which was removed and found to be slightly soluble in hot water (slightly acidic solution) but essentially insoluble in the common organic solvents. However, if this solid was suspended in boiling ethyl alcohol and a few drops of acetone were added, the solid dissolved completely. Cooling caused the separation of white needles, mp 187.5–189.5° dec. All of the properties of this compound were consistent with structure **4**.

Anal. Calcd for $C_{10}H_{17}N_2O_5P$: C, 43.48; H, 6.20; N, 10.14; P, 11.21. Found: C, 43.61, 43,83; H, 6.16, 6.06; N, 10.02, 9.95; P, 11.49, 11.52.

When the ether–alcohol solution of the acyl azide from **2i** was allowed to decompose overnight, a solid product (9.5 g) separated from solution. This solid had mp 248° dec, was soluble in cold water (neutral solution), and was insoluble in all common organic solvents. Hydrolysis of 1.0 g of this solid with 20% HCl allowed the recovery of 0.83 g of 1-amino-1-phenylmethylphosphonic acid (**3i**). Since no satisfactory recrystallization solvent was found, the unknown solid was washed thoroughly with ethyl alcohol, dried in a vacuum desiccator, and analyzed. All of the properties of the solid (mp 248°) were consistent with structure **5**.

Anal. Calcd for $C_9H_{14}NO_3P$: C, 50.23; H, 6.56; N, 6.51; P, 14.39. Found: C, 50.40, 50.47; H, 6.44, 6.57; N, 6.55, 6.68; P, 14.44, 14.48.

Approximate pK Values and Neutralization Equivalents.—Weighed quantities of the amino acids were dissolved in standardized HCl in a volumetric flask, and aliquots were taken and titrated with standardized NaOH with a Sargent Model D recording titrator. From at least three such plots, the approximate pK values and neutralization equivalents were read.

Preparation of Benzoyl Derivatives.—The amino acid (6–7 g) was dissolved in 25 ml of water and enough 3 M NaOH to give pH 10. The solution was cooled to 5° and 100% excess benzoyl chloride was added. While a temperature of 5° was maintained and while 3 M NaOH was added at a rate to maintain pH 10, the mixture was stirred with a high-speed stirrer. When there was no further reaction, concentrated HCl was added to pH 2 and the product was recovered as described earlier.[4] The derivatives were recrystallized usually from acetonitrile; see Table IV.

$$RR'C(CH_2)_xPO(OH)_2$$
$$|$$
$$NHCOC_6H_5$$

Highly purified samples of amino acids were obtained by the hydrolysis of the purified benzoyl derivatives and recovery of the amino acid by ion exchange chromatography.

Registry No.—**2b**, 35051-49-1; **2c**, 35051-50-4; **4**, 35045-80-8; **5**, 35045-81-9.

Amino Phosphonic Acids. III. The Synthesis and Properties of 2-Aminoethylphosphonic and 3-Aminopropylphosphonic Acids[1]

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2-Aminoethylphosphonic acid (2-AEP, **2**) is the first compound having a C–P bond to be isolated from biological materials. Because of its wide distribution in the animal kingdom, 2-AEP appears to be an important new biological compound. This paper reports our findings concerning the polymorphism of **2**, some of its other physical and chemical properties, and two new syntheses. The behavior of 3-aminopropylphosphonic acid is compared with that of **2**.

In 1959, Horiguchi and Kandatsu[3] first described the isolation of **2** from ciliate protozoa. Since then, **2** has been found in numerous other organisms and a new area of biochemistry has grown up around this compound. A review covering developments through March 1964 is available.[4] Although man has modest quantities of **2** available in his food, it has not been determined whether or not he makes any use of this compound.

2-Aminoethylphosphonic acid (**2**) was first synthesized by Finkelstein[5] by the use of the Hofmann reaction.

$$\underset{\mathbf{1}}{EtO_2CCH_2CH_2PO(OEt)_2} \xrightarrow{NH_3} H_2NOCCH_2CH_2PO(OEt)_2 \xrightarrow[\text{conc HBr}]{NaOBr} \underset{\mathbf{2}}{H_2NCH_2CH_2PO(OH)_2}$$

Finkelstein added that "the corresponding hydrazide was also prepared from the ester but would not undergo the Curtius rearrangement." In 1947 both Kosolapoff[6] and Chavane[7] reported an alternate synthesis of **2**.

In contrast to Finkelstein's findings, we have been able to synthesize **2** by the Curtius synthesis in yields as high as 83%. 2-Aminoethylphosphonic acid may also be prepared by the catalytic reduction of readily available diethyl cyanomethylphosphonate.

2-Aminoethylphosphonic acid (**2**) gives the characteristic color with ninhydrin reagent but the color yield is only about 3% of the color produced by 1-aminoethylphosphonic acid and the color yield varies with the nature of the ninhydrin reagent.

Horiguchi and Kandatsu[8] first found that samples of **2** from different sources occasionally give different ir spectra when the spectra are run on Nujol mulls or on KBr disks. They correctly interpreted this as the result of polymorphism. We have also studied this be-

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(2) (a) Taken in part from the Ph.D. dissertation submitted by J. P. B. to Texas A & M University, May 1963. (b) Taken in part from the M.S. thesis submitted by L. W. T. to Texas A & M University, Jan 1965.

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