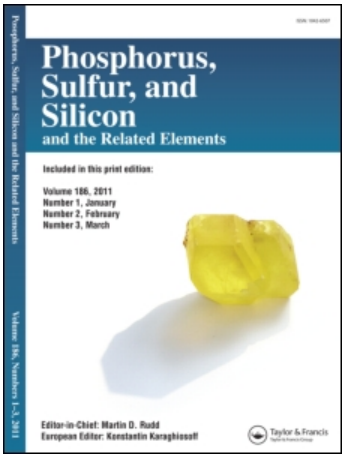

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THE SYNTHESIS OF. CYCLOPHOSPHONODIPEPTIDES

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THE SYNTHESIS OF CYCLOPHOSPHONODIPEPTIDES

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Dipeptides and cyclodipeptides containing aminoalkyl phosphonyl groups have been synthesized. The geometric isomers of some of them are separated and the molecular structures are confirmed by NMR, IR, MS or X-ray diffraction.

Key words: Cyclophosphonodipeptides; phosphonylrings; geometric isomers; X-ray structure, NMR

INTRODUCTION

Aminoalkylphosphonic acids discovered in a wide variety of living organisms[1] may be considered as phosphorus-containing analogues of amino acids. Peptides consisting of aminoalkylphosphonic acid are also found in nature. They exhibit certain biological activities, for example, antibacterial,[2] herbicidal,[3] and inhibitory activity to enzymes.[4] Artificial peptides containing aminoalkylphosphonic acid group at C-terminal show some important biological activities, for instance, L-alanyl-L-(1-aminoethyl) phosphonic acid (alafosfalin) and its di-to hexapeptides exhibit very strong antibacterial activity, especially against Gram-negative organisms.[5] Enkephalin analogue, a pentapeptide containing aminophosphonic acid at C-terminal, exhibit highly analgesic activity.[6] In addition, some synthetic peptide analogues containing aminophosphonic acid at C-terminal exhibit herbcidal activity and inhibitory activity to enzymes. Some phosphonopeptides containing the phosphonamide bond exhibit potent inhibitory activity to carboxypeptidase A[7] and angiotensin-converting enzymes.[8]

Unfortunately, the study of the synthesis and biological activities of phosphonopeptides containing P—N bonds is limited by the instability of the P—N bond in acidic aqueous media. There are only a few reports on phosphonopeptides containing P—N bonds in the literature so far, and no report of cyclopeptides containing aminoalkylphosphonyl groups. Since the P—N bond is less stable than the C—N bond in acidic solutions, hydrolysis of cyclodipeptides containing the P—N bond may give a product with a similar structure as alafosfalin. Therefore, we prepare cyclophosphonodipeptides **6** to see if they exhibit the same antibacterial activities as alafosfalin or some other biological activities.

In this paper, the synthesis of cyclodipeptides containing 1-aminoalkylphosphonic or phosphinic acid are described.

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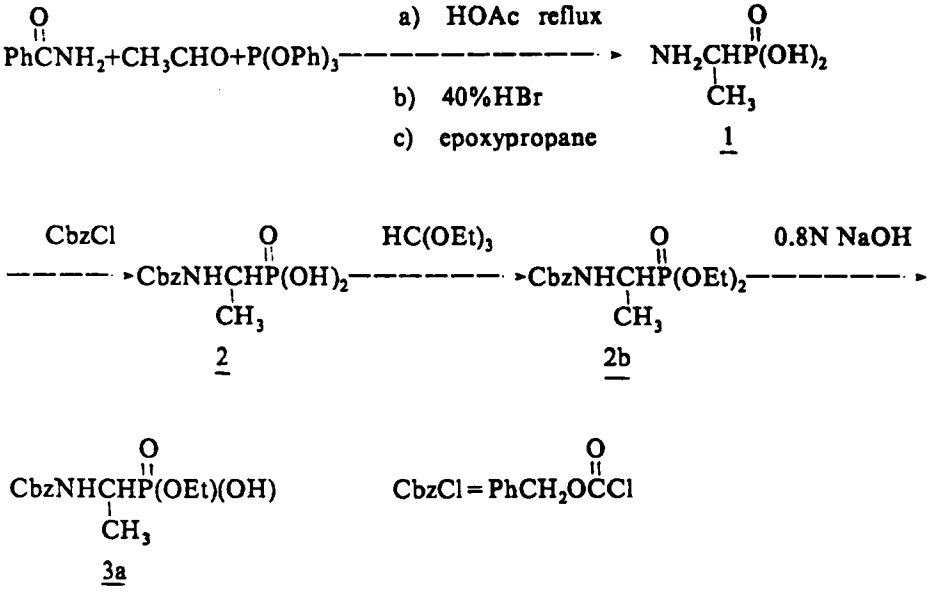
RESULTS AND DISCUSSION

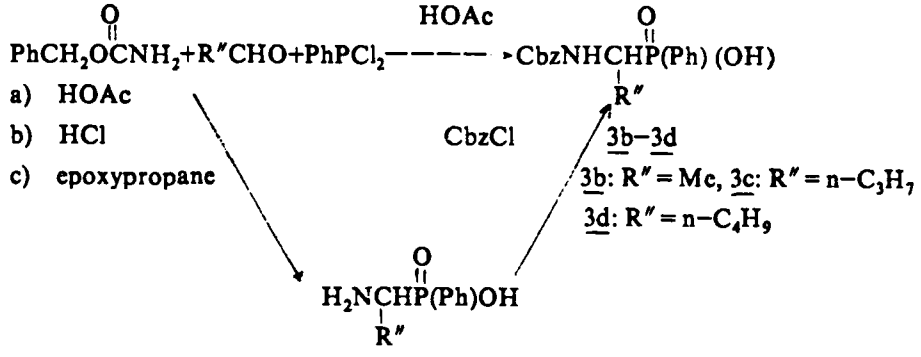
The amino group of aminoalkylphosphonic acids was as reactive to various reagents as that of amino acids. However, it was found that the phosphonic acid radical of the former differed in reactivity from the carboxylic acid radical of the latter. The phosphonopeptides containing the P—N bond could not be formed by the usual methods used in the synthesis of peptides. The N-protected aminoalkylphosphonic acids did not condense with amino acid esters by means of dicyclohexylcarbodiimide (DCC).[9] Thus, the main problem in the synthesis of a peptide containing the P—N bond was how to form the P—N bond from aminoalkylphosphonic acid and amino acid efficiently.

Since the P—N bond of the phosphonopeptide was easily hydrolyzed under acidic conditions, reactions of peptide intermediates having a P—N bond had to be performed under neutral or alkaline conditions. This fact limited the choice of protection group for aminophosphonic acid. In the present study, the amino group of aminophosphonic acid was blocked by carbobenzyloxylation, and the OH group of phosphonic acid was protected by esterification. 1-Aminoethylphosphonic acid **1** was prepared from triphenylphosphite, acetaldehyde and benzamide in a yield of 92%.[10] Compound **3a** was prepared by the esterification of **2** with triethylorthoformate followed by saponification with 0.8 N NaOH in an overall yield of 75% (Scheme I).[12] The condensation of **2** with alcohol in the presence of DCC and triethylamine in DMF gave a mixture which was very difficult to obtain pure **3a**. Compound **2** was treated with tetramethylammonium hydroxide and then reacted with methyl iodode to give **3a** in a yield of 23%.

According to the method reported in the literature, 1-aminoalkylphenylphos-



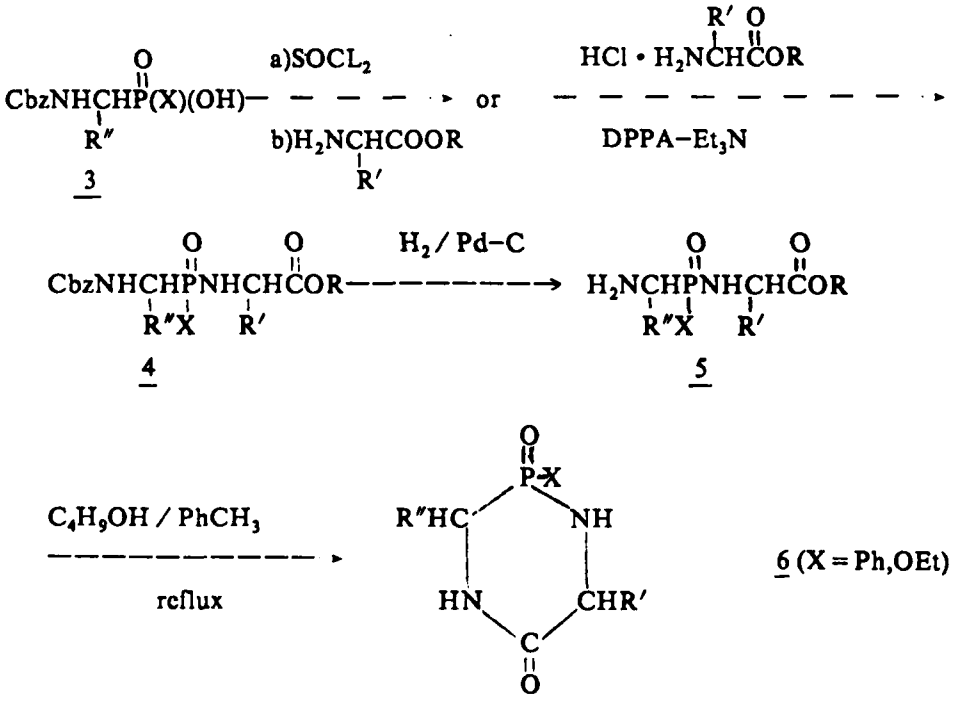
Scheme I



Scheme II

phinic acids[11] were prepared by the reaction of benzyl carbamate, aldehyde and phenyldichlorophosphine in glacial acetic acid, followed by reflux with 4 N HCl and then the treatment with epoxypropane in the yields of 40–50%. The amino group of these products was protected by carbobenzyloxylation to give **3b**, **3c** and **3d**. By the reaction with the same starting materials in glacial acetic acid and then treating the reaction mixture with a large amount of water at room temperature instead of reflux with 4 N HCl, the N-protected products **3b**, **3c** and **3d** were obtained directly in one step with the yields of 75–90% (Scheme II).

Phosphonodipeptides **4** were obtained by the reaction of **3** with $SOCl_2$ followed



Scheme III

TABLE I

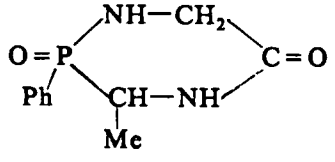
Physical data for compounds **4** and **6**

R″	R′	R	X	Yield (%)	MP (°C)	Formula	Elemental analysis (%) Found C	H	N	P	Calcd C	H	N
CH_3	CH_3	CH_3	OEt	87(A) 31(B)	88–90	$C_{16}H_{25}N_2O_6P$	51.99	6.87	7.47		51.61	6.77	7.52
CH_3	H	Et	OEt	73(B)	94–96	$C_{16}H_{25}N_2O_6P$	51.80	6.83	7.80		51.61	6.77	7.52
CH_3	H	Et	Ph	71(A) 37(B)	126–128	$C_{20}H_{25}N_2O_5P$	58.95	6.25	6.53	6.73	59.35	6.25	6.93
CH_3	CH_3	CH_3	Ph	62(A) 27(B)	145–150	$C_{20}H_{25}N_2O_5P$	59.20	6.49	7.61	7.86	59.35	6.25	6.93
CH_3	CH_2Ph	CH_3	Ph	65(A)	124–140	$C_{26}H_{29}N_2O_5P$	65.17	5.99	6.32		65.00	6.08	5.83
n-C_3H_7	H	Et	Ph	63(A)	134–137	$C_{22}H_{29}N_2O_5P$	61.18	6.18	6.22		61.10	6.78	6.48
n-C_4H_9	H	Et	Ph	49(A)	137–139	$C_{23}H_{31}N_2O_5P$	62.25	6.82	6.27		61.87	6.98	6.27
n-C_4H_9	CH_3	CH_3	Ph	34(A)	106–108	$C_{23}H_{31}N_2O_5P$	61.98	7.05	6.00		61.88	6.98	6.27
n-C_3H_7	CH_3	CH_3	Ph	60(A)	114–116	$C_{22}H_{29}N_2O_5P$							
CH_3	H	CH_3	Ph	64(A)	128–130	$C_{19}H_{23}N_2O_5P$	58.16	6.08	6.90		58.46	5.95	7.16
CH_3	H	Et	CH_3	63(A)	113–114	$C_{15}H_{23}N_2O_5P$	52.11	7.03	8.16	8.54	52.63	6.77	8.16
CH_3	H	Et	OMe	36(B)	87–89								
CH_3	$PhCH_2$	CH_3	OEt	67(A)	116–122	$C_{22}H_{29}N_2O_6P$	58.51	6.56	6.84	7.20	58.92	6.52	6.24
CH_3	CH_3		OEt	37	150–152	$C_7H_{15}N_2O_3P$	41.18	7.47	13.78		40.78	7.32	13.60
CH_3	H		OEt	32	126–130								
CH_3	H		Ph	61	234, dec.	$C_{10}H_{13}N_2O_3P$	53.65	5.87	12.03		53.55	5.84	12.50
CH_3	CH_3		Ph	70	250, dec.	$C_{11}H_{15}N_2O_3P$	55.50	6.35	11.79		55.46	6.35	11.76
Ch_3	CH_2Ph		Ph	40	222, dec.	$C_{17}H_{19}N_2O_3P$	64.99	6.13	9.03		64.96	6.03	8.91
n-C_3H_7	H		Ph	41.0	204, dec.								
n-C_4H_9	H		Ph	33	214, dec.								
n-C_4H_9	CH_3		Ph	48	211, dec.	$C_{14}H_{21}N_2O_3P$	59.95	7.53	9.61		59.99	7.55	9.99

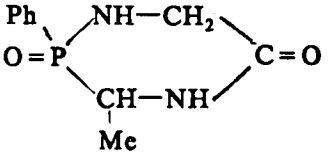
by coupling with the amino acid ester in good yield. The reaction was completed in only a few hours (Method A).[7] Phosphonodipeptides **4** could also be prepared by direct condensation of **3** with amino acid ester in the presence of 20% excess of diphenylphosphoryl azide (DPPA) and triethylamine at room temperature for three days (Method B). But Method B gave lower yields (see Table I).

Catalytic hydrogenation of **4** by using 5% palladium-active charcoal removed the carbobenzyloxy group and produced the corresponding dipeptide **5** quantitatively. Most of these dipeptides were cyclized directly by reflux in *n*-butanol/toluene (3:1) for 30–60 hours at room temperature to give cyclophosphonodipeptides **6** without further purification (Scheme III) (see Table I).

Cyclophosphonodipeptides **6** have two or three asymmetric atoms. Theoretically, **6c, 6f** and **6g** with two asymmetric atoms have two geometric isomers (*cis*- and *trans*-) respectively. For **6d, 6e** and **6h** with three asymmetric atoms, 4 geometric isomers might exist.



cis-6c



trans-6c

In fact the ^{31}P-NMR spectrum of **6c** showed only one signal at 31.36 ppm. Its ^{1}H-NMR, ^{13}C-NMR, and IR spectra indicated that **6c** had only one geometric isomer. The HPLC gave the peak of one component. The X-ray diffraction indicated that the isomer of **6c** had a *cis*-configuration (shown in Figure 1).

Compound **6c** and **6h** were separated into two components with different R_f values by TLC on silica gel. The ^{1}H-, ^{31}P-NMR, IR spectra and HPLC showed that each component contained only one isomer. X-ray diffraction exhibited that the two isomers of **6e** and **6h** had a boat conformation, and the phenyl group on the P atom and the alkyl group on the α-C atom were *cis* to each other. The molecular structures and the biological activities of cyclophosphonodipeptides **6** will be discussed in details in another paper.

EXPERIMENTAL

Amino acids were available commercially and used without purification. Benzyl carbamate[13] and phenyldichlorophosphine[14] were prepared as described. Chloroform was freed from ethanol by washing with concentrated H_2SO_4 and water, dried and distilled from P_2O_5.

1-Aminoethylphosphonic acid (**1**).[15] 1-Aminoethylphosphonic acid **1** was prepared by using triphenylphosphite (0.3 mol), acetaldehyde (0.32 mol) and benzamide (0.3 mol). Yield: 92%; mp: 276–277°C (lit. mp: 277–278°C).[15]

N-Carbobenzyloxy-1-aminoethylphosphonic Acid (**2**).[12] To a well stirred solution of 20 g (0.16 mol) of **1** in 100 ml of H_2O adjusted to Ph = 9–10 with 4 N NaOH was added 45 g (0.24 mol) of benzyl chloroformate at 0°C. Stirring was continued for 12 hr at 0°C and 8 hr at room temperature. The pH was maintained at 9–10 by the addition of 4 N NaOH during the reaction. The mixture was extracted

TABLE II

^{1}H-NMR, ^{31}P-NMR, IR of **4**

NO	R″	R′	R	X	^{1}H-NMR (ppm)	^{31}PNMR (ppm)	IR (cm^{-1})
4a	CH_3	Ch_3	CH_3	OEt	90MHz ($CDCl_3$) 1.4(*m*, 9H, CH_3), 3.64(*d*, 1.5H, OCH_3), 3.77(*d*, 1.5H, OCH_3), 3.90–4.3(*m*, 4H, CH, OCH_2), 5.1(*s*, 2H, $PhCH_2$), 7.3(*s*, 5H, C_6H_5).	29.88, 29.48 28.53, 28.13	1730, 1700 1210, 1030 1250, 1150
4b	CH_3	H	Et	OEt	90MHz ($CDCl_3$) 1.16–1.50(*m*, 6H, CH_3), 3.7(*m*, 2H, NCH_2), 3.9–4.3(*m*, 5H, OCH_2, NCH), 5.1(*s*, 2H, $PhCH_2$), 7.3(*s*, 5H).	30.55, 22.61	1710, 1690 1210, 1020
4c	CH_3	H	Et	Ph	90Mhz ($CDCl_3$) 1.16–1.48(*m*, 6H, CH_3), 3.6(*m*, 2H, NCH_2), 4.0–4.2(*q*, 3H, OCH_2, NCH), 4.96(*s*, 1H, NH), 5.05(*s*, 2H, OCH_2), 7.28–7.90(*m*, 10H, Ph).	34.86	1735, 1695 1290, 1260 1190, 1115
4d	CH_3	CH_3	CH_3	Ph	90MHz ($CDCl_3$) 1.18–1.50(*q*,*q*, 6H, CH_3), 3.60(*s*, 1.5H, OCH_3), 3.70(*s*, 1.5H, OCH_3), 3.9–4.6(*m*, 3H, CH, NH), 5.00, 5.04, 5.08(3 single peaks, 2H, OCH_2, a mixture of diastereomers), 5.2(broad, overlapped partially with the peaks of OCH_2, 1H, NH), 7.3–7.9(*m*, 10H).	34.19, 33.65	1737, 1688 1200.7
4e	CH_3	CH_2Ph	CH_3	Ph	60MHz ($CDCL_3$) R_f = 0.30; 1.0–1.4(*q*, 3H, CH_3) 3.0(*d*, 2H, $PhCH_2$), 3.4(*s*, 3H, OCH_3), 3.8–4.0(*m*, 2H, CH), 4.83(*s*, 2H, $PhCH_2O$), 7.0–7.4(*m*, 15H).	33.65	1730, 1690 1180, 1115
4e	CH_3	CH_2Ph	CH_3	Ph	60MHz ($CDCL_3$) R_f = 0.28: 0.8–1.2(*q*, 3H, CH_3), 2.8(*s*, broad, 2H, $PhCH_2$), 3.5(*s*, 3H, OCH_3), 3.6–4.2(*m*, 3H, CH, NH), 4.93(*s*, 2H, $PhCH_2$), 7.0–7.4(*m*, 15H).	34.32	1745, 1690 1180, 1115
4f	n-C_3H_7	H	Et	Ph	90MHz ($CDCl_3$) 0.9–1.5(*m*, 10H), 3.4(*m*, 2H, NCH_2) 4.0(*q*, 3H, OCH_2, NCH), 4.8(*d*, 2H, CH_2O), 7.1–7.8.		1743, 1691 1180, 1110

4g	n-C_4H_9	CH_3	Et	Ph	90MHz ($CDCl_3$) 0.94(m, 3H, CH_3), 1.1–1.4(m, 9H) 3.6(m, 2H, NCH_2), 4.0–4.4(m, 3H, OCH_2), 5.05(s, 2H, $PhCH_2$), 7.2–7.8(m, 10H).		
4h	n-C_4H_9	CH_3	CH_3	Ph	90MHz ($CDCl_3$) 0.8–1.4(m, 12H), 3.5(d, OCH_3), 3.6–4.3(m, 2H), 4.9(m, 2H), 7.0–7.8(m, 10H).		1741, 1688 1184, 1140
4j	CH_3	H	CH_3	Ph	60MHz ($CDCl_3$) 1–1.5(q, 3H, CH_3), 3.6(s, 5H, OCH_3, NCH_2), 4.1(m, NCH), 4.9(m, 2, $PhCH_2$), 5.3(d, 1H, NH), 7.2–7.8(m, 10H).		
4i	n-C_3H_7	CH_3	CH_3	Ph	90MHz ($CDCl_3$) 0.9(t, 3H, CH_3), 1.2–1.4(m, 7H, CH_2—CH_2, CH_3), 3.74(s, 3H, OCH_3), 3.80–4.3(m, 2H, CH), 5.06(d, 2H, $PhCH_2$) 7.3–7.9(m, 10H, C_6H_5).		1756, 1735 1689, 1181
4k	CH_3	H	Et	CH_3	60MHz ($CDCl_3$) 1.1–1.5(m, 9H, CH_3), 3.5–4.3(M, 5H, OCH_2 NCH_3 NCH), 5.06(s, 2H, $PhCH_2$), 7.3(s, 5H, CH).		1740, 1715 1260, 1215
4l	CH_3	H	Et	OMe	60MHz ($CDCl_3$) 1.0–1.5(m, 6H, CH_3), 3.5–4.2(m, 8H, OCH_3 OCH_2, NCH_2) 4.95(s, 2H, $PhCH_2$), 7.2(s, 5H, C_6H_5).		1740, 1710 1200, 1030
4m	CH_3	$PhCH_2$	CH_3	OEt	90MHz ($CDCl_3$), 1.0–1.4(m, 6H, CH_3), 2.8–3.0(m, 2H, $PhCH_2$), 3.6–4.3(m, 4H, NCH, OCH_2), 5.0(s, 2H, $PhCH_2$ O), 7.1–7.2(d, 10H, C_6H_5), 3.5–3.6(d, 3H, OCH_3)	29.07 25.71 29.47	1740, 1715 1680, 1200

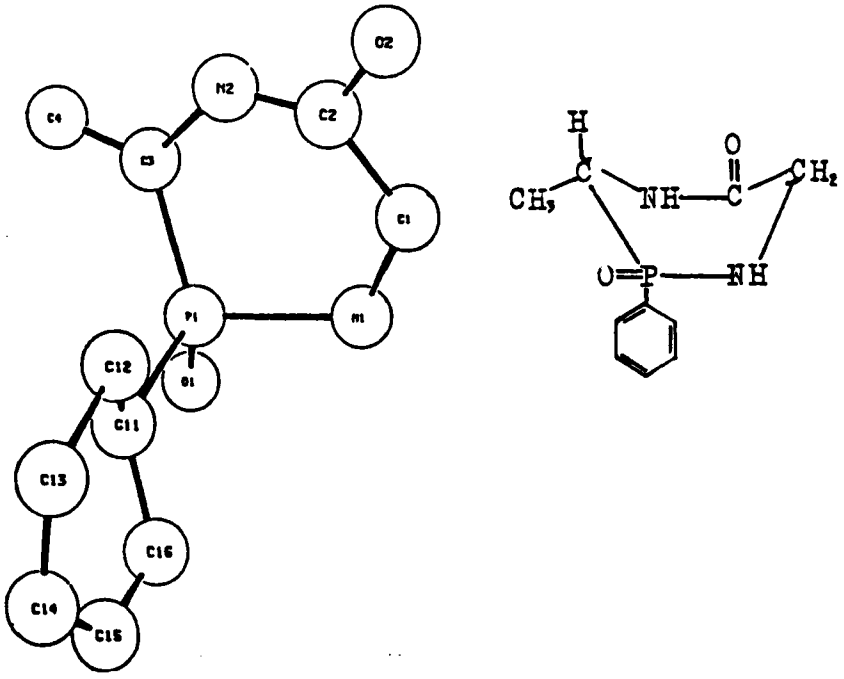


FIGURE 1 Molecular structure of **6c**.

with ether. To the aqueous layer was added some ice which was then acidified to pH = 1 with concentrated hydrochloric acid to give 38 g of white precipitate of **2** which was recrystallized from benzene. Yield: 90%, m.p. 108–110°C (lit. m.p. 111–113°C).

Diethyl N-benzyloxycarbonyl-1-aminoethylphosphonate (**2b**).[12] A suspension of 5.2 g (0.02 mol) of **2** in 25 g (0.17 mol) of triethylorthoformate was slowly heated with stirring. The ethyl formate and ethanol were continuously removed by distillation. The temperature was raised and kept at 135°C for 1 hr. Excess triethylorthoformate was removed under reduced pressure. The residue was purified by the chromatography on silica gel (petroleum ether/ethyl acetate 3:1) to give 5.9 g of **2b** as a viscous oil. Yield: 93.7%. The purity was detected by TLC.

Ethyl N-Carbobenzyloxy-1-aminoethylphosphonate (**3a**). A mixture of **2b** (1.4 g, 4.4 mmol), ethanol (70 ml), and 0.8 N NaOH solution (65 ml) was heated at 80°C for 3 hr. From the mixture about 70 ml of the solvent was removed under reduced pressure. The residue was washed with ether. The aqueous layer was acidified to pH = 3 with concentrated hydrochloric acid at 0°C, extracted with ethyl acetate, and dried with $MgSO_4$. After stripping off the solvent, a viscous oil was obtained, which solidified on standing, and was recrystallized from benzene-petroleum ether. 1.0 g, yield 79.4%; m.p. 90–93°C; ^{1}H-NMR; (90 MHz) $\delta(CDCl_3)$ 1.2–1.5 (*m*, 6H, CH_3), 4.0 (*m*, 3H, CH, CH_2), 5.1 (*s*, 2H, $PhCH_2$), 7.3 (*s*, 5H, C_6H_5). IR (KBr): 2500–3000, 1690, 1540, 1450, 1210, 1040 cm^{-1}. Calcd, C, 50.15; H, 6.27; N, 4.87. Found, C, 49.98; H, 6.40; N, 5.18.

N-(Benzyloxycarbonylamino ethyl ethoxyphosphinyl)-alanine methyl ester (**4a**). Method A: To a solution of **3a** (1.15 g, 4 mmol) in $CHCl_3$ (40 ml) was added $SOCl_2$ (0.95 g, 8 mmol) at 25°C. After 5 h the solvent and volatile by-products were removed under reduced pressure. The residue dissolved in 30 ml of $CHCl_3$ was cooled to 0°C and treated with DL-alanine methyl ester hydrochloride (0.6 g, 4.7 mmol) and triethyl amine (0.88 g). After stirring for 1 h at 25°C, the mixture was washed with H_2O, 1N H_2SO_4, and saturated $NaHCO_3$ separately, dried with $MgSO_4$, and evaporated to give **4a**, a viscous oil, which was chromatographed on silica gel (chloroform/1.4-dioxane: 20/1) and then recrystallized from benzene and petroleum ether. 1.3 g, yield: 87%, mp: 88–90°C. Phosphonodipeptides **4b–4m** were prepared by a similar method. The physical data and spectra were listed in Tables I and II.

TABLE III

^{1}H-NMR, ^{31}P-NMR, IR of **6**

No	R″	R′	X	^{1}H-NMR (ppm)	^{31}PNMR (ppm)	IR (cm^{-1})
6a	Me	Me	OEt	($CDCl_3$) 1.347–1.545(*m*, 9H, CH_3), 3.634(*m*, 1H, CH), 3.852(*m*, 2H), 4.156(*m*, 2H, OCH_2), 6.071(*d*, 1H, NH), 6.379(*d*, 1H, NH).	26.51 18.30	1660(broad) 1210(P=O)
6b	Me	H	OEt	($CDCl_3$) 1.0–1.6(*m*, 6H, CH_3), 3.5–4.3(*m*, 5H, OCH_2, CH_2, CH), 4.5(1H, NH).		1650(*s*, broad) 1210
6c	Me	H	Ph	(DMSO) 0.926(*q*, 3H, CH_3), 3.464(Octet, 1H, CH_2), 3.811(Octet, 1H, CH), 3.953(Octet, 1H, CH_2), 5.665(1H, NH), 7.7(*m*, 5H)	31.36	1675, 1640(C=O), 1180, 1160(P=O)
6d	Me	Me	Ph	(DMSO) 0.888–0.948(*q*, 3H, CH_3), 1.266, 1.283(*d*, 2.25H, CH_3), 1.436, 1454(*d*, 0.75H, CH_3), 3.84(*m*, 1H, CH), 4.06(*m*, 1H, CH), 5.47(1H, NH).	30.41 26.25	1670(broad, C=O), 1165(P=O)
6e	Me	CH_2Ph	Ph	($CDCl_3$) R_f = 0.53: 1.136(*q*, 3H, CH_3) 2.860–2.981(*a*, 2H, $PhCH_2$, NH) 3.503(*d*, 1H, CH_2Ph), 4.388(*m*, 1H, CH), 3.979(*m*, 1H, CH), 5.72(*d*, 1H, NH), 7.40(*m*). R_f = 0.42; 1.123(*q*, 3H, CH_3), 2.123(broad, 1H, NH), 3.119–3.29(*q*, *d*, 2H, CH_2Ph), 3.773(*m*, 1H, CH), 5.74(*d*, 1H, NH), 7.104–7.786(*m*, C_6H_5).	24.64 27.60	1650(C=O), 1175, 1163(P=O) 1667(C=O), 1155(P=O)
6f	*n*-C_3H_7	H	Ph	($CDCl_3$) 0.9(*m*, 3H, CH_3), 1.2–1.7(*m*, 4H), 4.7–5.1(*m*, 3H, CH_2, CH) 5.2(broad, 1H), 7.4–7.9(*m*, 5H).		1655(C=O) 1170(P=O)
6g	*n*-C_4H_9	H	Ph	($CDCl_3$) 0.6–1.4(*m*, 3H, CH_3), 1.2–1.7(*m*, 4H), 4.7–5.1(*m*, 3H, CH_2, CH) 5.2(broad, 1H), 7.4–7.9(*m*, 5H).		1660(C=O), 1200(P=O)
6h	*n*-C_4H_9	Me	Ph	R_f = 0.54: 0.812, 0.833, 0.849(*t*, 3H, CH_3), 1.2(*m*, 6H), 1.502, 1.518(*d*, 3H, CH_3) 3.09(broad, 1H, NH), 3.86(*m*, 1H, CH), 4.21(*m*, 1H, CH) 5.68(*d*, NH), 7.47–7.8(*m*, 5H). R_f = 0.41: 0.822, 0.805, 0.842(*t*, 3H, CH_3), 1.1–1.6(*m*, 5H), 1.655, 1.672(*d*, 3H, CH_3), 2.63(broad, 1H, NH) 3.830(*m*, 1H, CH), 4.14(*m*, 1H, CH) 5.74(*d*, 1H, NH), 7.6(*m*, C_6H_5).	31.36 27.05	1675, 1660(C=O), 1160(P=O)

N-(Benzyloxycarbonylamino ethyl ethoxyphosphinyl) glycine ethyl ester (**4b**). Method B: A mixture of **3a** (1.6 g, 5.6 mmol), DPPA (2.6 g, 9.4 mmol), triethyl amine (1.9 g, 19 mmol), and glycine ethyl ester hydrochloride (1.3 g, 9.4 mmol) in DMF (50 ml) was stirred at room temperature for 3 days. The solvent was stripped off under reduced pressure below 50°C. The residue was mixed with ethyl acetate. After the removal of the precipitate of triethyl ammonium chloride by suction, the filtrate was washed with H_2O, 1 N H_2SO_4 and saturated $NaHCO_3$, and dried with $MgSO_4$. The removal of the solvent gave a crude product **4b** which was chromatographed on silica gel (chloroform/1,4-dioxane: 20/1). 1.47 g, yield: 73.5%, mp: 75–77°C. **4a, 4c, 4d** were prepared by method B.

Cyclophosphonodipeptide (**6a**). Hydrogen gas was passed through a stirred mixture of **4a** (1.09 g, 2.9 mmol) and Pd-C (5%, 0.35 g) in 30 ml of ethanol at atmospheric pressure and 25°C for 16 h. The catalyst was removed by suction, and the filtrate was concentrated under reduced pressure to give **5a** which was homogeneous according to TLC. Without further purification, the residue was dissolved in 80 ml of *n*-butanol/toluene (3:1) and refluxed for 48 h, and then concentrated. The crude product was chromatographed on silica gel, eluted with a mixture of chloroform ethanol (6:1) to give white powder **6a**, 0.22 g yield: 36.7%, mp: 150–152°C. Cyclophosphonodipeptides **6b–6h** were prepared similarly. The physical data were listed in Tables I and III.

N-Benzyloxycarbonyl-1-aminoalkylphenylphosphinic Acid (**3b–3d**). Freshly distilled acetaldehyde (5 g, 110 mmol) was dripped slowly into a stirred mixture of benzyl carbamate (11.5 g, 76 mmol), phenylphosphine dichloride (12.5 g, 75 mmol) and glacial acetic acid (15 ml) at −10°C during 1.5 h. Stirring was continued for 2 h at 0°C. The mixture was treated with 60 ml of H_2O. The white precipitate obtained was washed with H_2O to pH = 5 and recrystallized from benzene to give **3b**, 18 g, yield: 71.5%; mp: 150–152°C; ^{1}H-NMR: δ($CDCl_3$) 1.2 (*q*, 3H, CH_3), 4.0 (*m*, 1H, CH), 4.8 (*s*, 2H, OCH_2), 5.1–5.4 (broad, 1H, NH), 7.1–7.8 (*m*, 10H, C_6H_5), 11.5 (*s*, 1H, OH); $C_{16}H_{18}NO_4P$(319). Calcd: C, 60.30; H, 5.64; N, 4.39; P, 9.70. Found: C, 60.78; H, 5.81; N, 4.38; P, 9.59. MS: 319(M^+).

3c and **3d** were prepared similarly.

3c) yield: 79.3%. mp: 136–149°C. ^{1}H-NMR: δ($CDCl_3$) 0.9 (*m*, 3H, CH_3), 1.5 (*m*, 4H, CH_2CH_2), 4.0 (*m*, 1H, CH), 4.8 (*s*, 2H, OCH_2), 4.9–5.1 (*m*, 1H, NH), 7.1–7.7 (*m*, 10H), 11.4 (*s*, 1H, OH). $C_{18}H_{22}NO_4P$(347). Calcd: C, 62.24; H, 6.40; N, 4.03. Found: C, 62.62; H, 6.77; N, 4.16.

3d) yield: 88%. mp: 124–128°C. ^{1}H-NMR: α($CDCl_3$), 0.7 (*m*, 3H, CH_3), 1.2 (*m*, 6H, CH_2), 4.0 (*m*, 1H, CH), 4.7 (*s*, 2H, OCH_2), 7.1–7.7 (*m*, 10H). $C_{19}H_{24}NO_4P$(361). Calcd: C, 63.16; H, 6.65; N, 3.88. Found: C, 62.95; H, 6.86; N, 3.73.

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