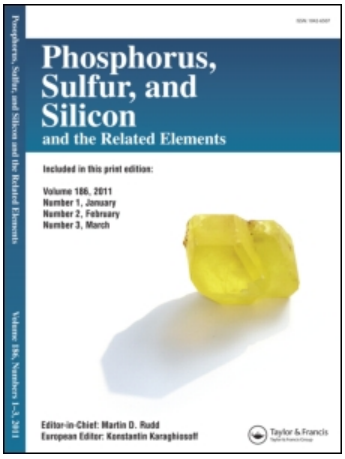

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Synthesis and Antitumor Activity of Novel α-Substituted Aminomethylphosphonates

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SYNTHESIS AND ANTITUMOR ACTIVITY OF NOVEL α-SUBSTITUTED AMINOMETHYLPHOSPHONATES

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Two series of novel α-substituted aminomethyl phosphonates (**1**) and (**2**) have been synthesized and the reaction conditions are discussed. All the products have been confirmed by ^{1}H NMR, IR spectra and elemental analysis, and x-ray diffraction. The bioassay showed that some of the compounds inhibit the growth of the leukemia L_{1210} cell in vitro.

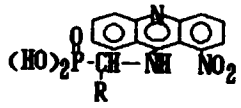
Key words: Aminomethylphosphonate; synthesis; antitumor activity; X-ray diffraction.

INTRODUCTION

α-Aminoalkylphosphonic acids and their derivatives appear to be very important because of their potential biological activities. Some were useful as inhibitors of enzymes[1,2] and some were effective plant growth regulators.[3,4] However, there have been few reports about their antitumor activity except for compounds (**A**) and (**B**).[5]

R: alkyl

(A)



R: Et, ect.

(B)

In this paper, two novel series of α-substituted aminomethylphosphonates (**1**) and (**2**) are reported. Preliminary bioassays indicated that some of them have anticancer activities.

RESULTS AND DISCUSSION

1. *Syntheses of α-Aminophosphonates*

The sterically hindered amino methylphosphonates were synthesized by the route shown in Scheme I.

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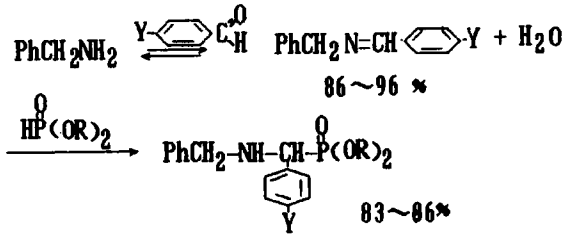

1: Y = OMe

2: Y = Cl

a b c d e f g h

R = Me, Et, Pr^n, Pr^i, Bu^n, Bu^i, Bu^{sec}, Pentyl

SCHEME I

Since the reaction of the aliphatic amines with an aldehyde forming imine is reversible, the yields are comparatively low (60–70%). It is probably due to the incomplete removal of water from the reaction system. In order to increase the yield, water was thoroughly removed under reduced pressure, resulting in yields of 86–94%.

The addition of dialkylphosphites to imines was affected remarkably by electronic and steric effects of the R groups in the phosphites as well as the substituent, Y (see Table I).

Data in Table I indicates that the reaction temperatures were raised and the reaction time prolonged when there were large alkyl groups of dialkylphosphites and strong electron-attracting substituents Y of imine. The products were proven to be a racemic mixture by determining the optical activity ($[\alpha]_D^{25} = 0$).

For the purpose of studying the mechanism of the reaction, hydrochloric acid was used as a catalyst, and the reaction time could be reduced to about $\frac{1}{3}$. This indicated the reaction was accelerated by acids. In addition, when solvent was added to the reaction system, at the same temperature, the addition was greatly slowed. Therefore, the reaction catalyzed by acids goes through a carbonium ion mechanism, resulting in the racemic products.

TABLE I

Data of the addition reaction

Temperature (℃) / Time (h.)	R=Me	Et	Pr^n	Pr^i	Bu^n	Bu^i	Bu^{sec}	Am
Y = OMe	25 / 0.5	50 / 1	60 / 1.5	60 / 3	80 / 3	80 / 3.5	80 / 4.0	80 / 5.5
Y = Cl	30 / 0.75	60 / 1.5	60 / 3	60 / 5	80 / 5	80 / 5.5	80 / 6	80 / 8

2. *The Structure of the Products*

The molecular structures of all new compounds obtained were confirmed by ^1H NMR, IR spectra and MS, elemental analyses. All results have been listed in Table II.

TABLE II

Data of compounds **1** and **2**

No	R	State (m.p. ℃)	^{1}HNMR (ppm)	IR (cm^{-1})	Elemental analysis (%)		
					C	H	N
1a	Me	solid (57~58)	2.5(sb,H,NH), 3.5 ~3.9 (m,12H,3OMe ,NCH_2,PCH),6.85 (d,2H), 7.2~7.4 (m,7H)	3310(m,NH),3040,29 88,1604,1478,1380, 1244,(s,P=O),1118, 1020,980	60.93 (60.89)	6.95 (6.81)	4.08 (4.17)
1b	Et	viscus liquid	1.05(t,3H,CH_3), 1.25 (t, 3H, CH_3 $^3J_{HCCH}$=7.1Hz), 2.15(sb,1H,NH) ,3.7 (q, 2H, NCH_2), 3.7(s,3H,OCH_3) ,3.95 (d,1H, PCH,$^2J_{PCH}$=19.5Hz), 3.8~4.1(m,4H,2OC H_2), 6.85 (d,2H) 7.24~7.35(m,7H)	3306(m), 3050, 2943(s),1639,1508 (m),1426,1382,1244 (s,P=O),1169,1021, 979	63.06 (62.79)	6.98 (7.21)	3.59 (3.85)
1c	Pr^n	solid (41~42)	0.7~1.0(q,8H,2CH_3),1.3~1.8(dm, ,4H,2CH_2), 2.0 (sb,1H,NH), 3.8(s, 3H,OCH_3),3.4~4.1 (m,7H,2OCH_2,NCH_2, PCH), 6.85 (d,2H),7.2~7.4(m,7H)	3382, 3040, 2980, 2877, 1604, 1508, 1426, 1382, 1242(s,P=O), 1170, 1118 1050, 89	64.58 (64.43)	7.94 (7.73)	3.67 (3.58)
1d	Pr^i	solid (44~45)	0.95 (d,3H,CH_3) ,1.25 (d,3H,CH_3), 2.05 (d, 6H, 2CH_3),2.45 (sb, 1H,NH), 3.6 (q, 2H,NCH_2),3.75(s,3 H,OCH_3), 3.82 (d,1H,PCH,$^2J_{PCH}$= 18.9Hz),4.2~4.8(m, 2H,2OCH), 6.75 (d, 2H),7.1~7.3 (m,7H)	3385, 3048,2924, 1605, 1507,1380, 1238(s,P=O),1198, 1133, 987	64.60 (64.43)	8.04 (7.73)	3.89 (3.58)
1e	Bu^n	viscus liquid	1.0 (t,6H,2CH_3),1.2~1.8(m,8H,2 CH_2CH_2),3.8(s,3H, OCH_3),3.4~4.2(m, 8H,2OCH_2,NCH_2,PCH, NH), 6.9 (d, 2H) ,7.2~7.4(m,7H)	3368,3049,2983, 1603,1510,1429, 1381,1234(s,P=O), 1157,1042,984	65.61 (65.85)	7.78 (8.16)	3.30 (3.33)

TABLE II (*continued*)

No	R	State (m.p. ℃)	^{1}HNMR (ppm)	IR (cm^{-1})	Elemental analysis (%)		
					C	H	N
1f	Bu^t	solid (53~54)	0.77 (d, 6H, 2 CH_3), 0.88 (d, 6H, $2CH_3$), 1.6~2.4 (m, 2H, 2CH), 3.4~3 .8(m, 8H, $2OCH_3$, NCH_2), 3.76(s, 3H, OCH_3), 3.95 (d, 1H, PCH, $^2J_{PCH}$=19.7Hz)	3386, 3055, 2950, 1804, 1507, 1458, 1381, 1240(s, P=O), 1176, 1023, 998	65.72 (65.85)	8.01 (8.18)	3.16 (3.33)
1g	Bu^{sec}	viscus liquid	0.7~1.1(m, 6H, $2CH_3$) ,1.3 (q, 6H, $2CH_3$) ,1.5~1.9(m, 4H, $2CH_2$) , 2.35 (sb, 1H, NH), 3.4~3.9(q, 2H, NCH_2), 3.8 (s, 3H, OCH_3), 3.95(d, 1H, PCH, $^2J_{PCH}$ =19Hz), 4.2~4.7(m, 2H 2OCH), 6.85 (d, 2H), 7.0~7.2(m, 7H)	3270, 3013, 2987, 2887, 1603, 1503 1446, 1373, 1232(s, P=O), 1169, 1118, 1020, 961	65.68 (65.85)	7.80 (8.18)	3.15 (3.33)
1h	Pen-tyl	viscus liquid	0.7~1.0(m, 6H, $2CH_3$), 1.1~1.8(m, 12H, $2CH_2$ CH_2CH_2), 2.35 (sb, 1H, NH), 3.5~4.2(m, 7H, $2OCH_2$, NCH_2, PCH), 3.8 (s, 3H, OCH_3), 6.9 (d, 2H), 7.3~ 7.5(m, 7H)	3308, 3056, 2945, 1645, 1508, 1427, 1247(s, P=O), 1174, 1022, 980	66.99 (67.09)	8.66 (8.56)	3.07 (3.12)
2a	Me	solid (80~82)	2.4 (sb, 1H, NH), 3.55(d, 3H, OCH_3), 3.73 (d, 3H, OCH_3 , $^3J_{POCH}$=10.77Hz), 3.3.8 (q, 2H, NCH_2), 4.01 (d, 1H, PCH $^2J_{PCH}$=19.9Hz), 7.2~ 7.35(m, 7H)	3382, 3085, 2993, 2886, 1603, 1805, 1480, 1231(s, P=O), 1055, 1018, 909	56.49 (56.55)	5.47 (5.63)	4.08 (4.10)
2b	Et	viscus liquid	1.2 (t, 3H, CH_3), 1.25 (t, 3H, CH_3), 2.6(sb, 1H, NH), 3.43~4.24(m, 7H, 2OC H_2, NCH_2, PCH), 7.3~7.5(m, 9H)	3298(m, NH), 3071, 2967, 1590, 1484, 1456, 1403, 1230(s, P=O), 1080, 1056, 988	58.49 (58.76)	6.10 (6.30)	4.09 (3.81)
2c	Pr^n	viscus liquid	0.75~1.1(dm, 6H, $2CH_3$), 1.4~1.9(dm, 4H, $2CH_2$), 2.3 (sb, 1H, NH), 3.4~ 4.2(m, 7H, $2OCH_2$, NCH_2, PCH), 7.3~7.4(m, 9H)	3328(m, NH), 3073 2954, 1590, 1425, 1459, 1403, 1236(s, P=O), 1086(s), 1050 991	60.80 (60.67)	6.73 (6.87)	3.80 (3.54)
2d	Pr^i	viscus liquid	1.0~1.4(qd, 12H, $4CH_3$), 2.4 (sb, 1H, NH) 3.7 (q, 2H, NCH_2) 3.91 (d, 1H, PCH, $^2J_{PCH}$=18.9Hz), 4.42~	3370(m, NH), 3052, 2967, 1486, 1462, 1381, 1228(s, P=O), 1104, 985	60.47 (60.67)	6.85 (6.87)	3.10 (3.54)

TABLE II (*continued*)

No	R	State (m.p. ℃)	^{1}HNMR (ppm)	IR (cm^{-1})	Elemental analysis (%)		
					C	H	N
			4.9(m,2H,2OCH),7.3～7.4(d,9H)				
2e	Bu^n	viscus liquid	0.73 (t,3H,CH_3) 0.89 (t,3H,CH_3) 1.24～1.58(m,8H,2CH_2 CH_2), 3.85 (sb,1H, NH),3.52～4.03(m,7H, 2OCH_2,NCH_2,PCH), 7.2～7.3(m,9H)	3380(m,NH), 3118, 2976,1642,1481, 1420,1381,1246(s, P=O),1176,1087, 1023	62.38 (62.32)	7.61 (7.37)	3.10 (3.30)
2f	Bu^t	solid (66～67)	0.78 (d, 6H, 2CH_3),0.86 (d,6H,2 CH_3), 1.2～2.0(m,2H ,2CH), 2.4 (sb, 1H,1NH),3.51～3.77(m,6H,2OCH_2,NCH_2), 3.98 (d, 1H, PCH ,$^2J_{PCH}$=20.19Hz),7.2 ～7.3(m,9H)	3257(m,NH),3022, 2981, 2875, 1485, 1408, 1381, 1237(s,P=O), 1110, 1080 ,1048,1010	61.98 (62.32)	7.04 (7.37)	3.07 (3.30)
2g	Bu^{sec}	viscus liquid	0.78 (d, 6H, 2CH_3),0.87 (d,6H,2 CH_3),1.8～2.0(m,4H, 2CH_2), 2.3 (sb, 1H,NH), 3.36 (m,4H, 2OCH, NCH_2), 3.98 (d,1H, PCH, $^2J_{PCH}$=20.18Hz),7.20 ～7.32(m,9H)	3268(m,NH), 3086, 2986, 2870, 1486, 1423, 1380, 1231(s,P=O), 1110, 1042, 1003	62.48 (62.32)	7.28 (7.37)	3.42 (3.30)
2h	Pen-tyl	viscus liquid	0.75～1.04(m,6H,2CH_3), 1.1～1.9(m,12H,2 $CH_2CH_2CH_2$), 2.3 (sb, 1H, NH), 3.4 ～4.22(m,7H,2OCH_2, NCH_2,PCH), 7.25～ 7.42(d,9H)	3181(m,NH), 3010, 2974, 2839, 1683, 1483, 1421, 1385, 1246(s,P=O),1176, 1087, 1023	63.38 (63.77)	7.46 (7.80)	3.12 (3.09)

For ^{1}H NMR spectra, whether Y groups were OMe or Cl, the hydrogens of the two OR attached to the P atom remained in different magnetic environments, giving different chemical shifts. If the Y group was Cl, the hydrogens of the phenyl group displayed one set of multiple peaks. Yet, if the Y group was OMe, the hydrogens of the phenyl group showed two sets of peaks.

The IR spectra of series 1 and 2 showed normal stretching absorption bands, indicating the existence of the =NH (~3300 cm^{-1}), Ph, —C—C— (~1600 cm^{-1}, 1500 cm^{-1}), P=O (~1180 cm^{-1}) and phosphonate diester groups (~1100, 1000 cm^{-1}).

The EI mass spectra of series 1 and 2 all displayed their molecular ion peaks. When Y was OMe or Cl, their m/e of basic peaks were 226 and 230, respectively, which are due to M^+-[P(O) $(OR)_2$]. All the other peaks did not exceed 50%.

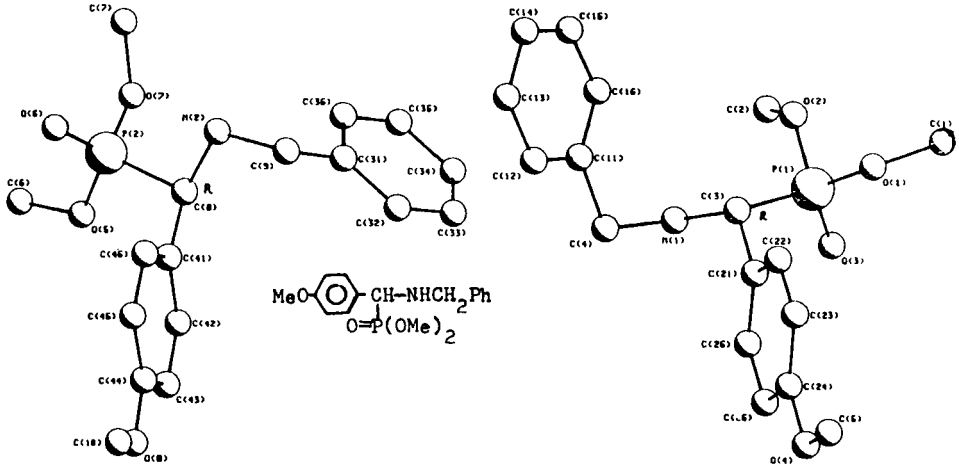

FIGURE 1

TABLE III

Selected bond distances (Å)

Molecule I			Molecule II		
P(1)	O(1)	1.556(7)	P(2)	O(5)	1.562(5)
P(1)	O(2)	1.561(5)	P(2)	O(6)	1.448(7)
P(1)	O(3)	1.442(6)	P(2)	O(7)	1.571(6)
P(1)	C(3)	1.829(9)	P(2)	C(8)	1.801(9)
O(1)	C(1)	1.46(2)	O(5)	C(6)	1.49(1)
O(2)	C(2)	1.44(1)	O(7)	C(7)	1.45(1)
O(4)	C(5)	1.47(2)	O(8)	C(10)	1.44(2)
O(4)	C(24)	1.374(9)	O(8)	C(44)	1.37(2)
N(1)	C(3)	1.48(1)	N(2)	C(8)	1.509(8)
N(1)	C(4)	1.47(2)	N(2)	C(9)	1.48(2)
C(3)	C(21)	1.51(2)	C(8)	C(41)	1.51(2)
C(4)	C(11)	1.52(1)	C(9)	C(31)	1.52(1)

TABLE IV

Selected bond angles (*)

Molecule I				Molecule II			
O(1)	P(1)	O(2)	101.5(4)	O(5)	P(2)	O(6)	116.4(3)
O(1)	P(1)	O(3)	116.2(4)	O(5)	P(2)	O(7)	102.2(3)
O(1)	P(1)	C(3)	102.0(4)	O(5)	P(2)	C(8)	101.0(3)
O(2)	P(1)	O(3)	114.9(4)	O(6)	P(2)	O(7)	113.6(4)
O(2)	P(1)	C(3)	105.9(4)	O(6)	P(2)	C(8)	115.3(5)
O(3)	P(1)	C(3)	114.8(3)	O(7)	P(2)	C(8)	106.7(4)
P(1)	O(1)	C(1)	119.3(6)	P(2)	O(5)	C(6)	118.3(5)
P(1)	O(2)	C(2)	122.3(6)	P(2)	O(7)	C(7)	122.1(7)
C(5)	O(4)	C(24)	117.5(7)	C(10)	O(8)	C(44)	118.7(7)
C(3)	N(1)	C(4)	111.9(7)	C(8)	N(2)	C(9)	112.3(6)
P(1)	C(3)	N(1)	103.7(6)	P(2)	C(8)	N(2)	103.5(5)
P(1)	C(3)	C(21)	111.7(6)	P(2)	C(8)	C(41)	112.5(5)
N(1)	C(3)	C(21)	116.4(5)	N(2)	C(8)	C(41)	115.2(7)
N(1)	C(4)	C(11)	111.6(5)	N(2)	C(9)	C(31)	111.8(7)

X-Ray diffraction analysis indicated that the single crystal of **1a** is triclinic, space group P1, cell parameter A = 10.866, B = 11.664, C = 14.034A, α = 88.39, β = 81.04, γ = 73.54°, v = 1687. 8A,[3] z = 4. In one symmetric unit, there are two molecules, and both of them have proven to have the R configuration (see Figure 1). The selected bond distances and angles are listed in Tables III and IV.

ANTITUMOR ACTIVITY

Preliminary tests indicated that some of compounds **1** and **2** are active against leukemia L_{1210} cells in vitro (see Table V). Other biological activities are currently being determined.

TABLE V
Data of antitumor activity

No	Cancer cell	Time (h)	IC_{50} (μmol/ml)
1a	L_{1210}	72	0.0045
1c	L_{1210}	72	0.0299
1d	L_{1210}	72	0.145
1f	L_{1210}	72	0.016
2a	L_{1210}	72	0.009
2c	L_{1210}	72	0.010
2e	L_{1210}	72	0.0082

EXPERIMENTAL

^{1}H NMR Spectra were recorded on a JEOL-FX-90Q and BRUKER AC-P200 spectrometer. The IR spectra were measured on a SHI-MADZU-435 instrument. Elemental analysis was performed with a CHN CORDERD MT-3 elementary analyzer. EI-MS spectra were recorded with a VG-7070E spectrometer. Melting points were determined using a Thomas-Hoover capillary melting point apparatus and are uncorrected. Column chromatography was carried out on silica gel H(10–40 μm Hal Yang Chemical Factory of Qingdao).

Y= OMe, m.p. 40-42℃; Y= Cl, m.p. 32-33℃.

Group (Y)	^{1}HNMR (ppm)	IR (cm^{-1})	ELEMENTAL ANALYSIS		
			C%	H%	N%
OMe	3.83(s,3H,OCH_3), 4.80(s,2H, NCH_2), 8.37(s,1H,N=CH),7.27(sb,5H,Ph), 6.8~7.8(dd,4H),	3010,2827 1590(s, N=C),1243	79.97 (79.87)	6.71 (6.70)	6.20 (6.21)
Cl	4.82(s,2H, CH_2), 8.34(s, 1H, N=CH), 7.28~7.70(m,9H)	3070,2838, 1653(s,N=C)1059(m,Cl -C), 1368	73.08 (73.19)	5.16 (5.26)	5.89 (6.09)

Benzylidene p-Substituted Aminobenzene. 0.1 mol of *p*-Substituted benzaldehyde, 80 ml of benzene and catalytic amount of *p*-toluenesulfonic acid were added into 250 ml of three necked flask with a water separater. A mixture of 0.1 mol of benzyl amine and 40 ml of benzene was added dropwise at room temperature with stirring. The reaction mixture was refluxed for 6–8 h, and the mixture of solvent and water was removed under reduced pressure giving a yellow oil after cooling and solidifying, the crude products were recrystallized from ether, petroleum ether (1:4), giving high yellow or colourless needle crystals, yield 86–94%.

N-Benzyl-α-(Substituted Phenyl) Aminomethylphosphonate. 8.9 mmol of imine and 0.5–1.5 mol of phosphite diester were added into a 25 ml reaction flask. The mixture was then heated at 25–80°C for 0.5–6 h. till the spot of the imine disappeared on silica gel TLC developed with the solvent, chloroform, petroleum ether (1:1). The phosphite diester was removed under vacuo and the crude products were recrystallized or purified by flash chromatography on silica gel column using chloroform, petroleum ether (1:2) as the eluent, yield of the product: 83–96%.

A Single crystal (**1a**) was cultured from chloroform, ether, petroleum ether (60–90°C) (1:2:2), and its molecular structure was determined by X-ray diffraction (see Figure 1).

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