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Synthesis and Pesticidal Activities of Phosphonate Analog of Amino Acids

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Phosphonate analogs of nine α - and ω -amino acids and some their derivatives were synthesized and examined for pesticidal activities. 2-Aminoethylphosphonic acid showed a considerable activity as a herbicide against some lowland weeds.

INTRODUCTION

Since the first discovery of 2-aminoethylphosphonic acid (ciliatine) from rumen protozoa by Horiguchi and Kandatsu (1959), the phosphorus analogs of amino acids and peptides have aroused interests in their biological activities (Hori *et al.*, 1984). For example, alaphosphin (α -alanyl-L-1-aminoethylphosphonic acid) inhibits the growth of various pathogenic bacteria (Allen *et al.*, 1978). Bialaphos [α -2-amino-4-methyl(hydroxy)phosphinylbutyryl-L-alanyl-L-alanine] produced by *Streptomyces viridochromogenes* (Bayer *et al.*, 1972) and its active hydrolysis product phosphinothricin [α -2-amino-4-methyl(hydroxy)phosphinylbutyric acid] are known as herbicides (Sekizawa and Takematsu, 1983). The latter is the phosphorus analog of glutamic acid and inhibits glutamine synthetase. The herbicide glyphosate [N -(phosphonomethyl)glycine] is regarded as one of derivatives of glycine phosphonate analog (Eto, 1974).

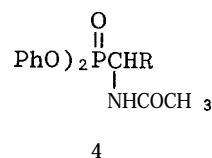
Glutamic acid and its decarboxylated metabolite, that is γ -aminobutyric acid (GABA), probably function in nervemuscle transmission in insects at excitatory and inhibitory synapses, respectively (Usherwood, 1974). The phosphonate analog of GABA has some affinity for GABA binding sites of rat brain (Cates *et al.*, 1984). The phosphonate analogs of these amino acids are, therefore, of interest to us to examine their activities against insects.

We have investigated many organophosphorus compounds, including phosphonates (Mihara and Eto, 1975 ; Tawata *et al.*, 1978) and amino acid derivatives (Eto *et al.*, 1978; Eto *et al.*, 1981), to find new lead compounds for pesticide development (Eto, 1983). This paper deals with the syntheses of aminoalkylphosphonates as the analogs of some α - and ω -amino acids and with their pesticidal activities. 2-Aminoethylphosphonic acid showed a considerable herbicidal activity.

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Table 1. Yields, melting points and spectral data of α -aminoalkylphosphonates and their derivatives.

Structure	R	Yield %	mp° C	IR (KBr) cm^{-1}	^1H NMR(CDCl_3) δ ppm
$\begin{array}{c} \text{O} \\ \parallel \\ (\text{PhO})_2\text{PCHR} \\ \\ \text{NHCO}_2\text{CH}_2\text{Ph} \end{array}$	H	22.7	110-4	3300, 3090, 1720, 1560, 1495, 1250, 1220, 1210, 1160, 960, 950, 930	3.95(2H, dd, $J=6$ & 20Hz, PCH_2), 5.10 (2H, s, OCH_2), 5.3-5.5 (1H, m, NH), 7.1-7.4(15H, m, Ar)
	CH_3	50.2	116-8	3300, 3070, 1720, 1540, 1490, 1240, 1190, 1020, 940	1.56 (3H, dd, $J=8$ & 19Hz, CH_3), 4.30-4.80 (1H, m, PCH), 5.00-5.30(1H, m, NH), 5.11 (2H, s, OCH_2), 6.98-7.44(15H, m, Ar)
	$\text{CH}(\text{CH}_3)_2$	36.4	103-6	3300, 3070, 2950, 1710, 1530, 1390, 1290, 1240, 1220, 1195, 940	1.08(6H, d, $J=7$ Hz, CH_3), 2.10-2.40(1H, m, $\text{CH}(\text{CH}_3)_2$), 4.22-4.58 (1H, m, PCH), 5.00-5.24(1H, m, NH), 6.10(2H, s, OCH_2), 6.98-7.42(15H, m, Ar)
	C_6H_5	79.7	157-9	3300, 3070, 1710, 1590, 1550, 1490, 1250, 1210, 1185, 1160, 1020, 940	5.05(2H, d, $J=3$ Hz, OCH_2), 5.37-5.70(1H, m, NH), 5.92-6.10(1H, m, PCH), 6.70-7.50(20 H, m, Ar)
$\begin{array}{c} \text{O} \\ \parallel \\ (\text{HO})_2\text{PCHR} \\ \\ \text{NH}_2 \end{array}$	H			see Table 2	
	CH_3	65.6	272-5	2980, 1620, 1540, 1230, 1210, 1150, 1040, 935,	(D_2O) 1.45(3H, dd, $J=8$ & 14Hz, CH_3), 3.12-3.50(1H, m, PCH)
	$\text{CH}(\text{CH}_3)_2$	72.4	257-260	2980, 2300, 1640, 1540, 1180, 1030, 1015, 940	(D_2O) 1.10(6H, dd, $J=4$ & 6Hz, CH_3), 1.98-2.20(1H, m, $\text{CH}(\text{CH}_3)_2$), 3.10 (1H, dd, $J=6$ & 15Hz, PCH)
$\begin{array}{c} \text{O} \\ \parallel \\ (\text{PhO})_2\text{PCHR} \\ \\ \text{NH}_2\text{HBr} \end{array}$	C_6H_5	42.3	278-281	3150, 2950, 2620, 2300, 1610, 1540, 1270, 1215, 1190, 1080, 920	(D_2O) 4.42(1H, d, $J=12$ Hz, PCH), 7.44(5H, s, Ar)
	H	92.3	137-141	3450, 3000, 2600, 1495, 1485, 1235, 1215, 1180, 1165, 960, 945, 765	(D_2O) 3.98(2H, d, $J=18$ Hz, PCH_2), 7.04-7.50 (10H, m, Ar)
	CH_3	85.0	140-2	3450, 2900, 1590, 1490, 1250, 1220, 1180, 1160,	(D_2O) 1.78(3H, dd, $J=7$ & 18Hz, CH_3), 4.1-4.5(1H, m, PCH), 7.05-7.50(10H, m, Ar)



CH(CH ₃) ₂	88.0	165-8	940, 780, 770, 690 3450, 2880, 1590, 1520, 1490, 1205, 1180, 1160, 960, 940, 770, 690	(D ₂ O) 1.26(6H, dd, J=3 & 7Hz, CH ₃), 2.40- 2.80(1H, m, CH(CH ₃) ₂), 4.10(1H, dd, J=6 & 16Hz, PCH), 7.03-7.50(10H, m, Ar)
C ₆ H ₅	84.5	180-2	3400, 2850, 1590, 1490, 1205, 1180, 1160, 950	(D ₂ O) 5.48(1H, d, J=18Hz, PCH), 6.75-7.70 (15H, m, Ar)
H	75.1		(neat) 3300, 3050, 1660, 1590, 1560, 1490, 1260, 1210, 1180, 1160, 930	1.95(3H, d, J=0.8Hz, COCH ₃), 4.02(2H, dd, J=6 & 12Hz, PCH ₂), 6.40-6.65(1H, m, NH), 7.04-7.40(10H, m, Ar)
CH ₃	68.9		(neat) 3250, 3050, 1660, 1590, 1540, 1490, 1250, 1210, 1185, 1160, 930,	1.50(3H, dd, J=7 & 18Hz, CH ₃), 1.90(3H, d, J=0.8Hz, COCH ₃), 4.65-5.16(1H, m, PCH), 6.50-6.72(1H, m, NH), 7.00-7.42(10 H, m, Ar)
CH(CH ₃) ₂	70.6		3300, 3000, 1685, 1595 1490, 1260, 1220, 1190 950, 930	1.10(6H, d, J=7Hz, CH ₃), 1.95(3H, d, J= 0.8Hz, COCH ₃), 2.10-2.60(1H, m, CH (CH ₃) ₂), 4.64-4.98(1H, m, PCH), 6.10-6.30 (1H, m, NH), 7.00-7.42(10H, m, Ar)
C ₆ H ₅	63.5		3300, 1680, 1490, 1280, 1250, 1205, 1180, 950	1.85(3H, d, J=0.8Hz, COCH ₃), 5.95(1H, dd, J=10 & 22Hz, PCH), 6.64-7.58(16H, m, NH & Ar)

EXPERIMENTAL

Syntheses

Melting points were uncorrected. IR spectra were recorded on a Shimadzu IR-420 spectrophotometer and proton NMR spectra were measured with a JEOL FX-100 spectrometer with tetramethylsilane as the internal standard.

Diphenyl α -(N-benzyloxycarbonyl)aminoalkylphosphonates (1)

These were synthesized according to Oleksyszyn *et al.* (1979), by heating a mixture of triphenyl phosphite, an aldehyde, benzyl carbamate in acetic acid. The compounds synthesized are listed in Table 1 with their yields, melting points and spectral data.

Diphenyl N-benzyloxycarbonylaminomethylphosphonate

This was synthesized by using paraformaldehyde as a starting material according to Oleksyszyn and Subotkowska (1980).

 α -Aminoalkylphosphonic acids (2)

A mixture of diphenyl α -(N-benzyloxycarbonyl) aminoalkylphosphonate (3.6 mmole) and conc. HBr (20 ml) was refluxed for 5 hr. The separated aqueous layer was concentrated under reduced pressure. The residue was dissolved in ethanol (25 ml) and 1,2-butylene oxide was added until no more precipitation occurred. The precipitates were filtered and recrystallized from a water-ethanol mixture. The compounds prepared with this general procedure are listed in Table 1.

Diphenyl α -aminoalkylphosphonate hydrobromides (3)

Diphenyl α -(N-benzyloxycarbonyl) aminoalkylphosphonates were treated with 30% HBr in acetic acid at room temperature according to Oleksyszyn *et al.* (1979). The compounds obtained are listed in Table 1.

Diphenyl α -acetamidoalkylphosphonates (4)

A mixture of diphenyl α -aminoalkylphosphonate hydrobromide (1.4 mmole), acetic anhydride (0.2 ml) and triethylamine (0.2 ml) in dichloromethane (10 ml) was stirred at room temperature for 20 hr. The reaction mixture was worked up in a usual manner and the product was purified by silica gel chromatography. The compounds prepared by this general procedure are listed in Table 1.

Diethyl α -(N-benzyloxycarbonyl)aminobenzylphosphonate

To the sodium ethoxide prepared from sodium (4.3 mmole) and ethanol (20 ml) was added diphenyl (N-benzyloxycarbonyl) aminobenzylphosphonate (2.1 mmole) and stirred for 24 hr. The solution was concentrated under reduced pressure and the residue was extracted with dichloromethane and worked up in a usual manner. The residue obtained by evaporating the solvent was recrystallized from ethyl acetate. Yield 25.1%, mp 156–9°C. IR (KBr) cm^{-1} ; 3300, 1710, 1555, 1520, 1245, 1035, 750, 700. NMR (CDCl_3) ppm; 1.09 (3H, t, $J=8\text{Hz}$), 1.26 (3H, t, $J=8\text{Hz}$), 3.05–4.20 (4H, m), 4.90–5.30 (3H, m), 5.65–5.92 (1H, m), 7.15–7.48 (10H, m).

Diethyl ω -phthalimidoalkylphosphonates (5)

These compounds were synthesized from corresponding ω -bromoalkylphthalimides and triethyl phosphite by modifying a reported method (Yamauchi *et al.*

1972) for the phthalimidomethylphosphonate. The typical procedure is exemplified with the synthesis of diethyl 3-phthalimidopropylphosphonate : A mixture of 3-bromopropylphthalimide (10.0 g) and triethyl phosphite (20 ml) was heated for 3 hr with removal of produced ethyl bromide by distillation. Unreacted triethyl phosphite was removed under reduced pressure. The residue was dissolved in chloroform and worked up in a usual manner. The chromatography on a silica gel column gave 11.5 g (94.8%) of the desired compound by elution with ethyl acetate.

Its physicochemical data and those of the homologous compounds prepared similarly are listed in Table 2.

ω -Aminoalkylphosphonic acids (6)

A mixture of diethyl o-phthalimidoalkylphosphonate (4 mmole) and conc. HBr (20 ml) was refluxed for 10 hr. After cooling, precipitated phthalic acid was removed by filtration. The filtrate was concentrated under reduced pressure and the residue was dissolved in ethanol. To the solution was added 1,2-butylene oxide until no more precipitation occurred. The precipitates were collected by filtration and recrystallized from a water-ethanol mixture. The physicochemical properties of the products prepared by this general procedure are listed in Table 2.

Diethyl aminomethylphosphonate (7 ; $n=1$)

A mixture of diethyl phthalimidomethylphosphonate (10 g) and hydrazine hydrate (2.6 ml) in ethanol (100 ml) was stirred for 12 hr at room temperature and then refluxed for 2 hr. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure. Tetrahydrofuran (100 ml) was added to the residue and chilled at 0 °C for 3 hr, then filtered. The filtrate was concentrated to give 7.2 g (96%) of the desired product. See Table 2 for the spectral data of the products.

Diethyl 3-aminopropylphosphonate was similarly obtained from the corresponding phthalimide.

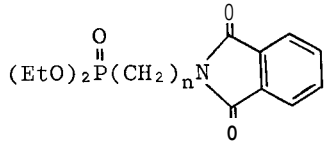
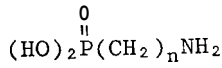
Diethyl 2-aminoethylphosphonate hydrochloride

A mixture of diethyl 2-phthalimidoethylphosphonate (5g) and hydrazine hydrate (0.8 ml) in absolute ethanol (100 ml) was stirred at room temperature for 48 hr. The mixture was acidified with conc. HCl and the precipitates were removed by filtration. The filtrate was concentrated under reduced pressure. To the residue was added water (20 ml). The aqueous solution was filtered and concentrated. The residue was recrystallized from a mixture of ethanol and ether to give 2.0 g (57.1%) of diethyl 2-aminoethylphosphonate hydrochloride. For physicochemical data see Table 2.

Diethyl ω -acylaminoalkylphosphonates (8 and 9)

A dichloromethane solution containing equimolar amounts of a diethyl aminoalkylphosphonate, acetic anhydride or benzoyl chloride, and triethylamine was stirred at room temperature for 10 hr. The reaction mixture was washed with 5% NaHCO₃, water, 5% HCl, and brine and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure. Chromatography on silica gel by elution with ethyl acetate gave the acylated product.

Table 2. Yields, melting points and spectral data of ω - aminoalkylphosphonates and their derivatives.

Structure	n	Yield %	mp °C	IR (KBr)cm ⁻¹	¹ H NMR(CDCl ₃) δ ppm
 5	2	70.3	64-6	3000, 1775, 1720, 1410, 1250, 1070, 1050, 1020, 970, 902, 735, 720	1. 36(6H, t, J=7Hz, CH ₃), 4.04-4.34 (6H, m, OCH ₂ , PCH ₂), 7.66-7.90(4H, m, Ar)
	3	67.0		3000, 1765, 1445, 1400, 1360, 1265, 1225, 1080, 1020, 950, 860, 840, 730	1. 28(6H, t, J=7Hz, CH ₃), 2.01-2.36(2H, m, PCH ₂), 3.80-4.23(6H, m, CH ₂ N & OCH ₂), 7.62-7.90(4H, m, Ar)
	4	94.8		(neat) 3000, 1775, 1710, 1400, 1370, 1250, 1020, 960, 720	1. 32(6H, t, J=7Hz, CH ₃), 1.54-2.16(4H, m, P(CH ₂) ₂), 3.75(2H, t, J=6Hz, CH ₂ N), 3.92-4.22(4H, m, OCH ₂), 7.64-7.85(4H, m, Ar)
	1	84.7	72-5	3000, 2950, 1770, 1710, 1400, 1375, 1250, 1050, 1030, 950, 725	1. 32(6H, t, J=7Hz, CH ₃), 1.50-2.00(6H, m, P(CH ₂) ₃), 3.68(2H, t, J=7Hz, CH ₂ N), 7.63-7.86(4H, m, Ar)
 6	1	92.6	302-6	2870, 2620, 2400, 1640, 1555, 1535, 1435, 1160, 1020, 930, 840, 730	(D ₂ O) 3.08(2H, d, J=13Hz, PCH ₂)
	2	90.2	279-283	2900, 2700, 1645, 1480, 1395, 1280, 1220, 1150, 1080, 1000, 960, 935, 905, 780, 760	(D ₂ O) 1.77-2.12(2H, m, PCH ₂), 3.04-3.30(2H, m, CH ₂ N)
	3	87.5	267-271	2900, 2300, 1630, 1540, 1240, 1130, 1030, 935	(D ₂ O) 1.45-2.10(4H, m, P(CH ₂) ₂), 3.90(2H, t, J=7Hz, CH ₂ N)
	4	40.3	270-4	2950, 2900, 2300, 1660, 1540, 1470, 1130, 1100, 1000, 940, 780	(D ₂ O) 1.50-1.85(6H, m, P(CH ₂) ₃), 2.90-3.12(2H, m, CH ₂ N)

$(\text{EtO})_2\overset{\text{O}}{\parallel}\text{P}(\text{CH}_2)_n\text{NH}_2$	1	96.0		(neat) 3390, 2990, 1390, 1223, 1020, 965, 770	1.25(6H, t, J=7Hz, CH_3), 1.62(2H, s, NH_2), 3.00(2H, d, J=10Hz, PCH_2), 3.97-4.25(4H, m, OCH_2)
7	2 (HCl salt)	57.1	117-9	3000, 1280, 1220, 1060, 1020, 980	(D ₂ O) 1.35(6H, t, J=7Hz, CH_3), 2.12-2.48(2H, m, PCH_2), 3.10-3.40(2H, m, CH_2N), 4.01-4.30(4H, m, OCH_2)
	3	100		3300, 3000, 1650, 1575, 1470, 1445, 1390, 1220, 1040, 960, 760	1.30(6H, t, J=7Hz, CH_3), 1.50-1.95(4H, m, $\text{P}(\text{CH}_2)_2$), 2.78(2H, t, J=7 Hz, CH_2N), 3.60(2H, s, NH_2), 3.90-4.20(4H, m, OCH_2)
$(\text{EtO})_2\overset{\text{O}}{\parallel}\text{P}(\text{CH}_2)_n\text{NHCOCH}_3$	1	63.9		(neat) 3300, 3000, 1660, 1550, 1370, 1310, 1220, 1020, 970, 830	1.37(6H, t, J=7Hz, CH_2CH_3), 2.05(3H, d, J=1Hz, COCH_3), 3.70(2H, dd, J=5 & 12Hz, PCH_2), 3.98-4.28(4H, m, OCH_2), 6.65-6.74(1H, m, NH)
8	3	24.7		(neat) 3450, 3000, 1700, 1375, 1250, 1175, 1030, 970	1.33(6H, t, J=7Hz, CH_2CH_3), 1.50-2.05(4H, m, $\text{P}(\text{CH}_2)_2$), 2.45(3H, s, COCH_3), 3.84-4.24(6H, m, OCH_2 , CH_2N)
$(\text{EtO})_2\overset{\text{O}}{\parallel}\text{P}(\text{CH}_2)_n\text{NHCOPh}$	1	40.0		(neat) 3260, 3000, 1650, 1600, 1580, 1540, 1490, 1390, 1315, 1215, 1020, 970, 700	1.36(6H, t, J=7Hz, CH_3), 3.90(2H, dd, J=8 & 12Hz, PCH_2), 3.98-4.30(4H, m, OCH_2), 6.80-6.92(1H, m, NH), 7.30-7.84(5H, m, Ar)
9	2	67.2		(neat) 3300, 2980, 1640, 1540, 1390, 1230, 1030, 960,	1.34(6H, t, J=7Hz, CH_3), 1.94-2.24(2H, m, PCH_2), 3.56-4.30(6H, m, CH_2N , OCH_2), 7.24-7.84(6H, m, NH , Ar)
	3	39.1		(neat) 3300, 3000, 1645, 1550, 1315, 1220, 1030, 970, 705	1.32(6H, t, J=7Hz, CH_3), 1.50-2.05(4H, m, $\text{P}(\text{CH}_2)_2$), 3.55(2H, q, J=7Hz, CH_2NH), 3.92-4.20(4H, m, OCH_2), 7.20-7.40(5H, m, Ar)

Diethyl aminoethylphosphonate hydrochloride was also treated in the same way except for using the twice amounts of triethylamine. The physicochemical properties of the acylated products are shown in Table 2.

Diethyl 2-dialkylaminoethylphosphonates

These were prepared from diethyl 2-bromoethylphosphonate and dialkylamines according to Kozolapoff (1948).

Diethyl 2-dimethylaminoethylphosphonate

Yield 46.9%. IR (neat) cm^{-1} : 2980, 1225, 1025, 980, 960. NMR (CDCl_3) ppm: 1.30 (6H, t, $J=7$ Hz), 1.72-2.08 (2H, m), 2.20 (6H, s), 3.90-4.20 (4H, m).

Diethyl 2-diethylaminoethylphosphonate

Yield 72%, IR (neat) cm^{-1} : 2980, 1380, 1240, 1030, 960, 790, 740. NMR (CDCl_3) ppm: 1.05 (6H, t, $J=7$ Hz), 1.34 (6H, t, $J=8$ Hz), 1.74-2.10 (2H, m), 2.54 (4H, q, $J=7$ Hz), 2.70-2.94 (2H, m), 3.90-4.20 (4H, m).

Tetraethyl acetamido(2-phosphonoethyl)malonate (10)

To a suspension of 62.5% sodium hydride (25 mmole) in DMSO (10 ml) was added a solution of diethyl acetamidomalonate (25 mmole) in DMSO (20 ml) with stirring at room temperature. After cessation of hydrogen gas evolution, diethyl 2-bromoethylphosphonate (25 mmole) was added to the reaction mixture. The mixture was stirred at room temperature for 4 hr, followed at 120°C for 3 hr. To the cooled mixture were added ethyl acetate (800 ml) and water (100 ml). The organic layer was separated and worked up in a usual manner. The concentrated residue was chromatographed on silica gel by elution with ethyl acetate. Yield 44.3%, IR (neat) cm^{-1} : 3220, 2960, 1740, 1670, 1505, 1365, 1220, 1020, 960, 790. NMR (CDCl_3) ppm: 1.26 (6H, t, $J=7$ Hz), 1.31 (6H, t, $J=7$ Hz), 1.40-1.80 (2H, m), 2.03 (3H, s), 2.45-2.70 (2H, m), 3.92-4.36 (8H, m), 6.77 (1H, s).

2-Amino-4-phosphonobutyric acid (11)

A solution of tetraethylacetamido(2-phosphonoethyl) malonate (9.4 mmole) in 6N hydrochloric acid (50 ml) was refluxed for 20 hr. The solvent was removed under reduced pressure and the residue was dissolved in ethanol (20 ml). 1, 2-butylene oxide was added dropwise until no more precipitate was formed. The precipitate was filtered and dried *in vacuo*. Yield 40.5%, mp $225-226^\circ\text{C}$. IR (KBr) cm^{-1} : 3360, 2850, 1710, 1615, 1535, 1255, 1187, 1105, 1045, 930, 800, 730, 545. Anal. Calcd. for $\text{C}_4\text{H}_{10}\text{NO}_5\text{P}$: C, 26.23; H, 5.52; N, 7.65. Found C, 26.14; H 5.50; N, 7.65%.

2-Amino-3-phosphonopropionic acid (13)

A mixture of 2-acetamidoacrylic acid (10 mmole), trimethyl phosphite (20 mmole) and dimethyl phosphite (20mmole) was heated at 110°C for 2 hr and then kept at room temperature for 48 hr. After the volatile materials were removed under reduced pressure, the residue was refluxed with conc. HCl (20 ml) for 48 hr. The solvent was removed under reduced pressure and ethanol (30ml) was added to the residue. Insoluble tarry substance was removed by filtration and 1, 2-butylene oxide was added dropwise to the filtrate until no more precipitate was separated. The precipitate was recrystallized from water and dioxane, yield 12.9%, mp 225°C . IR (KBr) cm^{-1} : 3400, 2930, 1740, 1520,

1230, 1140, 1060, 915, 710, 560. Anal. Calcd. for $C_3H_8NO_5P$: C, 21.37; H, 4.77; N, 8.28. Found C, 21.31; H, 4.92; N, 8.17%.

Ethyl 2-amino-3-(dimethoxyphosphinyl)propionate (15)

A mixture of ethyl dimethoxyphosphinylpyruvate (13.4 mmole), ammonium acetate (134 mmole), sodium cyanoborohydride (11.1 mmole), molecular sieve 4A (1.5 g) and ethanol (75 ml) was stirred at room temperature for 48 hr. After filtered, the reaction mixture was acidified to pH 2 by HCl and concentrated under reduced pressure. The residue was dissolved in water (20 ml). The aqueous solution was washed with ether, alkalized to pH 12 by KOH, saturated with NaCl, and extracted with dichloromethane. The desired ester was obtained by concentrating the extract. Yield 33. 2%. IR (neat) cm^{-1} ; 3350, 2960, 1740, 1460, 1240, 860. NMR ($CDCl_3$) ppm; 1.30 (3H, t, $J=7$ Hz), 1.95-2.58 (4H, m), 3.78 (6H, d, $J=10$ Hz), 4.08-4.65 (3H, m).

Bioassays

Insecticidal activity

Housefly female adults of WHO susceptible strain were treated topically with the acetone solution of a test chemical and kept at 25°C. Mortality was counted after 24 hr.

Inhibition of adult emergence

Six-day old larvae of housefly were treated topically with a test chemical dissolved in acetone and kept at 27°C in a Petri dish without feed. The number of adults emerged was counted after 9 days.

Inhibition, of plant growth

One ml of the aqueous or acetone solution of a test chemical was poured onto a sheet of filter paper placed on the bottom of a Petri dish (87 mm). After spontaneous evaporation of acetone, 10 ml of distilled water was poured into the dish. When the aqueous test solution was used, 9 ml of water was added. Twenty seeds were placed on the filter paper and placed at 30°C under light. The length of main roots and a stem were measured after 6 days.

Second screening test

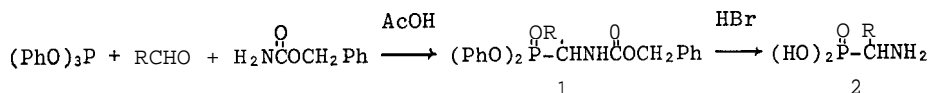
Seeds or tubers of *Echinochloa oryzicola* Vasing, *Cyperus difformis* L., *Scirpus juncoides* Roxb., *Sagittaria pygmaea* Miq. and broad leaf weeds including *Rotala indica* Koehne var. *uliginosa*, *Lindernia pyxidaria* L., and *Monochoria vaginalis* Presl var. *plantaginea* were planted on flooded soil (400g) in a plastic pot (21 × 15×5 cm). Test chemicals (23 mg) were formulated to the wettable powders and applied to the pot at the 1.5 leaf stage of *Echinochloa oryzicola*. The plants were kept for 3 weeks in a glass room the temperature of which was control at 25°C and 21°C in daytime and night, respectively.

RESULTS AND DISCUSSION

Syntheses of aminoalkylphosphonates

α -Aminoalkylphosphonic acids (2) and some their derivatives were obtained through diphenyl 1-(N-benzoyloxycarbonyl) aminoalkylphosphonates (**1**) by refluxing with conc.HBr. The intermediates 1 were derived from appropriate aldehydes by a Mannich type reaction with benzyl carbamate and triphenyl phosphite as

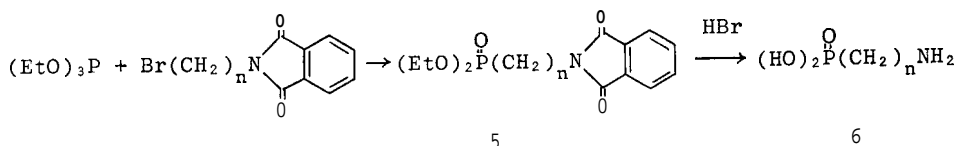
shown in Scheme 1 (Oleksyszyn *et al.*, 1979). Under a mild condition for the hydrolysis, only the benzyloxycarbonyl group of 1 could be removed to get diphenyl α -aminoalkyl phosphonates (3). The N-acetyl derivatives and the ethyl esters were also prepared from the intermediates.



Scheme 1. Synthesis of phosphonate analogs of α -amino acids

Table 1 shows some physicochemical properties of the products and the intermediates.

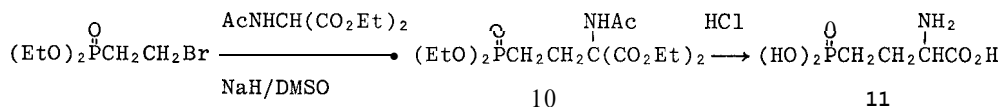
Although *o*-(N, N-dialkylamino)alkylphosphonates were readily synthesized by the reaction of dialkylamines with *w*-bromoalkylphosphonates, ω -aminoalkylphosphonic acids (6) were prepared by hydrolyzing the corresponding diethyl phthalimidoalkylphosphonates (5) with conc. HBr (Scheme 2). The intermediates were smoothly synthesized by the Michaelis-Arbuzov reaction of triethyl phosphite with N-*w*-bromoalkylphthalimides as shown in Scheme 2 (Yamauchi *et al.*, 1972). On the other hand, such a reverse process as to make potassium phthalimide react with 2-bromoethylphosphonate did not give the desired phthalimidoalkylphosphonate, but vinylphosphonate by occurring of hydrogen bromide elimination.



Scheme 2. Synthesis of phosphonate analogs of ω -amino acids

Hydrazine was used to remove the N-protective phthaloyl group without disruption of the phosphonate ester linkages, giving diethyl ω -aminoalkylphosphonates (7). The aminoalkylphosphonates were further converted into amides (8, 9) by treating with acetic anhydride or benzoyl chloride. Some physicochemical properties of the products as well as the intermediates are listed in Table 2.

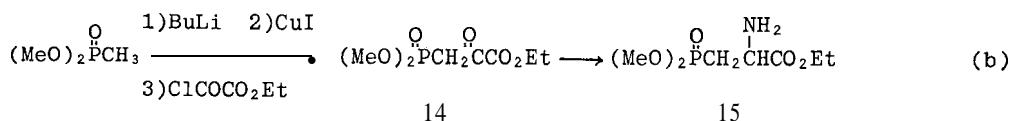
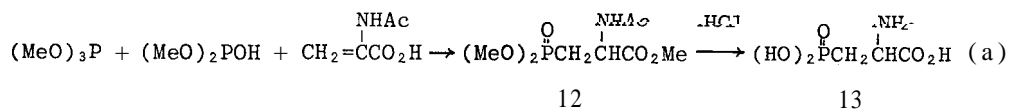
The mono-phosphonate analogs of aminodicarboxylic acids such as glutamic acid and aspartic acid were synthesized by modifying the method of Chambers and Isbell (1964). Thus, 2-amino-4-phosphonobutyric acid (**11**) was prepared by the hydrolysis and decarboxylation of tetraethyl acetamido (2-diethoxyphosphinylethyl)malonate (10) as shown in Scheme 3. The latter was obtained in a considerable yield (44%) by the reaction of diethyl 2-bromoethylphosphonate with diethyl acetamidomalonnate in the presence of sodium hydride in dimethyl sulfoxide. In dimethylformamide, however, no desired product was obtained. When sodium ethoxide was used instead of the hydride, the reaction gave only a poor yield, if at all, in ethanol or in diethyl carbonate.



Scheme 3. Synthesis of 2-amino-4-phosphonobutyric acid

All other attempts to synthesize the phosphonate analog of glutamic acid were unsuccessful. In applying the alkylideneglycine procedure for amino acid synthesis (Hoppe, 1975), the alkylation product of benzylideneglycine ester with diethyl 2-bromoethylphosphonate was too unstable to purify with a silica gel column. Addition of dimethyl methylphosphonate to ethyl 2-acetamidoacrylate in the presence of butyllithium was unsuccessful to get ethyl 2-acetamido-4-(bismethoxyphosphinyl)butyrate, an intermediate for the glutamate phosphorus analog synthesis.

On the other hand, trimethyl phosphite and dimethyl phosphite added to acetamidoacrylic acid to give trimethyl 2-acetamido-3-phosphonopropionate (12), which was then converted to the phosphonate analog of aspartic acid (13) as shown in Scheme 4a (Chambers and Isbell, 1964). The phosphonate analog (15) was synthesized in a higher yield from dimethyl methylphosphonate via phosphonopyruvate (14) according to Varlete *et al.* (1976) (Scheme 4b).



Scheme 4. Syntheses of 2-amino-3-phosphonopropionate

Pesticidal activities

Table 3 shows the herbicidal activity of n-amino acid phosphonate analogs. The analogs of aspartic acid, glutamic acid, glycine and phenylglycine showed relatively high inhibitory activity against the root growth of barnyardgrass (*Echinochloa oryzicola*). The phosphonate analogs of glycine and phenylglycine were non-selective against both rice and the grass or more toxic to rice rather than barnyardgrass, particularly in the free forms.

Table 4 shows the activity of o-aminoalkylphosphonic acids and their amide and ester derivatives. Except the phthalimide derivatives, 2-aminoethylphosphonate is most active in this series.

Second screenings carried out at the Institute of Physical and Chemical Research indicated that 2-aminoethylphosphonic acid and then 2-amino-4-phosphonobutyric acid were considerably active as herbicides against some lowland

Table 3. Plant growth inhibition by phosphonate analogs of α -amino acids.

Structure		Conc. ppm	Rice		Barnyardgrass	
R ¹	R ²		Root	Stem	-Root	Stem
$\begin{array}{c} \text{O} \\ \parallel \\ \text{R}^1\text{NCH}_2\text{P}(\text{OR}^2)_2 \end{array}$						
H ₂	H	500	+++	++	++	t t
		100	++	++	+	—
BrH ₃	Ph	500	++	—	+++	+
CH ₃ COH	Et	500	—	—	—	—
PhCOH	Et	500	—	—	+	—
Ph(CO) ₂	Et	500	++	++	++	•k
		100	—	—	++	—
PhCH ₂ OCOH	Ph	500	—	—	—	—
$\begin{array}{c} \text{O} \\ \parallel \\ \text{R}^1\text{NCHP}(\text{OR}^2)_2 \\ \\ \text{CH}_3 \end{array}$						
H ₂	H	500	++	+	++	+
BrH ₃	Ph	500	++	+	+	—
PhCH ₂ OCOH	Ph	500	—	—	+	—
$\begin{array}{c} \text{O} \\ \parallel \\ \text{R}^1\text{NCHP}(\text{OR}^2)_2 \\ \\ \text{Ph} \end{array}$						
H ₂	H	500	+++	++	+++	++
BrH ₃	Ph	500	+++	—	++	+
PhCH ₂ OCOH	Et	500	—	—	+	—
PhCH ₂ OCOH	Ph	500	—	—	—	—
$\begin{array}{c} \text{O} \quad \text{O} \\ \parallel \quad \parallel \\ \text{HOCCHCH}_2\text{P}(\text{OH})_2 \\ \\ \text{NH}_2 \end{array}$		500	++	+	+++	t t
		100	++	—	++	—
$\begin{array}{c} \text{O} \quad \text{O} \\ \parallel \quad \parallel \\ \text{HOCCHCH}_2\text{CH}_2\text{P}(\text{OH})_2 \\ \\ \text{NH}_2 \end{array}$		500	++	+	+++	++
		100	+	—	+	—

*Inhibition % : >80 +++ ; 80-50 tt ; 50-20 + ; 20> —

Table 4. Plant growth inhibition by phosphonate analogs of w-amino acids.

$\text{R}^1\text{N}(\text{CH}_2)_n\overset{\text{O}}{\parallel}\text{P}(\text{OR}^2)_2$			Conc. ppm	Rice		Barnyardgrass	
n	R ¹	R ²		Root	Stem	Root	Stem
2	HP	H	500	++	—	++	—
			100	—	—	+	—
2	PhCOH	Et	500	+	—	++	++
2	Ph(CO) ₂	Et	500	+	—	+	—
			100	—	—	+	—
3	HZ	H	500	+	—	+	—
			100	+	—	—	—
3	CH ₃ COH	Et	500	+	—	+	—
3	PhCOH	Et	500	+	—	+	—
3	Ph(CO) ₂	Et	500	+	—	ttt	+
			100	—	—	—	—
4	H ₂	H	500	—	—	—	+
4	Ph(CO) ₂	Et	500	+	+	t t	+
			100	—	—	+	—

For the marks of plant growth inhibition, see Table 3.

grasses (Table 5). It is interesting to note that they are the phosphorus analogs of β -alanine and glutamic acid, respectively. β -Alanine is one of the components of pantothenic acid and consequently co-enzyme A. The herbicide dalapon (2, 2-dichloropropionic acid) interferes the metabolism of pantothenic acid (Hilton *et al.*, 1963). As mentioned above, the herbicide phosphinothricin is the phosphinate analog of glutamic acid and is believed to kill grasses by inhibiting glutamine synthetase.

Table 5. Herbicidal activities of some aminoalkylphosphonic acids against lowland weeds.

Weed species	$(\text{HO})_2\overset{\text{O}}{\parallel}\text{PCH}_2\text{NH}_2$	$(\text{HO})_2\overset{\text{O}}{\parallel}\text{PCH}_2\text{CH}_2\text{NH}_2$	$(\text{HO})_2\overset{\text{O}}{\parallel}\text{PCH}_2\text{CH}_2\overset{\text{NH}_2}{\underset{ }{\text{CH}}}\text{CO}_2\text{H}$
<i>Cyperus difformis</i>	B	A	A
<i>Echinochloa oryzicola</i>	C	B	C
<i>Lindernia pyxidaria</i>	B	A	A
<i>Monochoria vaginalis</i>	B	A	A
<i>Rotala indica</i>	B	B	B
<i>Sagittaria pygmaea</i>	C	B	B
<i>Scirpus juncooides</i>	B	A	A

Herbicidal activity : A good; B moderate ; C no

No aminoalkylphosphonates tested were found to be effective against houseflies except for a weak inhibition of adult housefly emergence with diethyl acetamido(2-bisethoxyphosphinyloethyl)malonate (**10**) at 100 $\mu\text{g}/\text{fly}$.

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