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Phosphorus-containing Aminocarboxylic Acids: XIV.[1] Synthesis of Analogs of α-Substituted Glutamic Acid

I. V. Saratovskikh and V. V. Ragulin

Institute of Physiologically Active Substances, Russian Academy of Sciences, Chernogolovka, Moscow oblast, Russia

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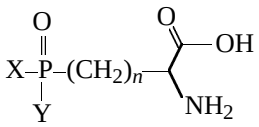
Abstract — Addition of Schiff bases derived from amino acid esters to appropriate vinylphosphoryl compounds, followed by hydrolysis of the adducts formed gives a series of new α-alkylated phosphorus-containing α-aminocarboxylic acids, viz. phosphonic and phosphinic analogs of glutamic acid.

Synthesis of phosphoryl analogs of natural amino acids and peptides represents a prospective route to potential physiologically active compounds [2–7]. Substitution of the carbonyl group in a natural amino acid molecule by phosphoryl leads to aminophosphonic acids [2–4]. The key step in constructing aminophosphinic acid analogs of peptides involves substitution of the amide fragment C(O)NH by methylenephosphoryl $CH_2P(O)$ [5–7].

Phosphorus-containing aminocarboxylic acids of general formula **I** possess diverse biological activity. Phosphonic analogs (X = Y = OH), such as 2-amino-4-phosphonobutyric acid (*n* = 2), and glutamic acid gomologs, such as 2-amino-5-phosphonovaleric (*n* = 3) and 2-amino-7-phosphonoheptanoic (*n* = 5) acids, are known as potent neuroprotectors [2–4].



I

The modification of the carbon chain in "canonical" molecule **I**, including the synthesis of unsaturated analogs [8, 9] and the introduction of aromatic [10, 11], pyperidine [12], and piperazine [13, 14] fragments, gave compounds with a high antispasmodic activity. Phosphinothricin, 2-amino-4-(methylphosphino)butyric acid (X = Me, Y = OH), the best phosphinic analog of glutamic acid, is glutaminsynthetase inhibitor and a highly active low-toxicity herbicide [15–17]. Glutamic acid analogs and homologs bearing a phosphine oxide fragment have also been described [18]. Modification of the phosphorus-containing fragment and hydrocarbon chain in "canonical" molecule **I** is the most studied approach to constructing new phosphorus-containing aminocarboxylic acids [8–20]. Over the past years, the physiologic activity of α-substituted phosphorus-containing α-aminocarboxylic acids, specifically α-methyl-4-phosphonophenylglycine and 2-amino-2-methyl-4-phosphonobutyric acids, as selective antagonists of metabotropic glutamate receptors has been reported [21–23]. In this respect, modification of the aminocarboxylic fragment in molecule **I** can open up a prospective route in searching for new agonists and antagonists of metabotropic glutamate receptors, as well as potential inhibitors of natural enzymes in the series of phosphorus-containing aminocarboxylic acids [24–26].

This work is devoted to the synthesis of new ω-phosphorylated α-alkyl-α-aminocarboxylic acids **II** (Scheme 1) along Scheme 2. Phosphonic glutamic acid analogs **IIb**–**IId** are homologs of 2-amino-2-methyl-4-phosphonobutyric acid (**IIa**), and, therefore, they offer interest as potential antagonists and agonists of metabotropic glutamate receptors [21–25]. Aminophosphonic acids with a hydroxycarbonylethyl fragment [**IIf**–**IIh**, X = OH, Y = $CH_2CH_2C(O)OH$] are phosphinic analogs of α-substituted γ-glutamylglycines [6, 7]. In this case, the role of pseudoglycine belongs to the propionic fragment, while the fragment of the phosphoryl analog of glutamic acid bears an α-substituent (Z). Phosphinic analogs of glutamic acid (**IIi** and **IIj**) can be considered as α-substituted lipophylic analogs of the herbicide glufosinate (phosphinothricin) [15–17].

Schiff bases derived from amino acid esters (compounds **III**) satisfactorily add to diethyl vinylphosphonate (**IVa**), ethyl [2-(ethoxycarbonyl)ethyl](vinyl)-phosphinate (**IVb**), and ethyl (2-phenylethyl)(ethyl)-phosphinate (**IVc**) in THF in the presence of potassium and cesium carbonates (Scheme 2). The use of

[1] For communication XIII, see [1].

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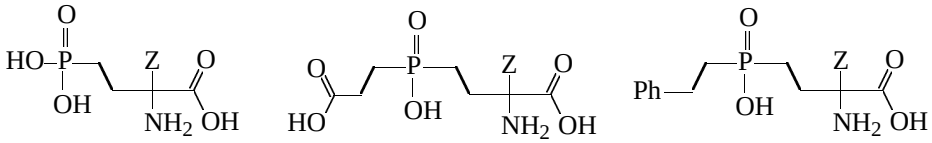
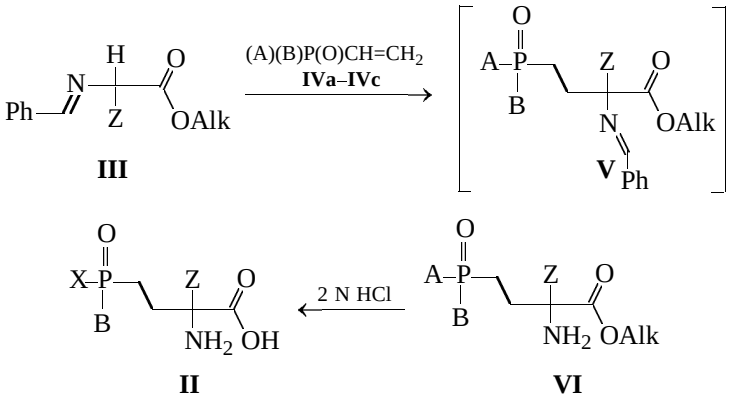
Scheme 1.



IIa–IId **IIf–IIh** **IIi, IIj**

[27] vinylphosphoryl compounds as alkylating agents instead of bromoethylphosphonate and bromoethylphosphine oxide results in slightly higher yields of the target amino acids.

Scheme 2.



III **V** **II** **VI**

The resulting alkylated Schiff bases, α-alkyl-α-benzylideneamino-ω-(dialkylphosphoryl)alkylcarboxylic esters **V**, could be easily converted *in situ* to desired amino acids **II** by means of acid hydrolysis followed by cation-exchange chromatography. The mild acid hydrolysis of esters **V** at room temperature results in formation of (dialkylphosphoryl)alkylcarboxylic esters **VI**. These esters can be isolated pure as, for example, with aminophosphine oxide **VIa** or aminophosphinic acid **VIf**.

The proposed synthetic route allows modification of the "canonical" structure of ωphosphorylalkyl-α-aminocarboxylic acids **I** [2] using a broad range of amino acid ester Schiff bases **II** and diverse vinyl- and ω-haloalkylphosphoryl compounds [27–30].

EXPERIMENTAL

The ^{1}H and ^{31}P NMR spectra were recorded on a Bruker DPX 200 Fourier spectrometer with TMS as internal and 85% H_3PO_4 as external references. The melting points were measured on a Boetius RNMK stage or in an open capillary tube. Thin-layer chromatography was performed on Silufol plates, eluent 5:1:1 chloroform–toluene–acetone, Merck UV254 plates (layer thickness 0.2 mm), and Kavalier Alufol plates (neutral alumina on an aluminum foil, eluent 5:1:1 1-butanol–acetic acid–water; development under UV light after treatment with iodine vapor or with ninhydrin followed by heating (for amino acids). Column chromatography was perfomed on Dowex 50WX8-200 (Lancaster) or Diasorb-Sulfo (BioKhimMak) cationites. Diethyl vinylphosphinate [28] and diphenyl(vinyl)phosphine oxide [31] were prepared by published procedures. Ethyl [2-(ethoxycarbonyl)ethyl](vinyl)phosphinate (**IVb**) [32] and ethyl (2-phenylethyl)(vinyl)phosphinate (**IVc**) [29] were prepared by a synthetic procedure we developed previously for vinylphophoryl compounds. The products were purified on Celite filter aid (Lancaster) and a mixture of silica gel L100/160 (Chemapol) with Brockmann neutral alumina (10–20 weight %). Schiff bases **III** were prepared by the reaction of methyl or ethyl esters of corresponding amino acid hydrochlorides with benzaldehyde, according to the procedures in [33–35].

2-Amino-2-methyl-4-phosphonobutyric acid (IIa, X = Y = OH, Z = Me). A mixture of 11.3 g of diethyl vinylphosphonate, 10.6 g of ethyl 2-(benzylideneamino)propanoate (prepared from alanine ethyl

ester hydrochloride and benzaldehyde), and 17.0 g of potassium carbonate was stirred in 40 ml of boiling THF with 1.0 g of tetrabutylammonium bromide until the Schiff base (R_f 0.8) disappeared from the chromatogram of the reaction mixture (about 15 h), the process was monitored by TLC in 5 : 1 : 1 chloroform–acetone–toluene. After cooling, inorganic salts precipitated and were filtered off, the filtrate was evaporated, the residue was dissolved in 50 ml of chloroform and washed with water (2 × 10 ml) until neutral washings. The organic phase was evaporated, and the oily residue was dissolved in 70 ml of 8N HCl. The solution was refluxed for 13–15 h, cooled, washed with ether (2 × 20 ml), and evaporated in a vacuum. The residue was chromatographed on a cationite (H^+, eluent $H_2O \cdot 0.5$ N HCl), fractions with a positive ninhidrin reaction were concentrated and treated with excess (ca. 4 ml) of propylene oxide in aqueous ethanol (1 : 4). Yield 5.7 g (55.4% per taken base). ^{31}P NMR spectrum (D_2O): δP 24.5 ppm. Found, %: C 30.46, 30.73; H 6.04, 5.90; N 6.87, 6.93. $C_5H_{12} \cdot NO_5P$. Calculated, %: C 30.46; H 6.14; N 7.11.

2-Amino-2-isopropyl-4-phosphonobutyric acid (IIb, X = Y = OH, Z = *i*-Pr). A mixture of 4.0 g of diethyl vinylphosphonate, 4.4 g of methyl 2-(benzylidenamino)-3-methylbutyrate (prepared from valine methyl ester hydrochloride and benzaldehyde), 7.0 g of potassium carbonate, and 1 g of tetrabutylammonium bromide was stirred in 40 ml of THF under reflux for 15 h, after which 3.0 g of cesium carbonate was added, and stirring was continued for 10–15 h. The reaction mixture was cooled and filtered (reaction progress was monitored by TLC and ^{31}P NMR). The filtrate was evaporated in a vacuum, and the residue was dissolved in 50 ml of chloroform, washed with water (3 × 10 ml, pH 7), and evaporated. The residue was treated with 30 ml of 8 N HCl, and the mixture was refluxed for 15 h. The reaction mixture was cooled and extracted with ether (3 × 20 ml). The aqueous layer was evaporated in a vacuum. The residue was chromatographed on a strongly acidic cationite (H^+), the eluent acidity was gradually increased (eluent H_2O and 1–1.5 N HCl). Fractions showing a positive ninhydrin reaction was evaporated, dissolved in aqueous ethanol, treated with 3.0 ml of propylene oxide, and evaporated in a vacuum. The oily residue was additionally purified by chromatography on a cationite (H^+) (eluent H_2O) and recrystallization from aqueous acetone (1 : 3). Yield 2.0 g (43.9% per taken base), mp 231–234°C. ^{1}H NMR spectrum (D_2O), δ, ppm: 0.93 d (3H, CH_3, *J* 6 Hz), 0.96 d (3H, CH_3, *J* 6 Hz), 1.56 m (2H, CH_2), 2.10 m (3H, CH_2 + CH). ^{31}P NMR spectrum (D_2O): δ_P 24.0 ppm. Found, %: C 37.05, 37.24; H 7.34, 7.33; P 13.35, 13.43. $C_7H_{16}NO_5P$. Calculated, % : C 37.34; H 7.16; P 13.75.

2-Amino-2-phenyl-4-phosphonobutyric acid (IIc, X = Y = OH, Z = Ph). To a mixture of 4.1 g diethyl vinylphosphonate and 8 g of potassium carbonate in 10 ml of THF, 4 g of methyl 2-(benzylideneamino)phenylacetate (prepared from phenylglycin methyl ether hydrochloride and benzaldehyde) and 0.5 g tetrabutylammonium bromide in 10 ml of THF were added. The reaction mixture was stirred in THF under reflux for 15 h, 3.0 g of cesium carbonate was added, and stirring was continued for 10 h (reaction progress was monitored by TLC and ^{31}P NMR). After cooling, the reaction was cooled, filtered, and treated as described for **IIa**. Amino acid **IIc** was recrystallized from 5 : 1 ethanol–ether and recrystallized from aqueous ethanol (1 : 5). Yield 1.5 g (36.6% per taken Schiff base), mp 247–249°C. ^{1}H NMR spectrum (D_2O + DCl), δ, ppm: 1.47 m (2H, CH_2), 2.25 m (2H, CH_2), 7.15 m (5H, Ph). ^{31}P NMR spectrum (D_2O + DCl), δ_P, ppm: 28.1. Found, %: C 44.36, 44.54; H 5.24, 5.48; N 11.14, 11.37. $C_{10}H_{14}NO_5P \cdot 0.5H_2O$. Calculated, % : C 44.78; H 5.64; P 11.55.

2-Amino-2-benzyl-4-phosphonobutyric acid (IId, X = Y = OH, Z = CH_2Ph). A mixture of 4.6 g of diethyl vinylphosphonate, 6.2 g of methyl 2-(benzylideneamino)-3-phenylpropanoate (prepared from phenylalanine methyl ester hydrochloride and benzaldehyde), 15.1 g of cesium carbonate, and 0.5 g of tetrabutylammonium bromide was stirred in 20 ml of THF under reflux for 18–20 h. After the reaction had been complete (reaction progess was followed by TLC and ^{31}P NMR), the reaction mixture was cooled and filtered. The filtrate was evaporated in a vacuum, the residue was dissolved in 50 ml of chloroform, washed with water (3 × 10 ml), and evaporated. The oily residue was treated with 30 ml of 8 N HCl, and the mixture was refluxed for 15 h. After cooling, the mixture was extracted with benzene (2 × 20 ml) and ether (2 × 20 ml), and the acidic water layer was evaporated in a vacuum. The residue was dissolved in aqueous ethanol (1 : 4) and treated with 3.0 ml of epichlorohydrin. The partially crystalline precipitate comprising primarily the free amino acid (^{1}H and ^{31}P NMR data) was chromatographed on Diasorb-Sulfo (H^+) (eluent water). Fractions showing a positive ninhydrin reaction were evaporated and recrystallized from 5 : 1 ethanol–ether and additionally recrystallized from aqueous ethanol (1 : 5). Yield 2.8 g (44.3% per taken Schiff base, mp 264–267°C. ^{1}H NMR spectrum (D_2O + DCl), δ, ppm: 1.35 m (2H, CH_2), 1.75 m (2H, CH_2), 2.62 d (1H, CH_2Ph), 2.90 d (1H, CH_2Ph), 6.73 m (2H, Ph) and 6.87 m (3H, Ph). ^{31}P NMR spectrum (D_2O + DCl): δ_P 28.7 ppm. Found, %: C 48.60,

48.30; H 6.23, 6.33; P 11.23, 11.54. $C_{11}H_{16}NO_5P$. Calculated, % : C 48.36; H 5.90; P 11.34.

2-Amino-2-methyl-4-(diphenylphosporyl)butyric acid (IIe, X = Y = Ph, Z = Me). A mixture of 7.8 g of diphenyl(vinyl)phosphine oxide, 11.0 g of potassium carbonate, 6.5 g of ethyl 2-(benzylideneamino)-propanoate (prepared from alanine ethyl ester hydrochloride and benzaldehyde), and 1.5 g of tetrabutylammonium bromide in 45 ml of THF was stirred under reflux for 12 h (reaction progress was followed by TLC and ^{31}P NMR), cooled, and filtered. The filtrate was evaporated in a vacuum and partitioned between 50 ml of chloroform and 50 ml of water. The aqueous layer was neutralized to pH 7 and extracted with chloroform (2 × 20 ml). The combined organic extract was evaporated, and the residue was dissolved in 30 ml of diethyl ether, 100 ml of 2 N HCl was added, and the resulting mixture was vigorously stirred for 4–5 h. The acidic aqueous layer was washed with ether (2 × 20 ml) and evaporated. The residue was dissolved in 20 ml of ethanol and treated with 5 ml of propylene oxide. The reaction mixture was stirred at 40–50°C for 10 min and evaporated. The residue was crystallized in succession from ether and 1 : 1 ethanol–ether to obtain 7.9 g (84.9% per taken Schiff base) of **ethyl 2-amino-2-methyl-4-(diphenylphosphoryl)butyrate (VIe, A = B = Ph, Z = Me, Alk = Et),** mp 137–139°C. ^{1}H NMR spectrum (D_2O), δ, ppm: 1.10 t (3H, CH_3), 1.44 s (3H, CH_3), 2.04 m (2H, CH_2), 2.40 m (2H, CH_2), 4.13 q (2H, CH_2O), 7.50 m (10H, Ph). ^{31}P NMR spectrum (D_2O), δ_P, ppm: 40.2. Found, %: C 60.09, 59.46; H 7.19, 7.48; P 8.30, 8.54. $C_{19}H_{24}NO_3P \cdot 2H_2O$. Calculated, %: C 59.83; H 7.40; P 8.12.

A mixture of 5.3 g of amino ester **VIa** and 20 ml of 8 N HCl was refluxed for 10 h. After cooling, the mixture was washed with ether (2 × 10 ml) and evaporated in a vacuum. The residue was dissolved in aqueous ethanol (1 : 10) and treated with 5 ml of propylene oxide to obtain 3.7 g (85% per ester **VIa**) of compound **IIe**, mp 251–253°C. ^{1}H NMR spectrum (D_2O + DCl), δ, ppm: 1.38 s (3H, CH_3); 1.96 m (2H, CH_2); 2.44 m (2H, CH_2); 7.42 m (10H, Ph). ^{31}P NMR spectrum (D_2O + DCl): δ_P 40.3 ppm. Found, %: C 61.97, 61.91; H 6.59, 6.57; P 9.48, 9.44. $C_{17}H_{20}NO_3P \cdot 0.5H_2O$. Calculated, %: C 62.38; H 6.47; P 9.46.

2-Amino-2-methyl-4-[[2-(hydroxycarbonyl)-ethyl]phosphoryl]butyric acid (IIf, X = CH_2CH_2·C(O)OH, Y = OH, Z = Me). A mixture of 3.9 g of ethyl 2-(benzylideneamino)propanoate (prepared from alanine ethyl ester hydrochloride and benzaldehyde), 4.8 g of ethyl [2-(ethoxycarbonyl)ethyl](vinyl)phosphinate (**IVb**), 7.0 g of potassium carbonate, and 1.0 g of tetrabutylammonium bromide was stirred in 20 ml of THF under reflux for 15 h, after which 2 g of cesium carbonate was added, and stirring was continued until the Schiff base disappeared disappeared from the chromatogram of the reaction mixture (R_f 0.8) (reaction progress was followed by TLC, eluent 5 : 1 : 1 chloroform–acetone–toluene, and by ^{31}P NMR). After cooling, the reaction mixture was filtered, the filtrate was evaporated in a vacuum, and the residue was partitioned between 30 ml of chloroform and 30 ml of water. The aqueous layer was extracted with chloroform (3 × 20 ml), and the combined dark brown extract was treated by two different procedures.

a. The extract was concentrated and passed through a bed of Celite (eluent chloroform), the eluate was evaporated in a vacuum, the light yellow oily residue (~8 g) was treated with 35 ml of 8 N HCl, and the mixture was refluxed for 16 h. After cooling, the reaction mixture was washed with ether (2 × 10 ml) and benzene (2 × 10 ml), the acidic aqueous phase was evaporated in a vacuum and then again evaporated with water. The residue was dissolved in 16 ml of aqueous ethanol (1 : 3), treated with 5 ml of propylene oxide, and evaporated in a vacuum. The partially crystalline residue comprising primarily the target free aminophosphinic acid (by ^{1}H and ^{31}P NMR) was mixed with water and evaporated and chromatographed on a weakly acidic cationite (H^+), eluent water. Fractions with a positive ninhydrin reaction were evaporated in a vacuum, and the residue was crystallized from 1 : 1 ethanol–ether. Recrystallization from aqueous ethanol gave 1.7 g (35.8% per taken Schiff base) of compound **IIf**, mp 261–262°C (decomp.). ^{1}H NMR spectrum (D_2O + DCl), δ, ppm: 1.10 s (3H, CH_3), 1.35 m (2H, CH_2), 1.62 m (4H, $2CH_2$), 2.10 m (2H, CH_2). ^{31}P NMR spectrum, δ_P, ppm: 46.7 (D_2O), 55.7 (D_2O + DCl). Found, %: C 37.68, 37.52; H 6.62, 6.51; P 12.01, 11.83. $C_8H_{16}NO_6P$. Calculated, %: C 37.95; H 6.37; P 12.23.

b. The extract was evaporated, and the residue was partitioned between 20 ml of ether and 100 ml of 2 N HCl. The two-phase system formed was vigorously stirred for 5 h at room temperature. The acidic aqueous layer was extracted with ether (2 × 20 ml) and evaporated in a vacuum. According ^{1}H and ^{31}P NMR data, the residue comprised primarily unreacted vinylphosphinate **IVb** [δ_P 41 ppm ($CDCl_3$)] [32] and aminophosphinic acid containing one ester group (two ester groups, C(O)OEt and POEt, obviously hydrolyzed during removal of the benzylidene protective group). The residue was dissolved in 10 ml of aqueous ethanol (1 : 4) and treated with a solution of 4 ml epichlorohydrin in 4 ml of ether. The partially crystalline residue was crystallized from aqueous

acetone (1 : 2) to obtain 1.45 g (25.8% per taken Schiff base) of **ethyl 2-amino-2-methyl-4-[[(2-hydroxycarbonyl)ethyl]phosphoryl]butyrate (VIf, X = $CH_2CH_2C(O)OH$, Y = OH, Z = Me, Alk = Et),** mp 154–157°C (decomp.). ^{1}H NMR spectrum (CD_3OD), δ, ppm: 1.35 t (3H, CH_3), 1.56 m (2H, CH_2), 1.57 s (3H, CH_3), 1.81 m (2H, CH_2), 2.16 m (2H, CH_2), 2.55 m (2H, CH_2), 4.33 q (CH_2O). ^{31}P NMR spectrum, δ_P, ppm: 39.9 (CD_3OD), 44.4 (D_2O). Found, %: C 40.29, 40.43; H 7.55, 7.57; P 10.23, 10.03. $C_{10}H_{20}NO_6P \cdot H_2O$. Calculated, %: C 40.14; H 7.41; P 10.35. The structural assessment is based on the ^{1}H and ^{31}P NMR spectra (absence of the ester group at phosphorus and presence of only one ester group in the molecule) and by analogy with amino ester **VIe** in which the ester group in the aminocarboxylic fragment remained intact.

A mixture of 1.2 g of amino ester **VIf** with 5 ml of 8N HCl was refluxed for 10 h. After cooling, it was washed with ether (2 × 20 ml), the acidic aqueous layer was evaporated in a vacuum and then evaporated with water. The residue was dissolved in 12 ml of aqueous ethanol (1 : 3) and treated with 2 ml of propylene oxide. The partially crystalline precipitate comprising primarily the free amino acid was recrystallized from aqueous ethanol to obtain 0.8 g of the target amino acid (80% per amino ester **VIf**). The total yield of acid **IIf** was 20.6% per parent Schiff base. The spectral and physicochemical characteristics of this compound were consistent with those of the sample of amino acid **IIf**, obtained by procedure *a*.

2-Amino-4-[[2-(hydroxycarbonyl)ethyl]phosphoryl]-2-isopropylbutyric acid (IIg, X = $CH_2CH_2C(O)OH$, Y = OH, Z = *i*-Pr). A mixture of 3.3 g of methyl 2-(benzylideneamino)-3-methylbutyrate (prepared from valine methyl ester hydrochloride and benzaldehyde), 3.7 g of ethyl [2-(ethoxycarbonyl)-ethyl](vinyl)phosphate (**IVb**), and 5.0 g of potassium carbonate was stirred in 20 ml of THF under reflux in the presence of 1.0 g of tetrabutylammonium bromide for 15 h. Stirring was then continued, and a finely devided cesium carbonate was intermittently added in portions of 1–2 g until the Shiff base (Rf 0.7–0.8) disappeared from the chromatogram of the reaction mixture (reaction progress was followed by TLC, eluent 7 : 1 : 1 chloroform–acetone–benzene, and by ^{31}P NMR). After cooling, the reaction mixture was poured into 30 ml of cold water with ice, and the aqueous layer was neutralized to pH 7 and extracted with ethyl acetate (3 × 30 ml). The combined organic extract was dried over sodium sulfate and evaporated in a vacuum. The brown oily residue was dissolved in a minimum of methylene chloride and passed through a bed of a mixture of silica gel and alumina (80 : 20 w/w), eluent methylene chloride. The eluate was evaporated in a vacuum, the light yellow residue (ca. 6 g) was treated with 30 ml of 8 N HCl, and the mixture was refluxed for 13 ½, cooled, and washed with benzene (2 × 15 ml). The acidic aqueous phase was evaporated in a vacuum and then evaporated with water. The residue was chromatographed on a strongly acidic cationite, the acidity of the eluent (water–1 N HCl) was therewith gradually raised. Fractions showing a positive ninhydrin reaction were evaporated in a vacuum, and the residue was dissolved in 16 ml of aqueous ethanol (1 : 3), treated with 3 ml of propylene oxide, and evaporated in a vacuum. The partially crystalline wet residue of the free amino acid was chromatographed again on a weakly acidic cationite (eluent water), and fractions with a positive ninhydrin reaction were collected. The eluate was evaporated in a vacuum, and the residue was crystallized from 1 : 1 ethanol–ether. Recrystallization from aqueous ethanol gave 1.4 g (33.3% per taken Schiff base) of acid **IIg**, mp 241–244°C (decomp.). ^{1}H NMR spectrum (D_2O), δ, ppm: 0.92 d (3H, CH_3, *J* 7 Hz), 0.97 d (3H, CH_3, *J* 7 Hz), 1.52 m (2H, CH_2), 1.75 m (2H, CH_2), 1.96 m (2H, CH_2), 2.18 m (1H, CH), 2.45 m (2H, CH_2). ^{31}P NMR spectrum (D_2O): δ_P 46.4 ppm. Found, %: C 42.65, 42.96; H 7.32, 7.11; P 10.71, 10.83. $C_{10}H_{20}NO_6P$. Calculated, %: C 42.71; H 7.17; P 11.01.

2-Amino-2-benzyl-4-[[2-(hydroxycarbonyl)-ethyl]phosphoryl]butyric acid (IIh, X = $CH_2CH_2 \cdot C(O)OH$, Y = OH, Z = CH_2Ph). A mixture of 5.4 g of methyl 2-(benzylideneamino)-3-phenylpropanoate (prepared from phenylalanine methyl ester hydrochloride and benzaldehyde), 6.2 g of ethyl [2-(ethoxycarbonyl)ethyl](vinyl)phosphinate (**IVb**), 0.5 g of tetrabutylammonium bromide, and 14.6 g of cesium carbonate was stirred in 30 ml of THF under reflux until the Schiff base disappeared from the thin-layer chromatogram of the reaction mixture (R_f ~0.7, 7 : 1 : 1 chloroform–acetone–benzene). After cooling, the reaction mixture was poured into 30 ml of cold water with ice, the aqueous layer (ca. 80 ml) was neutralized to pH 7 and extracted with ethyl acetate (3 × 30 ml). The combined organic extract was dried over sodium sulfate and evaporated in a vacuum. The browm oily residue was dissolved in a minimum of methylene chloride and passed through a bed of Celite (eluent methylene chloride). The eluate was evaporated in a vacuum, the light yellow residue (ca. 6 g) was treated 30 ml of 8 N HCl, and the mixture was refluxed for 13 h, cooled, and washed with ether (2 × 10 ml) and benzene (2 × 10 ml). The acidic aqueous phase was evaporated in a vacuum and then evaporated with water. The solid residue was dissolved

in 16 ml of aqueous ethanol (1 : 3), treated with 5 ml of propylene oxide, and evaporated in a vacuum. The partially crystalline residue that, according to 1H and ^{31}P NMR, comprised primarily the target aminophosphinic acid was repeatedly evaporated with water and chromatographed on a weakly acidic cationite (eluent water). Fractions with a positive ninhydrin reaction were evaporated in a vacuum, and the residue was crystallized from ethanol. Recrystallization from aqueous ethanol (1 : 7) gave 2.8 g (42.0% per taken Schiff base) of acid **IIf**, mp 231–234°C (decomp.). ^{1}H NMR spectrum (D_2O), δ, ppm: 1.40 m (2H, CH_2), 1.60 m (2H, CH_2), 1.80 m (2H, CH_2), 2.10 m (2H, CH_2), 2.64 d (1H, CH_2Ph), 2.92 d (1H, CH_2Ph), 6.72 m (2H, Ph) and 6.83 m (3H, Ph). ^{31}P NMR spectrum (D_2O + DCl): δ_P 55.4 ppm. Found, %: C 45.17, 45.05; H 6.32, 6.54; P 8.01, 7.93. $C_{14}H_{20}NO_6P \cdot 2.5H_2O$. Calculated, %: C 44.92; H 6.73; P 8.27.

2-Amino-2-methyl-4-[(2-phenylethyl)phosphoryl]butyric acid (IIi, X = CH_2CH_2Ph, Y = OH, Z = Me). A mixture 2.2 of g of ethyl 2-(benzylideneamino)propanoate (prepared from alanine ethyl ester hydrochloride and benzaldehyde), 2.6 g of ethyl (2-phenylethyl)(vinyl)phosphinate (**IVc**), 3.3 g of potassium carbonate, 1.5 g of cesium carbonate, and 0.3 g of tetrabutylammonium bromide was stirred in 20 ml of THF under reflux until the Schiff base (R_f ~0.8) disappeared from the chromatogram of the reaction mixture (reaction progress was followed by TLC, eluent 5 : 1 : 1 chloroform–acetone– toluene, and by ^{31}P NMR). After cooling, the reaction mixture was filtered, the filtrate was evaporated in a vacuum, the residue was partitioned between 30 ml of chloroform and 30 ml of water, and the aqueous layer was extracted with chloroform (3 × 20 ml). The combined dark brown organic extract was concentrated and passed through a bed of a mixture of silica gel and alumina (90 : 10 w/w), eluent chloroform. The eluate was evaporated in a vacuum, the light brown residue (ca. 5 g) was treated with 25 ml of 8 N HCl, and the mixture was refluxed for 13 ½, cooled, and washed with ether (2 × 10 ml) and benzene (2 × 10 ml). The acidic aqueous phase was evaporated in a vacuum and then evaporated with water. The residue was dissolved in 15 ml of aqueous ethanol (1 : 3), treated with 3 ml of propylene oxide, and evaporated in a vacuum. The partially crystalline residue that, according to ^{1}H and ^{31}P NMR, comprised primarily the target aminophosphinic acid was repeatedly evaporated with water and chromatographed on a weakly acidic cationite (eluent water). Fractions with a positive ninhydrin reaction were evaporated in a vacuum, and the residue was crystallized from 1 : 1 ethanol–ether. Recrystallization from aqueous acetone gave 1.6 g (53.3%) of acid **IIi**, mp 240–243°C (decomp.). ^{1}H NMR spectrum (D_2O + DCl), δ, ppm: 0.65 s (3H, CH_3), 0.78 m (1H, CH_2), 0.95 m (1H, CH_2), 1.28 m (4H, $2CH_2$), 2.02 m (2H, CH_2), 7.02 m (5H, Ph). ^{31}P NMR spectrum (D_2O + DCl): δ_P 56.4 ppm. Found, %: C 54.79, 54.60; H 7.02, 6.87; P 10.71, 10.63. $C_{13}H_{20}NO_4P$. Calculated, %: C 54.73; H 7.07; P 10.86.

2-Amino-2-isopropyl-4-[(2-phenylethyl)phosphoryl]butyric acid (IIj, X = CH_2CH_2Ph, Y = OH, Z = *i*-Pr). A mixture of 3.5 g of methyl 2-(benzylideneamino)-3-methylbutyrate (prepared from valine methyl ester hydrochloride and benzaldehyde), 4.5 g of ethyl (2-phenylethyl)vinylphosphinate (**IVc**), 11.5 g of cesium carbonate, and 0.3 g of tetrabutylammonium bromide was stirred in 15 ml of THF under reflux until the Schiff base (R_f ~0.8) disappeared from the chromatogram of the reaction mixture (reaction progress was followed by TLC, eluent 5 : 1 : 1 chloroform–acetone–toluene, and by ^{31}P NMR). After cooling, the reaction mixture was poured into 30 ml of ice with water, and the aqueous layer was neutralized to pH 7 and extracted with ethyl acetate (3 × 30 ml). The combined organic extract was dried over magnesium sulfate and evaporated in a vacuum. The brown oily residue was dissolved in a minimum of chloroform and passed through a bed of Celite (eluent chloroform). The eluate was evaporated in a vacuum, the light yellow residue (ca. 9 g) was treated with 45 ml of 8 N HCl, and the mixture was refluxed for 15 h, cooled, and washed with benzene (2 × 15 ml). The acidic aqueous phase was evaporated in a vacuum and then evaporated with water. The residue was dissolved in 25 ml of aqueous ethanol (1 : 5), treated with 3 ml of propylene oxide, and evaporated in a vacuum. The partially crystalline residue which, according to ^{1}H and ^{31}P NMR, comprised primarily the target free aminophosphinic acid was repeatedly evaporated with water and chromatographed on a cationite (H^+) (eluent 0.5N HCl). Fractions with a positive ninhydrin reaction were collected and evaporated in a vacuum, and the residue was crystallized from 1 : 1 acetone–ether. Recrystallization from 5 N HCl–acetone (9 : 1) gave 2.6 g (52.0%) of acid **IIj** hydrochloride, mp 225–227°C (decomp.). ^{1}H NMR spectrum (D_2O + DCl), δ, ppm: 0.15 d (3H, CH_3, *J* 7 Hz), 0.20 d (3H, CH_3, *J* 7 Hz), 0.75 m (1H, CH_2), 1.02 m (1H, CH_2), 1.30 m (5H, $2CH_2$ + CH), 1.98 m (CH_2), 6.45 m (5H, Ph). ^{31}P NMR spectrum (D_2O + DCl): δ_P 57.1 ppm. Found, %: C 51.44, 51.36; H 7.59, 7.57; P 8.71, 8.63. $C_{15}H_{24}NO_4P \cdot HCl$. Calculated, %: C 51.51; H 7.20; P 8.85.

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