Synthesis of α-substituted α-aminophosphinic and α-aminophosphonic acids

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The reaction of ketoximes with hypophosphorous acid resulted in previously unknown α-substituted-α-aminophosphinic acids, which were oxidized into the corresponding α-substituted-α-aminophosphonic acids.

Key words: phosphorus analogs of amino acids, α-alkyl-α-aminophosphinic acids, α-alkyl-α-aminophosphonic acids, ketoximes.

Among amino carboxylic acids, α-substituted α-amino acids form a special group; some of them are naturally occurring and enzymes of their metabolism are known.[1] Many α-substituted amino acids are used in biochemistry as competitive inhibitors of the corresponding enzymes of amino acid metabolism and are of practical value. Thus, *L*-α-methyl-3,4-dihydroxyphenylalanine is effective in therapy for parkinsonism,[2] 1-aminocyclopentanecarboxylic acid exhibits pronounced antitumor activity,[3] and α-methyl aspartate is used in investigations of the intermediate steps of pyridoxal-5′-phosphate-dependent enzymatic reactions (including high-resolution X-ray analysis).[4]

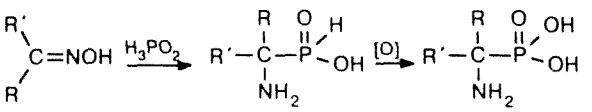
Various phosphonic analogs of α-methyl(alkyl)amino acids have been reported.[5] Among them are inhibitors of glutamine synthetase[6] and alanine racemase,[7] and the peptides derived from 1-amino-1-methylethylphosphonic acid exhibit pronounced antibacterial activity.[8]

Phosphinic analogs of natural α-substituted amino acids (**1**) have not been obtained yet, although amino phosphinic acids resemble aminocarboxylic acids and are capable of penetrating into cells.

The goal of this study was to develop a preparative method for the synthesis of α-substituted aminophosphinic acids and to obtain the corresponding phosphonic analogs derived from them.

The known methods for the synthesis of α-unsubstituted aminophosphonic acids involve the reaction of aldoximes with H_3PO_2,[9] the interaction of H_3PO_2 with substituted aldimines followed by removal of a protecting group,[10] and alkylation of aminomethylphosphinic acid derivatives.[11] α,α-Disubstituted aminophosphinic acids of type **1**, where R = Me, Pr; R′ = CH_2=$CHCH_2$; and R + R′ = $-(CH_2)_2$, have been obtained using the alkylation approach.[11] However, α-substituted analogs of natural amino acids have not been synthesized. The first method[9] is the simplest and provides α-amino phosphonites by a singlestep synthesis and in satisfactory yields. However, it has not been reported yet whether this reaction can be applied to ketoximes.

In this work we have demonstrated that the reaction of H_3PO_2 with aliphatic ketoximes, including functionally substituted ketoximes, and with acetophenone oxime occurs fairly smoothly to give the corresponding amino phosphinic acids **1** in 13—50 % yields. However, the products of the reaction with acetoacetic acid oxime, **1g** and **1a**, were isolated in very low yields (0.5% and 5.6%, respectively).



1a—g **2a—c,e,f**

	R	R′
a	Me	Me
b	Me	Et
c	Me	Ph
d	C_4H_8	C_4H_8
e	Me	$MeSCH_2CH_2$
f	CH_2=$CHCH_2OCH_2$	CH_2=$CHCH_2OCH_2$
g	Me	CH_2CO_2H*

* For starting oxime R′ = CH_2CO_2Et.

The structures of the synthesized aminophosphinic acids were confirmed by their ^1H NMR and mass spectra, the qualitative reactions of functional groups, and by

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their oxidation to the corresponding amino phosphonic acids. Therefore, the reaction of H_3PO_2 with ketoximes under conditions similar to those reported in Ref. 12 results in aminophosphinic acids **1**, rather than the products of addition to the double bond containing the hydroxyamino group. However, we should not discard the possibility of the intermediate formation of these products and their further reduction. (For example, the similar conversion of oximes to imines involving dialkylchlorophosphite has been reported.)[13] The reaction was carried out with anhydrous H_3PO_2 either without solvent at ~20 °C, or in polar solvents (alcohols, THF, dioxane) with heating. In the first case it may become difficult to monitor the reaction of lower oximes. When solvents are used, the reactions occur smoothly even when the amount of the oxime exceeds 1 mol. A twofold excess of H_3PO_2 favors an increase in the yield of the products.

Conversion of unsubstituted aminophosphinic acids to aminophosphonic acids has been reported under the action of $HgCl_2$ (for preparation of optically active aminophosphonates),[10] Br_2 in aqueous HCl,[9,10] and SO_2Cl_2 in glacial AcOH.[14] In the case of diallyloxy derivative **1f** product **2f** was smoothly obtained using $HgCl_2$. Aminophosphinic acids **1a—c** were oxidized with Br_2 to the corresponding aminophosphonates **2a—c** in almost quantitative yields. All the attempts to convert compound **1e** to **2e** failed using well known methods of oxidation of amino phosphinic acids. We have found that facile oxidation of aminophosphinic acids containing functional groups that are labile or sensitive to oxidants occurs when I_2 in an aqueous solution of HI is used; this makes it possible to obtain **2e** in a good yield.

Experimental

Thin-layer chromatography was carried out on Merck Kieselgel $60F_{254}$ plates in $Pr^iOH—NH_4OH—H_2O$, 7 : 2 : 1 (A) and $AcOH—H_2O$—acetone—Pr^iOH, 2 : 5 : 7.5 : 5.5 (B); vizualization was carried out using color reactions with ninhydrin and ammonium molybdate. Ion-exchange chromatography was carried out on Dowex-50×8 ion-exchange resin (100—200 mesh, H^+-form) (BioRad, USA). Melting points (with decomposition, uncorrected) were determined on an Electrothermals melting-point apparatus (U.K.). ^1H NMR spectra were recorded on a Varian XL-100-15 spectrometer (USA) with Bu^tOH as the internal standard. Chemical shifts are reported in p.p.m. with respect to TMS. Mass spectra were obtained on a MSBKh instrument (Ukraine) using plasma-desorption techniques.

1-Amino-1-methylethylphosphinic acid (1a). A solution of acetone oxime (7.3 g, 0.2 mol) in 15 mL Pr^iOH was added under nitrogen to a boiling solution of anhydrous H_3PO_2 (13.2 g, 0.2 mol) in 85 mL of dry Pr^iOH for 30 min with stirring, and the resulting mixture was refluxed for 2 h. An additional portion of acetone oxime (7.3 g, 0.1 mol) in 15 mL of Pr^iOH was then added for 30 min, and the resulting mixture was refluxed for an additional 4 h. The reaction mixture was cooled, and the precipitated crystals were filtered off and washed with Pr^iOH. Et_3N was added to the combined filtrates to pH ~4.0, the mixture was cooled to 4 °C, and an additional portion of the product was filtered off. The crude product was recrystallized from water to give 9.0 g (36%) of **1a**, m.p. 222—224°C; R_f 0.57 (A), R_f 0.63 (B). ^1H NMR (D_2O), δ : 1.42 (d, 6 H, Me, J = 13 Hz); 6.85 (d, 1 H, PH, J = 519 Hz). Found (%): C, 29.10; H, 8.44; N, 11.12. $C_3H_{10}NO_2P$. Calculated (%): C, 29.27; H, 8.19; N, 11.38. MS, m/z : 122.1 $[M-1]^+$.

1-Amino-1-methylpropylphosphinic acid (1b). Methyl ethyl ketone oxime (10 g, 0.115 mol) was added under argon to a boiling solution of anhydrous H_3PO_2 (15.18 g, 0.23 mol) in 80 mL of dry Pr^iOH with stirring. The resulting mixture was refluxed for 10 h and then evaporated to 1/3 of the initial volume, the residue was dissolved in water, and the product was isolated by ion-exchange chromatography (10% Pr^iOH as the eluent). Crystallization from a water-ethanol mixture gave 2.56 g (16.3%) of product **1b**; m.p. 212 °C; R_f 0.59 (A), R_f 0.65 (B). ^1H NMR (D_2O), δ : 1.00 (dd, 3 H, $\underline{Me}CH_2$, J_1 = J_2 = 7.5 Hz); 1.40 (d, 3 H, MeCP, J = 15 Hz); 1.65—2.05 (m, 2 H, CH_2); 6.87 (d, 1 H, PH, J = 519 Hz). $C_4H_{12}NO_2P$. Found (%): C, 35.27; H, 9.04; N, 9.96. Calculated (%): C, 35.04; H, 8.82, N, 10.22. MS, m/z: 136.2 $[M-1]^+$.

1-Amino-1-phenylethylphosphinic acid (1c). Acetophenone oxime (2.7 g, 20 mmol) was added to a boiling solution of anhydrous H_3PO_2 (2.64 g, 40 mmol) in 8 mL of dry Pr^iOH under argon for 30 min with stirring, and the resulting mixture was refluxed for 24 h, chilled, poured into water (15 mL), and extracted twice with EtOAc. The water layer was evaporated to dryness *in vacuo*, the residue was dissolved in a 10% aqueous solution of Pr^iOH, and the product was isolated by ion-exchange chromatography (10% solution of Pr^iOH as the eluent). Recrystallization from a water-ethanol mixture gave 1.28 g (34.6%) of product **1c**, m.p. 230 °C; R_f 0.65 (A), R_f 0.74 (B). ^1H NMR (0.2 *N* NaOH), δ: 1.85 (d, 3 H, Me, J = 14 Hz); 6.89 (d, 1 H, PH, J = 524 Hz); 7.35—7.50 (м, 5 H, Ph). Found (%): C, 52.02; H, 6.64; N, 7.78. $C_8H_{12}NO_2P$. Calculated (%): C, 51.89; H, 6.53; N, 7.57. MS, m/z: 184.2 $[M-1]^+$.

1-Amino-cyclopentylphosphinic acid (1d). A solution of cyclopentanone oxime (17.0 g, 0.17 mol) in 60 mL of Pr^iOH was added under argon to a boiling solution of anhydrous H_3PO_2 (20.6 g, 0.32 mol) in 110 mL of dry Pr^iOH for 30 min with stirring, and the resulting mixture was refluxed for 24 h and then evaporated to a syrupy state. The residue was dissolved in water, and the product was isolated by ion-exchange chromatography using water as the eluent). Recrystallization from a water-ethanol mixture gave 8.2 g (32%) of product **1d**, m.p. 212 °C; R_f 0.62 (A), R_f 0.67 (B). ^1H NMR (D_2O), δ: 1.50—2.40 (m, 8 H, $(CH_2)_4$); 6.91 (d, 1 H, PH, J = 521Hz). Found (%): C, 40.13; H, 8.27; N, 9.21. $C_5H_{12}NO_2P$. Calculated (%): C, 40.27; H, 8.11; N, 9.39. MS, m/z: 148.2$[M-1]^+$.

1-Amino-1-methyl-3-(methylthio)propylphosphinic acid (1e). Methyl(2-methylthioethyl)ketone oxime (33.2 g, 0.25 mmol) was added to a boiling solution of anhydrous H_3PO_2 (33.0 g, 0.5 mol) in 100 mL of dry Pr^iOH with stirring under nitrogen for 30 min. The resulting mixture was refluxed for 15 h and then evaporated to dryness, the residue was dissolved in a 15% solution of Pr^iOH, and the product was isolated by ion-exchange chromatography (15% aqueous solution of Pr^iOH as the eluent). Recrystallization from a water—alcohol mixture afforded product **1e** (22.2 g, 50%), m.p. 213 °C; R_f 0.66 (A), R_f 0.74 (B). ^1H NMR (D_2O), δ: 1.34 (d, 3 H, MeC, J = 16 Hz); 1.95—2.30 (m, 2 H, $C\underline{H}_2CH_2S$); 2.18 (s, 3 H, MeS); 2.60—2.85 (m, 2 H, $CH_2C\underline{H}_2S$); 6.89 (d, 1 H, PH, J = 523 Hz). Found (%): C, 32.93; H, 7.49;

N, 7.87. $C_5H_{14}NO_2PS$. Calculated (%): C, 32.78; H, 7.70; N, 7.65. MS, *m/z*: 182.3 $[M-1]^+$.

1,3-Diallyloxy-2-amino-2-propylphosphinic acid (1f). 1,3-Di(allyloxy)acetone oxime (14.0 g, 75 mmol) was added to a solution of 9.97 g (0.15 mol) of anhydrous H_3PO_2 in 55 mL of dry Pr^iOH at 70 °C for 30 min with stirring under nitrogen. The resulting mixture was stirred at 85°C for 2 h, cooled, and then evaporated by two thirds. The residue was poured into 50 mL of water, twice extracted with ether, and product **1f** was isolated by ion-exchange chromatography with gradient elution with 20% Pr^iOH-H_2O (0.5 L each). Product **1f** (2.26 g, 12.7%) was obtained in the form of a viscous oil, R_f 0.70 (A), R_f 0.77 (B). ^1H NMR (D_2O), δ: 3.64—3.85 (m, 4 H, CH_2CPCH_2); 4.09 (ddd, 4 H, $C\underline{H}_2CH=CH_2$, J_1 = 6 Hz, $J_2 = J_3$ = 1.2 Hz); 5.18—5.46 (m, 4 H, $C\underline{H}_2CH$); 5.74—6.14 (m, 2 H, CH); 7.08 (d, 1 H, PH, J = 548 Hz). Found (%): C, 46.29; H, 7.42; N, 5.70. $C_9H_{18}NO_4P$. Calculated (%): C, 45.96; H, 7.71; N, 5.96. MS, *m/z*: 234.1 $[M-1]^+$.

1-Amino-1-(carboxymethyl)ethylphosphinic acid (1g). A solution of ethyl acetoacetate oxime in 100 mL of ethanol (obtained from 32.5 g (0.25 mol) of ethyl acetoacetate and 8.25 g (0.25 mol) of NH_2OH) was added to a boiling solution of anhydrous H_3PO_2 (33.0 g, 0.50 mol) in 100 mL of absolute EtOH for 30 min with stirring under nitrogen. The resulting mixture was refluxed for 21 h and evaporated to dryness and the residue was dissolved in a 15% solution of Pr^iOH. The reaction products were isolated by chromatography (15% Pr^iOH as the eluent). When the solvent was evaporated, the residue was dissolved in 160 mL of 20% HCl, refluxed for 2 h, and then evaporated to dryness, and the resulting residue was dissolved in a 15% solution of Pr^iOH. The products were isolated by chromatography (15% Pr^iOH as the eluent). Products **1g** (0.29 g, 0.5%) and **1a** (1.73 g, 5.6%) were obtained. **1g**: m.p. 210—211 °C; R_f 0.26 (A), R_f 0.34 (B). ^1H NMR (D_2O), δ: 1.49 (d, 3 H, Me, J = 14 Hz); 2.65—2.80 (m, 2 H, CH_2); 6.60 (d, 1 H, PH, J = 506 Hz). Found (%): C, 28.41; H, 5.96; N, 8.28. $C_4H_{10}NO_4P$. Calculated (%): C, 28.75; H, 6.03; N, 8.28. MS, *m/z*: 166.3 $[M-1]^+$.

1-Amino-1-methylethylphosphonic acid (2a). Bromine (Br_2) (0.6 mL, 11.8 mmol) was added dropwise to a solution of 1.25 g (10 mmol) of compound **1a** in 10 mL of 1.0 *M* HCl with stirring and the resulting mixture was then stirred for an additional 30 min at 20°C and evaporated to dryness. The residue was dissolved in MeOH and propylene oxide was added to pH 5. The crude product **2a** (1.38 g) was obtained. Recrystallization from water gave 1.1 g of compound **2a**, m.p. 277—278 °C (*cf.* Ref. 15: m.p. 274—275 °C).

The corresponding aminophosphonates **2b** and **2c** were obtained similarly from aminophosphinic acids **1b** and **1c**. Compound **2b**, m.p. 245 °C. Found (%): C, 31.01; H, 8.09; N, 8.96. $C_4H_{12}NO_3P$. Calculated (%): C, 31.38; H, 7.90; N, 9.15. Compound **2c**, m.p. 205 °C. Found (%): C, 47.69; H, 6.21; N, 6.77. $C_8H_{12}NO_3P$. Calculated (%): C, 47.77; H, 6.01; N, 6.96. Yields, R_f, melting points, and ^1H NMR spectral data of the compounds are summarized in Table 1.

1-Amino-1-methyl-3-(methylthio)propylphosphonic acid (2e). A 1 *M* solution of I_2 in EtOH (10.5 mL) was added dropwise to a solution of compound **1e** (1.83 g, 10 mmol) in a mixture of concd. HI (2.5 mL) and EtOH (10 mL) with stirring at 20 °C for 1 h. Propylene oxide was added to the resulting mixture. The crude product **2e** (1.85) was obtained. Its recrystallization from water yielded 1.42 g of compound **2e** (it decomposes without melting at >200 °C). Found (%): C, 30.31; H, 7.00; N, 7.19. $C_5H_{14}NO_3PS$. Calculated (%): C, 30.15; H, 7.08; N, 7.03. MS, *m/z*: 198.3 $[M-1]^+$.

Table 1. Characteristics of α-alkyl-α-aminophosphonic acids

Compound	R_f(A)	Yield (%)	^1H NMR (D_2O) (δ, J/Hz)
2a	0.08	79	1.51 (d, 6 H, Me, J = 14)
2b	0.09	82	1.05 (dd, 3 H, $MeCH_2$, $J_1 = J_2$ = = 7.5); 1.45 (d, 3 H, MeCP, J = 14); 1.60—2.10 (m, 2 H, CH_2)
2c	0.20	76	1.89 (d, 3 H, Me, J = 13); 7.10—7.18 (m, 5 H, Ar—H)
2e	0.18	71	1.50 (d, 3 H, MeC, J = 13); 1.95—2.40 (m, 2 H, CH_2CP); 2.12 (s, 3 H, MeS); 2.55—2.80 (s, 2 H, CH_2S)
2f	0.25	64	3.77—3.93 (m, 4 H, CH_2CPCH_2); 4.10 (ddd, 4 H, $C\underline{H}_2$-C, J_1 =6, $J_2 = J_3$ = 1.2); 5.18—5.46 (m, 4 H, CH_2=); 5.76—6.14 (m, 2 H, CH)

1,3-Diallyloxy-2-aminopropylphosphonic acid (2f). A solution of compound **1f** (1.86 g, 7.9 mmol) and $HgCl_2$ (4.29 g, 15.8 mmol) in 20 mL of H_2O was heated with stirring for 1 h to 95°C. The mixture was chilled and filtered, the precipitate was washed with water, and $Na_2S \cdot 10\,H_2O$ (2.56 g, 10.0 mmol) was added to the filtrate. The resulting mixture was filtered through Celite, and the precipitate was washed with water. The combined filtrate was evaporated to dryness and the residue was dissolved in 20% Pr^iOH. Product **2f** was isolated by ion-exchange chromatography in a gradient with a 20% solution of Pr^iOH-H_2O (0.4 L each). Product **2f** (1.27 g) was obtained in the form of a partially crystallized oil. Found (%): C, 42.71; H, 7.49; N, 5.37. $C_9H_{18}NO_5P$. Calculated (%): C, 43.03; H, 7.22; N, 5.58. MS, *m/z*: 250.1 $[M-1]^+$.

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