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Method for the synthesis of phosphinic acids from hypophosphites V. The synthesis of pseudo-α,α-dipeptides*

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Summary. The method for the synthesis of 2-substituted 2-hydroxycarbonylethyl-1-aminoalkylphosphinic acids (I) (pseudo-α,α-dipeptides) from ammonium and potassium hypophosphites (II) is described. The proposed route to the synthesis of pseudo-α,α-dipeptides consists in addition hypophosphite to acrylic compounds and formation of the first phosphorus–carbon bond with following addition of aminoacid fragment and formation of the second phosphorus–carbon bond. The key intermediates of the synthesis – phosphonous acids (III) and their silylic esters (IV) were obtained at the first stage of the process as the result of the addition of the bis(trimethylsilyl)hypophosphite *in situ* to suitably substituted acrylates. The modificated procedure for the Kabachnik-Fields reaction of 2-substituted 2-alkoxycarbonylethyl phosphonous acids (III), acetamide, benzaldehyde in acetic anhydride with following hydrolysis results in 2-substituted 2-hydroxycarbonylethyl-α-aminobenzyl phosphinic acids (Ia–c) (pseudo-phenylglycylpeptides). Bis(trimethylsilyl) 2-substituted 2-alkoxycarbonylethylphosphonites (IV) *in situ* were added to N-tritylmethanimine and following alcoholysis and acid hydrolysis of addition products gave 2-substituted 2-hydroxycarbonylethyl-aminomethylphosphinic acids (Id–f) (pseudo-glycylpeptides).

Keywords: Pseudo-α,α-dipeptides – Phosphinic acid peptides – 2-Substituted 2-alkoxycarbonylethylphosphonous acids – Potassium and Ammonium hypophosphites – Amino phosphinic acids

Introduction

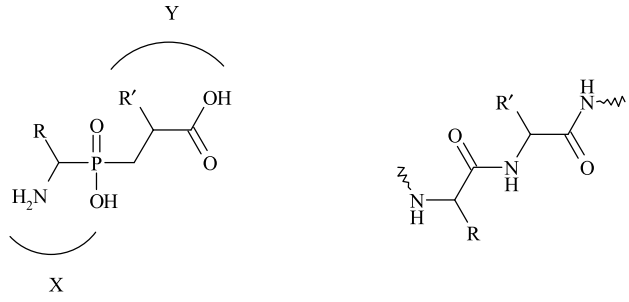
Phosphinic acid peptides (pseudo-peptides) are peptide isosters where one peptide bond {–C(O)NH–} is substituted by nonhydrolysable phosphinate moiety {–P(O)CH_2–}. This substitution represents a very convenient mimic of a substrate in the transition state for at least two big classes of hydrolytic enzymes, Zn – metalloproteinases and aspartic acid proteinases (Collinsova and Jiracek, 2000).

The elaboration of convenient methods for the synthesis of pseudo-α,α-dipeptides (A) – phosphinic analogues of corresponding peptides (B) (Fig. 1) is a perspective way to potential physiologically active compounds as matrix metalloproteinase-9 (MMP-9) inhibitors (Buchardt et al., 1999), selective aminopeptidase N (EC 3.4.11.2) inhibitor (Chen et al., 1999), inhibitors of D-Ala–D-Ala adding enzyme (Miller et al., 1998), dual enkephalin-degrading enzyme inhibitors (Chen et al., 2000), inhibitors of meso-diaminopimelic acid-adding enzyme (Zeng et al., 1998), mixed inhibitors of MMP-2, MMP-8, MMP-9 (Matziari et al., 2001).

The known method for the construction of phosphinic analogues of peptides (Fig. 1) usually consists in the synthesis of N-protected aminoalkylphosphonous component of pseudo-peptide as phosphorylic analogue of amino acid (X) with following Michael addition to suitably substituted acrylates and formation of pseudo-peptide fragment (Y) of desired molecules (Buchardt and Meldal, 2000; Chen et al., 1999, 2000; Matziari et al., 2001; Zeng et al., 1998). The synthesis of the aminoalkylphosphonous building blocks with the formation of the first phosphorus–carbon bond of pseudo-peptides can be carried out successfully by methods described earlier (Baylis et al., 1984; McCleery and Tuck, 1989). In this case the protection of the nitrogen and phosphorus atoms of aminoalkylphosphonous building blocks are necessary, and therefore the synthesis of aminoalkylphosphinic acid fragment (X) of pseudo-peptide represents a few steps process.

The synthesis of the pseudo-peptide fragment (Y) with the formation of the second phosphorus–carbon bond

* Communication IV (Ragulin, 2004b).



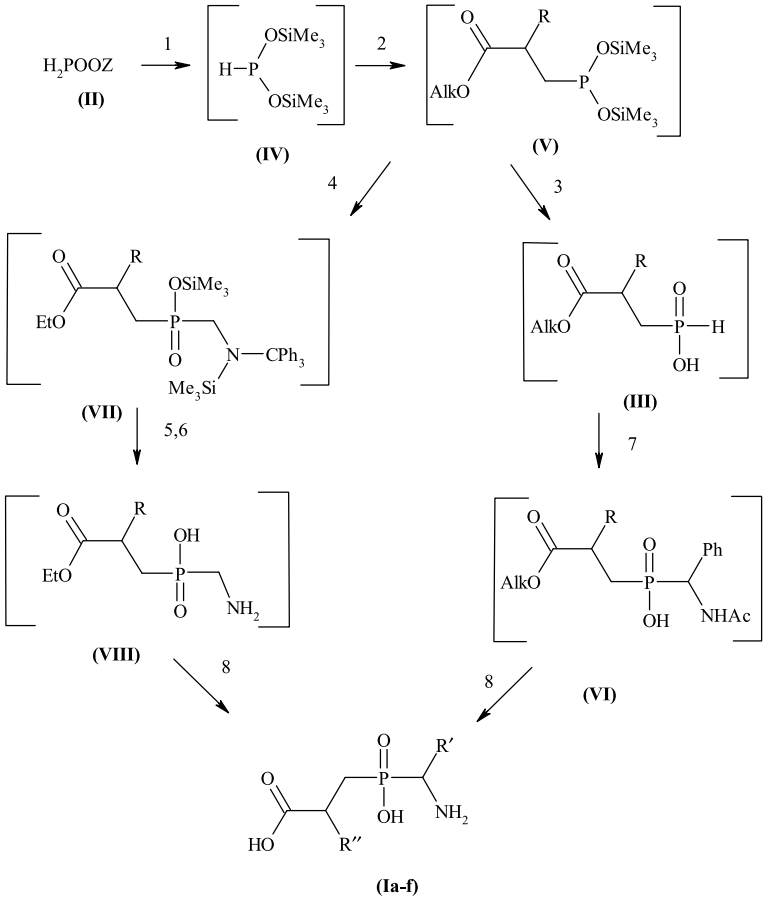
A. Phosphinic acid pseudo-dipeptide B. Peptide fragment

Fig. 1.

usually is carried out by the addition of trimethylsilyl esters of aminoalkylphosphonous acid to acrylates (Boyd et al., 1990). However, this general procedure have some limitations for complicated aminoalkylphosphonous building blocks. For example, many attempts to synthesize phosphinic pseudo-AspAla-dipeptide by addition of trimethylsilyl esters of aspartyl aminophosphonous acid to ethyl methacrylate were unsuccessful (Georgiadis et al., 1999). In this connection, the development of alternative methods for the construction of pseudo-peptides can produce a simple and perspective way to novel inhibitors for enzymes.

Results and discussion

We would like to propose the another synthetic route to the pseudo-α,α-dipeptides with the reverse construction of desired molecules, consisting in the addition of the hypophosphite to acrylic compounds and the formation of the first phosphorus–carbon bond with the following addition of the aminoacid fragment and the formation of



Z: NH_4 or K; R: H, Me, i-Bu, $CH_2C(O)OMe$, $CH_2CH_2C(O)OEt$
R′: Ph R″: Me (Ia), i-Bu (Ib), $CH_2C(O)OH$(Ic);
R′: H R″: H (Id), i-Bu (Ie), $CH_2CH_2C(O)OH$ (If)

1. $(Me_3Si)_2NH$ or $(Me_3Si)_2NH$, NH_4Cl; 2. EtO(O)C-C(R)=CH_2; 3. H_2O; 4. CH_2=$NCPh_3$; 5. EtOH; 6. 1N HCl, r.t.; 7. PhCH(O), $AcNH_2$, Ac_2O; 8. 6N HCl, reflux; Dowex 50W(H^+)

Scheme 1. Synthesis of pseudo-α,α-dipeptides (I)

the second phosphorus–carbon bond (Kurdyumova et al., 1997a; Ragulin et al., 2000, 2001).

This method for the synthesis of phosphinic acids can be more convenient procedure for the construction of both phosphorus–carbon bonds in ***one-pot*** process. We are developing this methodology for the synthesis of different functionally substituted phosphinic acids from hypophosphites (Ragulin and Tsvetkov, 1988; Ragulin et al., 1994; Kurdyumova et al., 1994, 1996, 1997a, b).

The procedure for the synthesis of 2-substituted 2-hydroxycarbonylethyl-1-aminoalkyl phosphinic acids (I) (pseudo α,α-dipeptides) from hypophosphite salts (II) as starting material is reported in this paper (Scheme 1). The proposed synthesis of phosphinic pseudo-peptides (I) can be represent as two-stage process. The key intermediates of the synthesis – phosphonous acids (III) were obtained at the first stage of the process as the result of the addition of the bis(trimethylsilyl)hypophosphite (IV) *in situ* to substituted acrylates and following hydrolysis of obtained corresponding trimethylsilylic esters of phosphonous acids (V).

Phosphonous acids (III) were used on the second stage of the synthesis of pseudo-peptides for the modified procedure (Oleksyszyn and Gruszecka, 1981) of the reaction of Kabachnik-Fields. The using of trimethylsilylic esters of phosphonous acids (III) for Kabachnik-Fields reaction can be satisfactory for benzylamine as amino-component of the reaction (Ragulin, 2004a), and therefore hydrogenation is required for the removal of the benzyl group and the isolation of the desired amino acid.

We have found that the using of acetamide as amino-component (Oleksyszyn and Gruszecka, 1981) for the interaction with phosphonous acids (III) *in situ* and benzaldehyde in acetic anhydride and the followed hydrolysis of products of Kabachnik-Fields reaction can be more simple procedure for the synthesis of amino phosphinic acids (**Ia–c**). It should be mentioned that the method is not stereoselective. Pseudo-phenylglycylpeptides (**Ia–c**) were isolated as thermodynamic mixture of diastereomers.

On the other side trimethylsilylic esters of phosphonous acids (V) is more preferable for the procedure of the addition to N-tritylmethanimine with formation of corresponding trimethylsilylic esters of N-trimethylsilyl-N-trityl phosphinic acids (VII) in according to procedure earlier proposed for bis(trimethylsilyl)hypophosphite (Jiao et al., 1994). The latter (VII) without isolation were subjected to alcoholysis and soft acid hydrolysis at room temperature (Scheme 1). The following hydrolysis of intermediated amino ether-acids (VIII) *in situ* leads to aminomethylphosphinic acids (Id–f) (pseudo-glycylpeptides).

2-Substituted 2-hydroxycarbonylethyl-1-aminoalkyl phosphinic acids (I) (pseudo-α,α-dipeptides) was isolated with 19–44% yield (based on ammonium or potassium hypophosphite) by using chromatography on Dowex 50W(H^+) (Scheme 1) as the final procedure of the process.

In conclusion, the proposed route for the construction of aminoalkylphosphinic acids (I) can be more convenient general procedure for the synthesis of pseudo-α,α-dipeptides.

Experimental section

General procedures

All of the compounds, for which spectral and analytical data are given, were homogenous by TLC. TLC analyses were performed using 0.2 mm silica gel F 254 (Merck) glass plates and Alufol plates (aluminium oxide neutral on aluminium foil as base) (Kavalier). The chromatograms were visualized under ultraviolet light or iodine vapor or ninhydrin solution and subsequent heating (for analysis of amino acids). All reactions involving moisture-sensitive reagents were performed under an atmosphere of dry argon. Used solvents for moisture-sensitive reactions were carefully dried. Ethyl α-i-butylacrylate was purchased from Chimex Ltd. (Russia). Ethyl acrylate, ethyl methacrylate and dimethyl itaconate were purchased from Acros Organics and Lancaster Synthesis Ltd. Diethyl α-methylene glutarate was prepared in according to earlier proposed procedure (Amri et al., 1989).

Ion-exchange chromatography was performed on Dowex 50 WX8-100 (Lancaster Synthesis Ltd.). Melting points were determined on a Boetius PHMK apparatus or in open glass capillaries and are uncorrected. The ^{1}H, ^{31}P and ^{13}C NMR spectra were recorded on a Bruker DPX-200 Fourier spectrometer. ^{31}P and ^{13}C NMR spectra are fully proton decoupled. ^{31}P NMR chemical shifts are reported on a δ scale (in ppm) downfield from 85% H_3PO_4.

The synthesis of 2-substituted 2-hydroxycarbonylethyl α-aminobenzyl phosphinic acids (**Ia–c**)

Potassium hypophosphite (0.10 mol), ammonium chloride (0.10 mol) and hexamethyldisilazane 0.15 mol were stirred together for 2 h at 120–130°C (Kurdiumova et al., 1996). The substituted acrylate (0.10 mol) slowly dropwise was added to precooled reaction mixture (5–10°C), which then was stirred for 2–3 h at 40°C and was cooled again to 5–10°C. Chloroform or dichloromethane (50–70 ml) was added to mixture and then 10 ml of 2N hydrochloric acid slowly dropwise was added to obtained solution. The organic phase was washed twice by 10 ml of 2N hydrochloric acid and dried over magnesium sulphate and the mixture was filtered. The filtrate was evaporated *in vacuo*. The process was controlled by NMR ^{31}P spectroscopy, obtained residue represented colourless or pale yellow oil containing 2-substituted 2-alkoxycarbonylethylphosphonous acid (III) (δ_P 31–35 ppm) (90–95%) and bis(2-substituted 2-alkoxycarbonylethyl)phosphinic acid of symmetrical structure (δ_P 45–50 ppm) (5–10%) (Kurdiumova et al., 1997), unreacted hypophosphorous acid was absent. Approximate yields of phosphonous acids (III) were 77–83% (based on starting potassium hypophosphite), and this oil was used for next transformations without additional purification and isolation of intermediated acids (III).

The mixture of corresponding phosphonous acid (III), acetamide and benzaldehyde in acetic anhydride {1:0.8:0.8:5 (molar equivalent)} was refluxed and stirred for 3–4 h (process was controlled by NMR ^{31}P spectroscopy). Cooled to r.t. mixture was evaporated *in vacuo* and residue was dissolved in chloroform and washed twice by 0.5N hydrochloric acid. The

chloroform solution was concentrated to give brown oil, which was filtered through celite and evaporated *in vacuo*. The NMR ^{31}P ($CDCl_3$) spectrum of the pale yellow residue represented two characteristic diastereomeric signals of desired N-acetyl derivatives (VI) (48–53 ppm) and singlet of mentioned above symmetrical phosphinic acids (about 50 ppm) and two characteristic diastereomeric signals (about 45–48 ppm), which can correspond to O-acetyl derivatives of α-hydroxyphosphinic acids. The presence of α-hydroxy-analogues can be caused by Abramov' reaction of phosphonous acid (III) and benzaldehyde.

This residue was subjected by acid hydrolysis with 6–8N hydrochloric acid, cooled reaction mixture was washed with chloroform and concentrated *in vacuo*. The residue was purified by using of column chromatography on Dowex 50W(H^+), (eluent – water, $0.5 \div 0.7$N HCl), ninhydrin-positive fractions were collected, evaporated *in vacuo* and the residue was treated by excess of propylene oxide in water/ethanol. The crystalline precipitate was filtered off and dried to afford (**Ia**, **b**). For isolation of hydrochlorides (**Ib**, **c**) eluate was concentrated and residue was treated by the mixture of 5N HCl and acetone (about $7 \div 9$:1). The crystalline precipitate was filtered off and dried to afford desired hydroclorides (**Ib**, **c**). Yields 29–37% (based on acetamide), total yield 19–24% (over five steps, based on potassium hypophosphite).

2-(Hydroxycarbonyl)propyl-α-aminobenzyl phosphinic acid (**Ia**)

Yield 33%; mp 207–210°C. ^1H NMR ($D_2O + DCl$, δ, ppm): 0.45 (d, 3H, J_{HH} *7.5 Hz*), 1.18 (m, 1H from PCH_2), 1.52 (m, 1H from PCH_2), 1.95 (m, 1H), 4.00 (d, 1H, J_{PH} *10.8 Hz*), 6.48 (br. s, 5H). ^{13}C NMR ($D_2O + DCl$, δ, ppm): 17.52 (d, $\underline{C}H_3$, *J 10.96 Hz*), 17.42* (d, $\underline{C}H_3$, *J 10.85 Hz*), 28.98 (d, $P\underline{C}H_2CH$, *J 94.41 Hz*), 29.07* (d, $P\underline{C}H_2CH$, *J 95.11 Hz*), 32.72 (d, $\underline{C}H$-CO, *J 4.83 Hz*), 52.93* (d, $P\underline{C}HN$, *J 92.90 Hz*), 53.00 (d, $P\underline{C}HN$, *J 93.41 Hz*), 127.12 (d, $PCH\underline{C}$, *J 4.53 Hz*), 127.22* (d, $PCH\underline{C}$, *J 4.53 Hz*), 128.49* (s), 128.56 (s), 128.60 (s), 128.94 (s), 128.98 (s) 129.02* (s), 178.23 (d, CO, *J 7.34 Hz*). ^{31}P NMR ($D_2O + DCl$, pH ~ 1, δ, ppm): 41.9*, 41.8 (1:2). Found: C 51.33, 51.09; H 6.31, 6.38; N 5.47, 5.51; P 11.81, 11.89. Calc. for $C_{11}H_{16}NO_4P$: C 51.36, H 6.27, N 5.45, P 12.04.

2-Hydroxycarbonyl-4-methylamyl-α-aminobenzyl phosphinic acid (**Ib**)

Yield 37%; mp 199–202°C. ^1H NMR ($D_2O + NaOD$, pH ~ 7, δ, ppm): 0.72–0.87 (m, 6H), 1.15 (m, 1H), 1.35 (m, 2H), 1.63 (m, 1H, one of PCH_2), 1.88 (m, 1H, one of PCH_2), 2.48 (m, 1H), 3.92 (d, 1H, J_{PH} *10.6 Hz*), 7.32 (br. s, 5H). ^{13}C NMR ($D_2O + NaOD$, pH ~ 7, δ, ppm): 21.36* (s, $\underline{C}H_3$), 21.53 (s, $\underline{C}H_3$), 23.09 (s, $\underline{C}H_3$), 23.33* (s, $\underline{C}H_3$), 26.27 (s, $\underline{C}HCH_3$), 26.48* (s, $\underline{C}HCH_3$), 31.21 (d, PCH_2, *J 87.77 Hz*), 41.53* (s, $\underline{C}HCO$), 41.78 (s, $\underline{C}HCO$), 44.01 (d, $CH\underline{C}H_2CH$, *J 8.10 Hz*), 55.67 (d, $P\underline{C}HN$, *J 89.28 Hz*), 56.47* (d, $P\underline{C}HN$, *J 89.28 Hz*), 127.38, 127.86, 128.00, 128.10, 128.54, 138.58, 139.11* (s, for all), 185.38 (d, $\underline{C}O$, *J 8.25 Hz*). ^{31}P NMR ($D_2O + NaOD$, pH ~ 7, δ, ppm): 39.4*, 40.0 (1:2). Found: C 56.29, 56.17; H 7.31, 7.23; N 4.47, 4.51; P 10.21, 10.17. Calc. for $C_{14}H_{22}NO_4P$: C 56.18, H 7.41, N 4.68, P 10.35.

Mp 185–187°C (**Ib** as hydrochloride). ^1H NMR (CD_3OD, δ, ppm): 0.75–0.92 (m, 6H), 1.37 (m, 1H), 1.57 (m, 2H), 1.88 (m, 1H, one of PCH_2), 2.23 (m, 1H, one of PCH_2), 2.71 (m, 1H), 4.70 (d, 1H, J_{PH} *11.7 Hz*), 7.52 (m, 5H). ^{13}C NMR (CD_3OD, δ, ppm): 20.47 (s, $\underline{C}H_3$), 21.14 (s, $\underline{C}H_3$), 25.03 (s, $\underline{C}HCH_3$), 28.71 (d, $P\underline{C}H_2CH$, *J 95.57 Hz*), 36.69 (d, $\underline{C}H$-CO, *J 4.48 Hz*), 42.35 (d, $CH\underline{C}H_2CH$, *J 11.47 Hz*), 53.36 (d, $P\underline{C}H$, *J 93.41 Hz*), 127.66 (d, $PCH\underline{C}$, *J 4.53 Hz*), 127.93* (d, $PCH\underline{C}$, *J 5.03 Hz*), 128.41, 128.44, 128.68, 128.71, 128.73*, 130.56 (s, for all), 176.74 (d, $\underline{C}O$, *J 5.28 Hz*). ^{31}P NMR (CD_3OD): 41.2, 41.4* (2:1). Found: C 50.31, 50.11; H 6.81, 6.83; Cl 10.46, 10.53; P 9.13, 9.17. Calc. for $C_{14}H_{22}NO_4P \cdot HCl$: C 50.08, H 6.90, Cl 10.56, P 9.22.

2,3-Bis(hydroxycarbonyl)propyl-α-aminobenzyl phosphinic acid (**Ic**)

Yield (29%; mp 188–191°C (hydrochloride). ^1H NMR (D_2O, pH ~ 1, δ, ppm): 1.58 (m, 1H), 1.92 (m, 1H), 2.52 (m, 2H), 2.77 (m, 1H), 4.31 (d, 1H, J_{PH} *10.7 Hz*), 7.30 (br. s, 5H). ^{13}C NMR (D_2O, pH ~ 1, δ, ppm): 29.11 (d, $P\underline{C}H_2$, *J 96.58 Hz*), 35.76 (d, $\underline{C}HCO$, *J 3.59 Hz*), 36.65 (d, $\underline{C}H_2CO$, *J 7.21 Hz*), 55.05 (d, $P\underline{C}HN$, *J 90.03 Hz*), 128.02, 128.09, 128.18, 129.54, 131.70, 131.77 (s, for all), 175.82 (s, $\underline{C}OCH_2$), 178.11 (d, $\underline{C}OCH$, *J 10.06 Hz*), 178.75* (d, $\underline{C}OCH$, *J 10.06 Hz*). ^{31}P NMR (D_2O, pH ~ 1, δ, ppm): 33.1*, 33.3 (5:2). Found: C 40.43, 40.31; H 5.44, 5.47; Cl 9.96, 9.87; P 8.53, 8.45. Calc. for $C_{12}H_{16}NO_6P \cdot HCl \cdot H_2O$: C 40.52, H 5.38, Cl 9.97, P 8.71.

The synthesis of 2-substituted 2-hydroxycarbonylethyl aminomethyl phosphinic acids (**Id–f**)

The suitably substituted acrylate (0.11 mol) slowly dropwise was added to precooled to r.t. bis(trimethylsilyl)hypophosphite (IV) *in situ* easily formed from ammonium hypophosphite (0.10 mol) and silazane(0.15 mol) (Voronkov and Marmur, 1970) and then the mixture was stirred at 40°C for 2–3 h {until bis(trimethylsilyl)hypophosphite (IV) (δ_P 142 ppm) was disappeared, the process was controlled by NMR^{31}P spectroscopy}. N-Tritylmethanimine (0.09 mol) in 20 ml of dry toluene was added to precooled to r.t. reaction mixture, which further was refluxed under stirring for 5–7 h. The mixture was evaporated *in vacuo* and the residue was dissolved in 30–50 ml of chloroform or ether. Then 100 ml of 1N hydrochloric acid was slowly dropwise added under vigorous stirring to obtained solution. The aqueous acid phase was washed by 30 ml of chloroform or ether and was evaporated *in vacuo*. The residue represented the mixture of the desired aminomethylphosphinic ether-acid (VIII) (δ_P 36–37 ppm) (70–80%), bis(2-substituted 2-alkoxycarbonylethyl)phosphinic acid of symmetrical structure (δ_P 45–50 ppm) (~10–15%) (Kurdiumova et al., 1997), unreacted phosphonous acid (III) (δ_P 28–35 ppm) (~10–15%). The residue was refluxed with 6–8N hydrochloric acid, cooled reaction mixture was washed with chloroform and concentrated *in vacuo*. The residue was purified by using column chromatography on Dowex 50W(H^+) (eluent – water, $0.5 \div 0.7$N HCl), ninhydrin-positive fractions were collected, evaporated *in vacuo* and residue was crystallized from acid water–acetone solution and afford hydrochloride (**Id**). The treatment of the residue by excess of propylene oxide in water/ethanol gave the crystalline precipitate which was filtered off and dried to afford (**Ie**, **f**). Yields 31–44% (over five steps, based on ammonium hypophosphite).

2-Hydroxycarbonylethyl-aminomethyl phosphinic acid (**Id**)

Yield (31%) (hydrochloride); mp 132–135°C. ^1H NMR (D_2O, ppm): 1.90 (dt, 2H, J_{PH} *14.4 Hz*), 2.55 (dt, 2H, J_{PH} *13.6 Hz*), 3.07 (d, 2H, J_{PH} *10.2 Hz*). ^{13}C NMR (D_2O, δ, ppm).: 23.90 (d, $P\underline{C}H_2C$, *J 97.28 Hz*), 26.75 (d, $C\underline{C}H_2CO$, *J 3.62 Hz*), 37.23 (d, $P\underline{C}H_2N$, *J 93.81 Hz*), 176.95 (d, CO, *J 13.53 Hz*). ^{31}P NMR (D_2O, pH ~ 1, δ, ppm): 37.5. Found: C 23.48, 23.37; H 5.43, 5.38; Cl 17.36, 17.47; P 15.13, 15.38. Calc. for $C_4H_{10}NO_4P \cdot HCl$: C 23.60, H 5.45, Cl 17.42, P 15.22.

2-Hydroxycarbonyl-4-methylamyl-aminomethyl phosphinic acid (**Ie**)

Yield (44%), mp 222–224°C (with decomp.). ^1H NMR ($D_2O + DCl$, δ, ppm): 0.64 (d, 3H, J_{HH} *6.4 Hz*), 0.70 (d, 3H, J_{HH} *6.4 Hz*), 1.21 (m, 1H), 1.37 (m, 2H), 1.75–2.15 (m, 2H), 2.61 (m, 1H), 3.07 (d, 2H, J_{PH} *10.0 Hz*). ^{13}C NMR (D_2O, δ, ppm): 21.57 (s, $\underline{C}H_3$), 22.13 (s, $\underline{C}H_3$), 25.54 {s, $\underline{C}H(CH_3)$}, 30.82 (d, $P\underline{C}H_2C$, *J 95.57 Hz*), 37.47 (d, $P\underline{C}H_2N$, *J 94.36 Hz*), 37.68 (d, $\underline{C}HCO$, *J 4.38 Hz*), 42.81 (d, $CH\underline{C}H_2CH$ *J 12.37 Hz*), 176.84 (d, CO, *J 4.97 Hz*). ^{31}P NMR ($D_2O + DCl$, pH ~ 1, δ, ppm): 40.9. Found: C 42.89, 42.83; H 8.19, 8.23; N 6.17, 6.23, P 13.67, 13.61. Calc. for $C_8H_{18}NO_4P$: C 43.05, H 8.13, N 6.28, P 13.88.

2,4-Bis(hydroxycarbonyl)butyl-aminomethyl phosphinic acid (**If**)

Yield {as 3:1 EtOH solvate} (41%); mp 165–168°C. ^{1}H NMR ($D_2O + DCl$, δ, ppm): 1.20 (t, 3/3H), 1.75–2.30 (m, 2H + 2H), 2.48 (t, 2H), 2.77 (s, br., 1H), 3.08 (d, 2H, J_{PH} *9.9 Hz*), 3.48 (q, 2/3H). ^{13}C NMR (D_2O, δ, ppm): 17.12 (s, $\underline{C}H_3$), 28.99 (d, $C\underline{C}H_2CH$, *J 12.07 Hz*), 31.86 (s, $\underline{C}H_2CO$), 32.42 (d, $P\underline{C}H_2CH$, *J 96.07 Hz*), 38.34 (d, $P\underline{C}H_2N$, *J 90.54 Hz*), 40.06 (d, $\underline{C}HCO$, *J 2.75 Hz*), 57.75 (s, $\underline{C}H_2O$), 178.33 (s, $\underline{C}OCH_2$), 180.23 (d, *J 5.95 Hz*, $\underline{C}OCH$). ^{31}P NMR ($D_2O + DCl$, pH ∼ 1, δ, ppm): 31.4. Found: C 36.07, 35.91; H 6.29, 6.11; N 5.37, 5.33; P 12.07, 11.93. Calc. for $C_7H_{14}NO_6P \cdot 1/3C_2H_5OH$: C 36.18, H 6.34, N 5.50, P 12.17.

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References

Amri H, Rambaud M, Villiers J (1989) A short large scale synthesis of (±) sarkomycin esters. Tetrahedron Lett 30: 7381–7382

Baylis EK, Campbell CD, Dingwall JG (1984) 1-Aminoalkylphosphonous acids. Part 1. Isosters of the protein amino acids. J Chem Soc Perkin Trans I: 2845–2853

Boyd EA, Corless M, James K, Regan AC (1990) A versatile route to substituted phosphinic acids. Tetrahedron Lett 33: 813–814

Buchardt J, Ferreras M, Krog-Jensen C, Delaisse J-M, Foged NT, Meldal M (1999) Phosphinic peptide matrix metalloproteinase-9 inhibitors by solid-phase synthesis using a building block approach. Chem Eur J 5: 2877–2884

Collinsova M, Jiracek J (2000) Phosphinic acid compounds in biochemistry, biology and medicine. Current Medicinal Chemistry 7: 629–647

Chen H, Roques BP, Fournie-Zaluski M-C (1999) Design of the first highly potent and selective aminopeptidase N (EC 3.4.11.2) inhibitor. Bioorg Med Chem Lett 9: 1511–1519

Chen H, Noble F, Mothe A, Meudal H, Coric P, Danascimento S, Roques BP, George P, Fournie-Zaluski M-C (2000) Phosphinic derivatives as new dual enkephalin-degrading enzyme inhibitors: synthesis, biological properties, and antinociceptive activities. J Med Chem 43: 1398–1408

Georgiadis D, Matziari M, Vassiliou S, Dive V, Yiotakis A (1999) A convenient method to synthesize phosphinic peptides containing an aspartyl or glutamyl aminophosphinic acid. Use of the phenyl group as the carboxyl synthon. Tetrahedron 55: 14635–14648

Jiao X-Y, Verbruggen C, Borloo M, Bollaert W, DeGroot A, Dommisse R, Haemers A (1994) A novel synthetic route to 1-aminoalkylphosphinic acids. Synthesis: 23–24

Kurdyumova NR, Ragulin VV, Tsvetkov EN (1994) The synthesis of acyclic and cyclic dialkylphosphinic acids from ammonium hypophosphite. Russ J Gen Chem (Engl Transl) 64: 380–383

Kurdyumova NR, Ragulin VV, Tsvetkov EN (1996) The synthesis of phosphinic acids from potassium hypophosphite. Russ J Gen Chem (Engl Transl) 66: 750–752

Kurdyumova NR, Ragulin VV, Tsvetkov EN (1997a) The synthesis of the Phosphinothricine and other phosphorylic analogues of glutamic acid. Mendeleev Commun 2: 69–70

Kurdyumova NR, Rozhko LF, Ragulin VV, Tsvetkov EN (1997b) Method for the synthesis of phosphinic acids from hypophosphites. I. Acrylates as Unsaturated Component. Russ J Gen Chem (Engl Transl) 67: 1852–1856

Matziari M, Georgiadis D, Dive V, Yiotakis A (2001) Convenient synthesis and diversification on dehydroalanyl phosphinic peptide analogues. Org Lett 3(5): 659–662

McCleery PP, Tuck B (1989) Synthesis of 1-aminoalkylphosphinic acids. Part 2. An alkylation approach. J Chem Soc Perkin Trans I: 1319–1329

Miller DJ, Hammond SM, Anderluzzi D, Bugg TDH (1998) Aminoalkylphosphinate inhibitors of D-Ala-D-Ala adding enzyme. J Chem Soc Perkin Trans I: 131–142

Oleksyszyn J, Gruszecka E (1981) Amidoalkylation of phosphorous acid. Tetrahedron Lett 22(36): 3537–3540

Ragulin VV (2001) The synthesis of phosphinic analoge of glutamylglycine. Russ J Gen Chem 71: 1928–1929

Ragulin VV (2004a) One-pot synthesis of α-aminophosphinic acids. Russ J Gen Chem 74: 154–156

Ragulin VV (2004b) The method for the synthesis of phosphinic acids from hypophosphites. IV. The synthesis of pseudo-γ-glutamylglycine and its enantiomers. Russ J Gen Chem 74: 1273–1278

Ragulin VV, Tsvetkov EN (1988) A simple method for the synthesis of dialkylphosphinic acids. Bull Acad Sci USSR Div Chem Sci 11: 2652

Ragulin VV, Kurdyumova NR, Tsvetkov EN (1994) Phosphorus – containing aminocarboxylic acids. Communication V. Method for synthesis of phosphinic acids. Phosphorus, Sulfur and Silicon 88: 271–274

Ragulin VV, Rozhko LF, Saratovskikh IV, Zefirov NS (2000) The synthesis of 2-(hydroxycarbonyl)ethyl-3-amino-3-(hydroxycarbonyl)propyl phosphinic acid. Patent of Japan 2000-18568. Jan 27.2000; Chem Abs 2001, AN 2001: 552806

Voronkov MG, Marmur LZ (1970) Trialkylsilylic esters of hypophosphorous acid. Zh Obshch Khim 40(9): 2135–2136

Zeng B, Wong KK, Pompliano DL, Reddy S, Tanner ME (1998) A phosphinate inhibitor of the *meso*-diaminopimelic acid-adding enzyme (MurE) of peptidoglycan biosynthesis. J Org Chem 63: 10081–10086

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