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CONVERSION OF AMINO ACIDS AND DIPEPTIDES INTO THEIR PHOSPHONIC ANALOGS

Aminoalkylphosphonic acids and peptides II.

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Abstract - Acylamino carboxylic acids were degradated by the Hunsdiecker-reaction; the bromo-derivatives were reacted with $NaPO(OC_2H_5)_2$. Aminophosphonic acids were obtained by acidic hydrolysis, and half-blocked derivatives by the selective removal of masking substituents. Two phosphonopeptides [e.g. Alafosfalin (**4i**)] were also prepared by this route.

There is growing interest in modifying the peptide back-bone by substitution of C or N atoms in the chain or at the terminals with different atoms, e.g. with phosphorus. Therefore our new synthetic method leading to phosphorus analogs of amino acids and peptides can be very useful for the planning of peptide synthesis.

In the first publication[1] of this series we presented a synthetic route with a genetical connection between the natural amino acids and the appropriate aminophosphonic acids. (A series of amino acids or their derivatives having two or more functional groups can be degradated by sodium hypochlorite to the appropriate aldehydes, which are shorter with one carbon atom, forming the analog aminoalkyl-phosphonic acid derivatives with urethans and triphenylphosphite.)

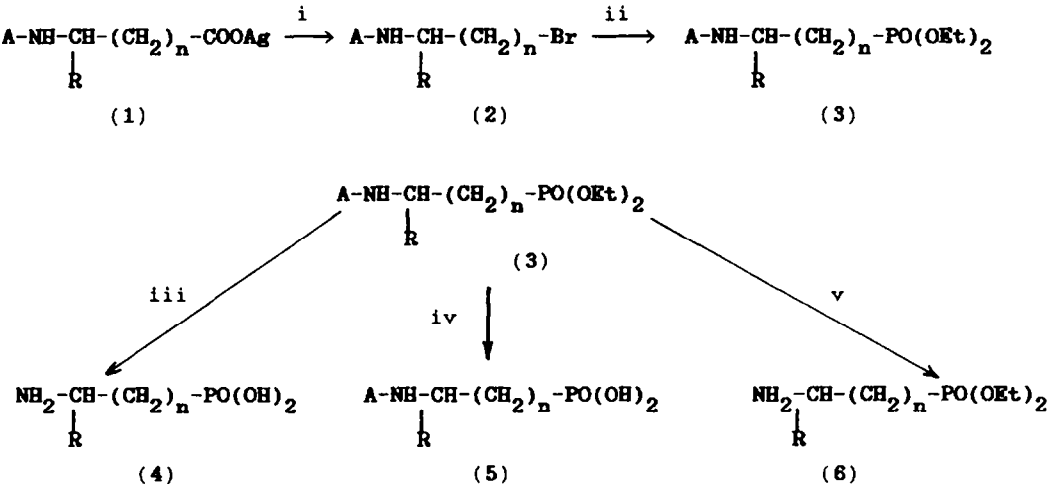
In this communication a similar, almost general method is presented. From acylamino acids the appropriate free aminophosphonic acids or their derivatives blocked only at one of the two terminals can be prepared by a four-step synthetic route according to Scheme 1.

Different acyl groups (phthaloyl, benzoyl, carbobenzoxy) were tried as protecting groups during the synthesis. Our results show that it is not necessary to substitute both of the hydrogens in the amino groups even for α-amino acids. So far only a few experiments have been published[2-4] in the literature for decarboxylation the silver salt of amino acid derivatives. The main problem is how to avoid the very quick hydrolysis of α-aminoalkylbromides to aldehydes. The only way is: working with absolutely dry materials and equipment. Generally without further purification, the bromo-derivatives were phosphonated by using sodium diethylphosphite[5] or triethylphosphite. Better yields were obtained on the first way.

The blocking groups can be removed totally or selectively according to further synthetic aims. Total hydrolyses were carried out in the case of carbobenzoxy[6], and benzoyl derivatives[7] by acidic cleavage. From phthaloylamino-

phosphonic acid esters the free acids were obtained in two steps[8]: 1) dephthalylation, 2) acidic hydrolysis.

Selective removal of the carbobenzoxy groups by catalytic hydrogenation under pressure[9] and that of the phthaloyl groups by hydrazinolysis[10] were realized. The ester bonds were cleavaged by the trimethylsilyl iodide method[11].



A = Bz, Z, Pht, Z-Gly, Z-Ala;
R = H, CH_3, $CH_3CH_2CH_2$, $(CH_3)_2CHCH_2$;
n = 0, 1, 2

Reagents:
(i) Br_2; CCl_4;
(ii) $NaPO(OEt)_2$; $HPO(EtO)_2$;
(iii) HCl/H_2O or HBr/AcOH;
(iv) Me_3SiI; CH_2Cl_2;
(v) H_2/Pd-C; MeOH.

Scheme 1

DISCUSSION

Our procedure seems to be applicable for the synthesis of aminophosphonic acids from amino acids having aliphatic side-chains or blocked side groups. Furthermore, our experiments (3j-k) show a good possibility to prepare small phosphonopeptides from analogous peptides by this route. In such cases, instead of the procedure 4 in Experimental the fully protected phosphonodipeptides were treated with HBr/AcOH for removing the blocking groups. Acyl derivatives (5) and free phosphonopeptides are available to prepare the diastereomer and enantiomer forms[19,20].

For the preparation of the simple aminophosphonic acids our method is not so economic as the syntheses described in the literature. Nevertheless, it has an important advantage when preparing for biological tests small quantities of various phosphonic analogs of a) biologically active amino acids of complicated structure [with several functional groups and/or asymmetric centers (e.g. 3c)], b) polypeptides built by fragment condensation. In the latter case the C-terminal diastereomer di- or tripeptide fragments can be easily separated from each other to be built separately into the polypeptide. This method together with the common synthetic route resulting in side chain labelled amino acids and peptides gives a possibility to prepare labelled aminophosphonic acid derivatives.

Table 1. Yields, physical and analytical data of silver salts (1) of amino acid and dipeptide derivatives.

Compound	Formula	M.w.	Yield (%)	M.p. (°C)	Analysis for Ag % calcd.	found
1a Pht=Gly-OAg	$C_{10}H_8NO_4Ag$	312.03	94	298-300	34.57	35.10
1b Bz-Gly-OAg	$C_9H_9NO_3Ag$	286.04	70	205-7	37.71	37.17
1c Bz-L-ω-Ape-OAg	$C_{12}H_{14}NO_3Ag$	328.12	71	275-6.5	32.87	33.21
1d Z-Gly-OAg	$C_{10}H_{10}NO_4Ag$	316.07	82	196-8.5	34.13	33.73
1e Z-DL-Ala-OAg	$C_{11}H_{12}NO_4Ag$	330.09	70	153-6.5	32.68	32.24
1f Z-β-Ala-OAg	$C_{11}H_{12}NO_4Ag$	330.09	92.5	223.5-5	32.68	31.81
1g Z-DL-Leu-OAg	$C_{14}H_{18}NO_4Ag$	372.17	79	175.5-7	28.98	28.76
1h Z-DL-Ape-OAg	$C_{13}H_{16}NO_4Ag$	358.15	90	160-3	30.12	30.20
1i Z-L-Ala-DL-Ala-OAg	$C_{11}H_{17}N_2O_5Ag$	401.17	80	211-3	26.88	27.00
1j Z-Gly-DL-Leu-OAg	$C_{16}H_{21}N_2O_5Ag$	429.23	75	194.5-7	25.13	25.31

EXPERIMENTAL

Melting points were measured by a Boetius melting point apparatus and are uncorrected. NMR spectra were obtained in $CDCl_3$, CF_3COOD, DMSO-d_6 or D_2O solution by a Bruker WP-80 instrument. Chemical shifts are given in ppm relative to Me_4Si as an internal standard. Infrared spectra were taken on a Spekord M-80 spectrophotometer. Column chromatography was carried out using silicagel (Merck, 60 mesh). TLC analysis was performed on silicagel (Merck, precoated sheet, $60F_{254}$). Solvents were: (A) $CHCl_3$-MeOH-AcOH = 90/8/2; (B) n-BuOH-Pyr-AcOH-H_2O = 30/20/6/24; (C) cyclohexane-EtOAc = 3/1; (D) n-BuOH-AcOH-H_2O = 4/1/1; (E) n-BuOH- EtOAc-AcOH-H_2O = 1/1/1/1; (F) $CHCl_3$-CCl_4-MeOH = 8/5/1; (G) benzene-dioxane-ethanol-25% NH_3 = 50/40/5/5; (H) Pyr-H_2O = 1/1; (I) benzene-MeOH-EtOH = 8/1/1.

Starting phthaloylglycine[22], benzoylglycine[23] and benzoyl-ω-amino-pentanoic acid for 1a were synthetized according to the illustrative procedures 10-33 and 10-178 of the handbook Greenstein and Winitz[21]. The preparations of carbobenzoxyamino acids[26-27] for 1d-h were carried out by the Bergman and Zervas procedure[25] as it is described in illustrative procedures 10-28 and 10-29 by Greenstein and Wintz[21]. The carbobenzoxy-dipeptides[28,29] have been obtained from their esters through the hydrolytic action of dilute aqueous sodium-hydroxide in admixture with acetone.

1) Silver salts:

10 mmol of N-acyl amino acid was dissolved in 16.8 ml of 5 % sodium hydrogencarbonate. After removing the carbon dioxide by evacuation (two minutes on rotavapor) 10 mmol of $AgNO_3$ in 15 ml water was given to the strongly stirred solution kept in dark. After 15 minutes the white precipitated material was filtered at 10°C, washed with ice water, acetone and anhydrous CCl_4. The salt was dried over P_2O_5 and H_2SO_4 in vacuum at 45°C for 24 hrs. Yield: 70-94 %.

2) Bromo-derivatives:

Bromination was carried out with some modification of the procedure of Fromm[4]. Thus, 10 mmol silver salt (1) was stirred with 50 ml abs. CCl_4 in a flame-dried round-bottomed flask under dry nitrogen. At 35-40°C 20 ml CCl_4 solution of 12.5 mmol bromine was added dropwise over 5 min. The mixture was allowed to cool to room temperature, stirred two hours, then filtered and concentrated in vacuo at room temperature to give a yellow-brown residue. The further precipitated material was filtered by using a mixture of methanol and dioxane. Neutralization of the solution was carried out at 0°C with an abs. methanol solution containing 5% ammonia. The refiltered solution was evaporated. Table 2 shows that a few materials could be crystallized.

3) Phosphonation:

To 50 ml of stirred diethylphosphite (DEP) 11 mmol NaH was added under dry N_2 atmosphere. After ending the reaction 10 ml DEP solution of 10 mmol bromo-derivative (2) was slowly dropped in the flask at 30°C. The mixture was stirred overnight. The precipitated salt was filtered and DEP was destilled out. The residue was taken up in ethyl acetate, washed 3 times with aqueous $NaHCO_3$ and water. The organic solution was dried over sicc. Na_2SO_4 and concentrated in vacuo. In several cases the residue could be crystallized, in other cases it was chromatographed on silica gel by eluent of $CHCl_3/CH_3OH/CH_3COOH$ = 90/8/2 under 1.5 bar overpressure. After evaporation of the solvent of the appropriate fraction an oil could be obtained.

4) Acidolysis:
5 mmol acylaminoalkylphosphonate was refluxed with 25 ml cc. hydrochloric acid for 20 hrs. The solution was evaporated to dryness under reduced pressure. The residue was taken up in 50 ml water, benzoic acid (in the case of benzoyl derivative starting materials) was removed by extraction with petrolether-120. From the reevaporated residue ethanol was volatiled two times. Then the ethanolic solution of **4** hydrochloride was treated with propylene oxide at 10°C. The precipitated powder was recrystallized from water-ethanol.

Table 2. Yields, physical and spectroscopical data of compounds **2** - **6**.

Compound Formula M.w.	Yield (%)	M.p. (°C)	R_f	IR ν(cm^{-1})[a]	^{1}H-NMR δ(ppm)[b]
Pht=NCH$_2$Br (**2a**) C$_9$H$_6$BrNO$_2$; 240.05	54	140-4 [149-50][12]	-	1725 (C-O) 1770 2990 (C-H)	+8.00(s,4H,Pht) 5.90(s,2H,CH$_2$)
Bz-NHCH$_2$Br (**2b**) C$_9$H$_8$BrNO; 214.06	35	oil (crude)	-	*1680 (C=O) 3450 (N-H)	×8.0-7.0(d,6H,Ph,NH) 5.55(d,2H,CH$_2$)
PhtGlyp(OEt)$_2$[c] (**3a**) C$_{13}$H$_{16}$NO$_5$P; 297.25	47	64-6 [67][13]	0.65(G) 0.75(B)	1025 (P-O) 1260 (P=O) 1736 (C=O) 3600 (N-H)	×7.83(m,4H,Pht) 4.25(q,4H,OCH$_2$) 4.12(d,2H,PCH$_2$, $^2J_{H-P}$=11.5 Hz) 1.35(t,6H,2CH$_3$)
BzGlyp(OEt)$_2$ (**3b**) C$_{12}$H$_{18}$NO$_4$P; 271.24	41	oil	0.35(F)	F1070 (P-O) 1240 (P=O) 1700 (C=O) 2980 (C-H) 3210 (N-H)	×7.10-8.20(m,6H,Ph,NH) 3.80(d,2H,NHCH$_2$) 3.00(q,2H,OCH$_2$) 1.10(t,6H,2CH$_3$)
Bz-L-α-Apep(OEt)$_2$ (**3c**) C$_{15}$H$_{24}$NO$_4$P; 313.32	27	oil	0.40(F)	F1030 (P-O) 1210 (P=O) 1735 (C=O) 3200 (N-H)	×7.90-7.30(m,5H,Ph) 6.00(s,1H,NH) 4.10(m,1H,CH) 3.90(q,4H,OCH$_2$)
Z-Glyp(OEt)$_2$ (**3d**) C$_{13}$H$_{20}$NO$_5$P; 301.27	24	oil	0.39(F) 0.53(G)	F1100 (P-O) 1260 (P=O) 1720 (C=O) 2900 (C-H) 3180 (N-H)	×+y7.20(s,5H,Ph) 5.25(s,1H,NH) 4.95(s,2H,PhCH$_2$) 3.90(q,4H,OCH$_2$) 3.40(dd,2H,NCH$_2$, ^3J=6 Hz,$^2J_{H-P}$=12 Hz) 1.03(t,6H,2CH$_3$)
Z-DL-Alap(OEt)$_2$ (**3e**) C$_{14}$H$_{22}$NO$_5$P; 315.29	21.5	oil	0.62(A)	F1030 (P-O) 1220 (P=O) 1690 (C=O) 2900 (C-H) 3100 (N-H)	×7.40(s,5H,Ph) 5.15(s,2H,PhCH$_2$) 4.65(m,4H,OCH$_2$) 3.85(m,1H,CH) 1.48(d,3H,CH$_3$) 1.30(t,6H,2CH$_3$)
Z-β-Alap(OEt)$_2$ (**3f**) C$_{14}$H$_{22}$NO$_5$P; 315.29	29	oil	0.55(A)	1040 (P-O) 1280 (P=O) 1690 (C=O) 2900 (C-H) 3120 (N-H)	×7.40(s,5H,Ph) 5.30(s,1H,NH) 4.95(s.2H,PhCH$_2$) 3.90(d,4H,NCH$_2$) 3.50(m,2H,NCH$_2$) 3.25(m,2H,CH$_2$P) 1.05(t,6H,2CH$_3$)
Z-DL-Leup(OEt)$_2$ (**3g**) C$_{18}$H$_{30}$NO$_5$P; 359.31	20	oil	0.78(A)	F1040 (P-O) 1240 (P=O) 1750 (C=O) 3050 (C-H) 3320 (N-H)	×7.25(s,5H,Ph) 5.90(t,1H,NH) 5.00(s,2H,PhCH$_2$) 4.45(m,1H,CH) 4.20(qq,4H,OCH$_2$) 1.50(m,1H,CH$_2$CH) 1.35(t,6H,2CH$_3$) 0.70(d,6H, CH(CH$_3$)$_2$,^3J=5 Hz)

Table 2. (cont.)

Compound Formula M.w.	Yield (%)	M.p. (°C)	Rf	IR ν(cm⁻¹)[a]	¹H-NMR δ(ppm)[b]
Z-DL-Apep(OEt)₂ (3h) $C_{18}H_{28}NO_5P$; 343.34	21	oil	0.75(A)	[f]1060 (P-O) 1240 (P=O) 1755 (C=O) 3000 (C-H) 3200 (N-H)	[x]7.35(s,5H,Ph) 6.35(d,1H,NH,J=10 Hz) 5.10(s,2H,PhCH₂) 4.50(m,1H,CH) 3.90(d,4H,OCH₂) 1.80(m,2H,CHCH₂) 1.50(m,2H,CH₂CH₃) 1.30(t,6H,2OCH₂CH₃) 0.95(t,3H,CH₃)
Z-L-Ala-DL-Alap(OEt)₂ (3i) $C_{17}H_{27}N_2O_8P$; 386.37	11	oil $[\alpha]_{25}$=-4.8(c=1.4;CHCl₃)	0.27(E)	[f]1030 (P-O) 1235 (P=O) 1690,1720 (C=O) 3300 (N-H)	[x]7.25(s,5H,Ph) 6.60(d,1H,NH) 5.37(d,1H,NH) 4.20(m,2H,2CH) 1.32(m,6H,2CH₃)
Z-Gly-DL-Leup(OEt)₂ (3j) $C_{18}H_{31}N_2O_8P$; 414.42	13	76-9	0.65(A)	1040 (P-O) 1235 (P=O) 1720 (C=O) 3100 (N-H)	[x]7.20(s,5H,Ph) 5.80(t,1H,NH) 4.95(s,2H,PhCH₂) 4.40(m,1H,N-CH) 3.95(qq,4H,2OCH₂) 3.73(d,2H, NCH₂,³J=7 Hz) 1.35(m,.3H,CH₂CH) 1.05(t,6H,2CH₃) 0.62(d,6H, CH(CH₃)₂,³J=5 Hz)
Glyp (4a) CH_6NO_3P; 111.04	70	285-7 [320][14a] [286.5][14b] [310][14c]	0.22(E)	1030 (P-O) 1220 (P=O) 2600-3400 (C-H,N-H,O-H)	[w]3.1(d,2H,CH₂, ²J$_{H-P}$=13 Hz)
DL-Alap (4e) $C_2H_8NO_3P$; 125.06	59	270.5-2 [270-2][15]	0.41(E)	1030 (P-O) 1240 (P=O) 2600-3350 (C-H,N-H,O-H)	[w]3.40(m,1H,CH) 1.45(dd,3H,CH₃, ³J=7 Hz,²J$_{H-P}$=13.5 Hz)
β-Alap (4f) $C_2H_8NO_3P$; 125.06	90	295-6 [294-6][16]	0.25(E)	1030 (P-O) 1230 (P=O) 2600-3400 (C-H,N-H,O-H)	[w]3.20(m,2H,CH₂P) 2.15(m,2H,NCH₂)
DL-Leup (4g) $C_5H_{14}NO_3P$; 167.14	87	279-84 [270-2][15]	0.51(E)	1030 (P-O) 1190 (P=O) 2500-3150 (C-H,N-H,O-H)	[w]3.10(m,1H,NCH) 1.48(m,3H,CH₂CH) 0.78(d,6H,2CH₃)
DL-Apep (4h) $C_4H_{12}NO_3P$; 153.11	75	270-2 [273-4][15]	0.45(E)	1060 (P-O) 1240 (P=O) 2600-3400 (C-H,N-H,O-H)	[v]3.80(m,1H,CH) 2.3-1.3(m,4H,CH₂CH₂) 1.00(t,3H,CH₃)
L-Ala-DL-Alap (4i) $C_5H_{13}N_2O_4P$; 196.14	65	270-5 [260-5][17] $[\alpha]_{25}$=+17(c=0.5;H₂O) [+15(c=0.5;H₂O)][15]	0.54(H)	1060 (P-O) 1240 (P=O) 1670 (C=O) 2600-3400 (C-H,N-H,O-H)	[w]4.05(q,2H,2CH) 1.55(d,3H,CH₃, ³J=7.5 Hz) 1.31(dd,3H,CH₃, ³J=7.5Hz,²J$_{H-P}$=15Hz)
Gly-DL-Leup (4j) $C_7H_{17}N_2O_4P$; 224.19	35	266-9	0.54(E)	1060 (P-O) 1260 (P=O) 1660 (C=O) 2640-3400 (C-H,N-H,O-H)	[w]4.00(m,1H,NCH) 3.65(s,2H,NCH₂) 1.40(m,3H,CH₂CH) 0.65(t,6H,CH₃)
Pht=Glyp(OH)₂ (5a) $C_8H_8NO_5P$; 241.14	40	274-7	0.50(D)	1045 (P-O) 1200 (P=O) 1720,1770 (C=O)	[x]7.80(m,4H,Pht) 4.10(d,2H,CH₂)

Table 2. (cont.)

Compound Formula M.w.	Yield (%)	M.p. (°C)	R_f	IR ν(cm^{-1})[a]	^{1}H-NMR δ(ppm)[b]
Z-DL-Alap(OH)$_2$ (**5e**) $C_{10}H_{14}NO_5P$; 259.19	36	111-3 [111-3][9]	0.38(D)	1100 (P-O) 1240 (P=O) 1670 (C=O) 2800 (C-H) 3120 (N-H)	x8.30(s,2H,OH) 7.32(s,5H,Ph) 7.14(d,1H,NH,^3J=11 Hz) 5.03(s,2H,CH_2) 3.75(m,1H,CH) 1.47(dd,3H,CH_3, ^3J=7 Hz, $^2J_{H-P}$=15 Hz)
Z-β-Alap(OH)$_2$ (**5f**) $C_{10}H_{14}NO_5P$; 259.19	27	103-5 [105][18]	0.30(D)	1010 (P-O) 1210 (P=O) 2500-3400 (C-H,N-H,O-H)	x7.40(s,5H,Ph) 5.35(s,1H,NH) 5.00(s,2H,$PhCH_2$) 3.40(m,2H,NCH_2) 3.20(m,2H,CH_2P)
-Z-DL-Leup(OH)$_2$ (**5g**) $C_{13}H_{20}NO_5P$; 301.27	30	72-5	0.28(A)	1020 (P-O) 1285 (P=O) 1705 (C=O) 3005 (C-H) 3480 (N-H)	x7.50(s,2H,OH) 7.25(s,5H,Ph) 5.65(s,1H,NH) 5.05(s,2H,CH_2) 4.05(m,1H,NCH) 1.55(m,3H,CH_2CH) 0.85(d,6H,$2CH_3$)
Z-L-Ala-DL-Alap(OH)$_2$ (**5i**) $C_{12}H_{19}N_2O_8P$; 330.27	25	152-5	0.34(I)	1060 (P-O) 1270 (P=O) 1660,1670 (C=O) 3320 (N-H)	v7.30(s,5H,Ph) 5.10(s,2H,CH_2) 4.42(m,2H,2CH) 1.40(d,3H,CH_3, ^3J=7 Hz,q,3H,CH_3)
H-Glyp(OEt)$_2$ (**6a**) $C_5H_{14}NO_3P$; 167.14	98	oil	0.13(A)	F1020 (P-O) 1210 (P=O) 2995 (C-H) 3370 (N-H)	y3.90(q,4H,$2OCH_2$) 3.50(d,2H,NH_2,^3J=10 Hz) 3.00(dd,2H,CH_2, ^3J=10 Hz,$^2J_{H-P}$=22 Hz) 1.05(t,6H,$2CH_3$)
H-DL-Alap(OEt)$_2$ (**6e**) $C_6H_{16}NO_3P$; 181.16	96	oil	0.25(A)	F1020 (P-O) 1220 (P=O) 2890 (C-H) 3400,3475 (N-H)	x4.10(m,4H,OCH_2) 3.50(s,2H,NH) 2.95(dq,1H,CH, ^3J=7 Hz,$^3J_{H-P}$=24 Hz) 1.40(d,3H,CH_3,J=7 Hz) 1.30(t,6H,$2CH_3$)
H-β-Alap(OEt)$_2$ (**6f**) $C_6H_{16}NO_3P$; 181.16	81	oil	0.22(A)	F1010 (P-O) 1210 (P=O) 2500-3400 (C-H,N-H)	x3.90(d,4H,OCH_2) 3.50(d,2H,NH_2) 3.35(m,2H,NCH_2) 3.15(m,2H,CH_2P) 1.10(t,6H,$2CH_3$)
H-DL-Leup(OEt)$_2$ (**6g**) $C_9H_{22}NO_3P$; 223.24	95	oil	0.38(A)	F1035 (P-O) 1240 (P=O) 2995 (C-H) 3450,3510 (N-H)	5.15(s,2H,CH_2) 4.21(qq,4H,$2OCH_2$) 3.90(m,1H,NCH) 2.05(s,2H,NH_2) 1.62(m,1H,CH_2CH) 1.30(t,6H,$2CH_3$) 0.80(d,6H,$CH(CH_3)_2$)
H-DL-Apep(OEt)$_2$ (**6h**) $C_8H_{20}NO_3P$; 209.21	90	oil	0.35(A)	F1050 (P-O) 1240 (P=O) 3010 (C-H) 3450 (N-H)	x4.25(m,4H,OCH_2) 4.00(m,1H,CH) 2.30-1.50(m,4H,CH_2CH_2) 1.10(t,6H,2 OCH_2CH_3) 0.95(d,3H,CH_3)

a) IR spectra were taken in $CHCl_3$ solution (*), films (F) or KBr pellets.
b) NMR spectra were taken in $CDCl_3$ (x), CF_3COOD (v), DMSO-d_6 (y) and D_2O (w).
c) Four-letter symbols are used to indicate the phosphonic acid analogs of the appropriate amino acids[31].

REFERENCES

1. G. Ösapay, Symposion of the Hungarian Chemical Society - Debrecen (July 1983).
2. K. Heyns, K. Stange: Z. Naturforsch., 1952, 7b, 677.
3. K. Heyns, K. Stange: ibid., 1955, 10b, 129.
4. H.J. Fromm: J. Org. Chem., 1957, 22, 611.
5. V. Chavanne: Ann. Chim. (Paris), 1949, [12]4, 372.
6. J. Oleksyszyn, R. Tyka: Tetrahedron Lett., 1977, 32, 2823.
7. E. Fischer: Ber., 1899, 32, 2454.
8. J.C. Sheehan, V.S. Frank: J. Am. Chem. Soc., 1949, 71, 1856.
9. J.W. Huber, W.F. Gilmore, L.W. Robertson: J. Med. Chem., 1975, 18, 106.
10. K. Jamonchi, J. Mitsuda, M. Kinoshita: Bull. Chem. Soc. Japan, 1975, 48, 3285.
11. J. Zygmunt, P. Mastalerz: Pol. J. Chem., 1981, 55, 411; M.M. Campbell, N.J. Carruthers, S.J. Mickel: Tetrahedron, 1982, 38, 2513; J. Rachon: Synthesis, 1984, 219.
12. F. Sachs: Ber., 1898, 31, 1225.
13. K. Yamauchi, M. Kinoshita, M. Imoto: Bull. Chem. Soc. Japan, 1972, 45, 2531.
14. a) M.J. Pulwer, T.M. Balthazor: Synth. Commun., 1986, 16(7), 733; b) J.R. Chambers, A.F. Isbell: J. Org. Chem., 1964, 29, 832; c) M.I. Kabachnik, T.Y. Medved: Izv. Akad. Nauk. SSSR; Otd. Khim. Nauk., 1950, 635.
15. J. Oleksyszyn, R. Tyka: Tetrahedron Lett., 1977, 32, 2823.
16. J.B. Berry, A.F. Isbell, G.E. Hunt: J. Org. Chem., 1972, 37, 4396.
17. Y. Okada, S. Iguchi, M. Mimura, M. Yagyu: Chem. Pharm. Bull., 1980, 28, 1320.
18. K. Yamauchi, S. Ohtsuki, M. Kinoshita: J. Org. Chem., 1984, 49, 1158.
19. J. Szewczyk, B. Lejczak, P. Kafarski: Experientia, 1982, 38, 983.
20. F.R. Atherton, C.H. Hassal, R.W. Lambert: J. Med. Chem., 1986, 29, 29.
21. J.P. Greenstein, M. Winitz: in Chemistry of the Amino Acids., J. Wiley, New York - London, 1961, Vol. 2. pp. 891, 902, 1267.
22. J.H. Billman, W.F. Harting: J. Am. Chem. Soc., 1948, 70, 1473.
23. A. Reissert: Ber., 1890, 23, 2239.
24. Synthesis of ω-Ape will be published elsewhere.
25. M. Bergman, L. Zervas: Ber. 1932, 65, 1192.
26. R.H. Sifferd, V. du Vigneaud: J. Biol. Chem., 1935, 108, 753.
27. W. Grassmann, E. Wünsch: Ber., 1958, 91, 462.
28. W.H. Stein, S. Moore, M. Bergmann: J. Biol. Chem., 1944, 154, 191.
29. S. Goldschmidt, H. Lautenschlager: Ann., 1953, 580, 68.
30. Abbreviations used are those recommended by the IUPAC-IUB Joint Comission on Biochemical Nomenclature: Biochem. J., 1984, 219, 345.
Bz-: benzoyl; Z-: benzyloxycarbonyl; Pht-: phtaloyl;
Ape: α-amino-pentanoic acid (norvaline; Nva); ω-Ape: ω-amino-pentanoic acid; AcOH: acetic acid; EtOAc: ethylacetate; MeOH: methanol; EtOH: ethanol;
n-BuOH: n-butanol; Pyr: pyridine; TLC: thin-layer chromatography.
31. Note. Besides the traditional and well-known three-letter symbols (Aaa) of the common amino acids we recommend four-letter-symbols (Aaap) for their phosphonic acid analogs (similarly to their thiocarbonyl analogs[32]). In these molecules a phosphono group [-PO(OH)2] substitutes the 1-carboxyl group of an amino acid. For the representation of their derivatives and peptides, the following hyphen-modified symbols are applicable. There are six distinct forms for the free aminophosphonic acid (e.g. Glyp) and the five residues, viz.:

a) Glyp	$H_2N-CH_2-PO(OH)_2$	free aminophosphonic acid
b) Glyp-	$H_2N-CH_2-PO(OH)-$	left hand units in peptides
c) Glyp=	$H_2N-CH_2-P(O)=$	left hand units in peptides
d) -Glyp-	$-HN-CH_2-PO(OH)-$	middle units in peptides
e) -Glyp=	$-HN-CH_2-P(O)=$	middle units in peptides
f) -Glyp	$-HN-CH_2-PO(OH)_2$	right-hand unit in peptides

These symbols agree with the roles recommended by JCBN (1983)[30].
32. W.C. Jones, Jr., J.J. Nestor, Jr., V. du Vigneaud: J. Am. Chem. Soc. 1973, 95, 5677.