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LETTERS TO THE EDITOR

One-Pot Synthesis of α-Amino Phosphinic Acids

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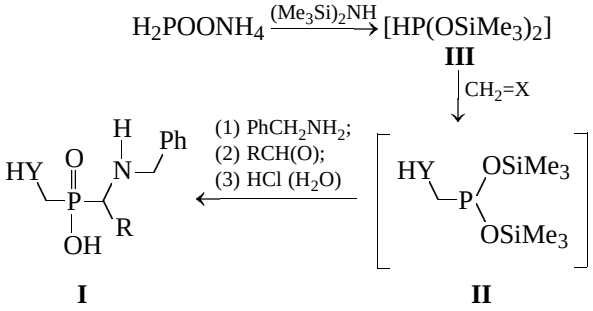
A promising line in the search for new physiologically active compounds involves synthesis of phosphinic acids, the pseudopeptides, potential inhibitors of natural enzymes [1, 2]. In this connection, development of methods for the synthesis of α-amino phosphinic acids, which can be considered as phosphoryl analogs of dipeptides formed by α-amino acids [2–4], is an important challenge.

Here we suggest an approach to the synthesis of such α-amino phosphinic acids **I** based on the method that we develop for the synthesis of functionally substituted phosphinic acids [5–7], in which silylphosphinic intermediates are involved in the Kabachnik–Fields reaction. We found that bis(trimethylsilyl) phosphonites **II** formed *in situ* by adding bis(trimethylsilyl) hypophosphite **III** to activated CH_2=X compounds are capable, in turn, of *in situ* reaction with an equimolar mixture of benzylamine with the appropriate aldehyde, yielding α-(*N*-benzylamino) phosphinic acids **I** according to the following scheme:



I **II**

R = *i*-Pr, Ph; X = CHPh, CHC(O)OEt, C(*i*-Bu)C(O)OEt; Y = CHPh, CHC(O)OH, C(*i*-Bu)C(O)OH.

2-Hydroxycarbonylethyl-α-(benzylamino)-benzylphosphonic acid Ia. A mixture of 1.0 g of H_2POONH_4 and 5 ml of hexamethyldisilazane was stirred for 1.5 h at 120°C. The reaction mixture was cooled to room temperature in an argon flow, 1.3 ml of ethyl acrylate was slowly added dropwise, and the stirring was continued for 2.5 h at 5°C. After that, 1.3 ml of benzylamine and then 1.2 ml of benzaldehyde were added. The temperature of the reaction mixture rose to 90°C, and the mixture was stirred at 110–120°C for 3 h. The mixture was cooled to room temperature, 15 ml of aqueous ethyl alcohol was added dropwise, and the mixture was evaporated in a vacuum. The residue was dissolved in 50 ml of methylene chloride and washed with water (2 × 10 ml). The organic layer was dried over $MgSO_4$, concentrated, and filtered through a Celite bed. The eluate was evaporated, and residue was crystallized from ether. For additional purification, the amino acid was dissolved in a minimal volume of water and subjected to chromatography on Diasorb-Sulfo (H^+) weakly acidic cation exchanger. The aqueous eluate was evaporated in a vacuum, and the residue was crystallized from an alcohol–ether mixture. **2-(Ethoxycarbonyl)ethyl-α-(benzylamino)benzylphosphinic acid Ia'** was isolated, yield 1.3 g (31% based on ammonium hypophosphite), mp 131–134°C. ^{1}H NMR spectrum (CD_3OD, δ, ppm): 1.20 t (3H, CH_3), 1.75 m (2H, CH_2), 2.38 m (2H, CH_2), 4.04 br.s (2H, CH_2), 4.08 q (2H, CH_2O), 4.70 d (1H, CH, J_{PH} 13 Hz), 7.40 m (10H, 2Ph). ^{31}P NMR spectrum, δ_P, ppm: 37.1 (CD_3OD), 50.1 (D_2O + DCl).

A mixture of 0.9 g of acid **Ia'** and 10 ml of 8 N HCl was refluxed for 8 h and then evaporated in a vacuum; the residue was dissolved in a 1:3:1 water–alcohol–ether mixture and treated with 1 ml of propylene oxide. 2-(Hydroxycarbonyl)ethyl-α-(*N*-benzylamino)-benzylphosphinic acid **Ia** was isolated, yield 0.7 g (84% based on **Ia'**), mp 163–166°C. 1H NMR spectrum (D_2O + DCl), δ, ppm: 1.12 m (2H, CH_2), 1.50 m (2H, CH_2), 3.28 d (1H, CH_2Ph), 3.45 d (1H, CH_2Ph), 3.72 d (1H, CH, J_{PH} 11 Hz), 6.50 m (10H, 2Ph). ^{31}P NMR spectrum (D_2O + DCl), δ_P, ppm: 41.8. Found, %: C 61.45; 61.48; H 5.87, 5.78; P 9.31, 9.43. $C_{17}H_{20}NO_4P$. Calculated, %: C 61.26; H 6.05; P 9.29.

2-Phenylethyl-1-(benzylamino)-2-methylpropylphosphinic acid Ib. A mixture of 1.0 g of H_2POONH_4 and 1.4 g of styrene in 5 ml of hexamethyldisilazane

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was stirred for 1.5 h at 120°C and then cooled under argon to 50°C. To the reaction mixture 1.3 ml of benzylamine and then 1.1 ml of isobutyric aldehyde were added. The mixture warmed up to 70–80°C spontaneously. The reaction mixture was stirred additionally for 3 h at 90–100°C. To the mixture cooled to room temperature, 10 ml of alcohol was added dropwise, and then the reaction mixture was evaporated in a vacuum. The residue was distributed in a mixture of 40 ml of chloroform and 10 ml of water, and the aqueous phase was extracted additionally with 50 ml of methylene chloride. The combined organic phase was dried over $MgSO_4$ and evaporated in a vacuum. The residue was dissolved in a minimal volume of alcohol and passed through a Celite bed (eluent alcohol). The eluate was evaporated in a vacuum, and the residue was recrystallized from acetone. For additional purification, the amino acid was dissolved in 5 ml of 1 N HCl, the mixture was evaporated with water, and the concentrated hydrochloride solution was evaporated on Diasorb-Sulfo (H^+) weakly acidic cation exchanger (eluent water–0.5 N HCl). The acidic eluate was evaporated in a vacuum, and the residue was dissolved in aqueous alcohol (1 : 3) and treated with 1 ml of propylene oxide. Compound **Ib** was isolated, yield 1.2 g (30% based on ammonium hypophosphite), mp 115–118°C. ^{1}H NMR spectrum (D_2O + NaOD, pH ~10), δ, ppm: 0.88 br.d (6H, $2CH_3$), 1.62 m (2H, CH_2), 2.02 m (1H, CH), 2.37 d (1H, CHP, J_{PH} 10 Hz), 2.57 m (2H, CH_2), 3.70 br.s (2H, CH_2Ph), 7.18 m (10H, 2Ph). ^{1}H NMR spectrum (CD_3OD), δ, ppm: 1.08 d (3H, CH_3), 1.18 d (3H, CH_3), 1.85 m (2H, CH_2), 2.28 m (1H, C*H*Me_2), 2.82 m (3H, C*H*$_2$Ph + CHP), 4.30 d (1H, NC*H*$_2$Ph), 4.47 d (1H, NC*H*$_2$Ph), 7.21 m (5H, Ph), 7.47 m (3H, Ph'), 7.58 m (2H, Ph'). ^{13}C NMR spectrum (CD_3OD), δ_C, ppm: 17.9 d (Me, *J* 5.6 Hz), 18.8 d (Me, *J* 4.8 Hz), 26.4 s (*C*HMe_2), 27.5 d (*C*H$_2$Ph, *J* 3.9 Hz), 33.4 d (*C*H$_2$P, *J* 95.3 Hz), 50.2 s (*C*H$_2$N), 61.1 d (*C*HP, *J* 82.3 Hz), 125.1–130.8 m + 141.6 d (*J* 14.9 Hz) (2Ph). ^{31}P NMR spectrum, δ_P, ppm: 31.3 (CD_3OD); 44.1 (D_2O + NaOD, pH ~10). Found, %: C 62.45; 62.48; H 7.97, 8.08; P 8.21, 8.03. $C_{19}H_{26}NO_2P \cdot 2H_2O$. Calculated, %: C 62.11; H 8.23; P 8.43.

2-Hydroxycarbonyl-2-isobutylethyl-α-(benzylamino)benzylphosphinic acid Ic. A mixture of 1.2 g of H_2POONH_4 and 7 ml of hexamethyldisilazane was stirred for 2 h at 120°C. To the mixture cooled under argon flow to 60°C, 2.3 ml of ethyl α-isobutylacrylate was slowly added dropwise. The mixture was stirred for 2 h at 60°C, then heated to 100°C, and 1.6 ml of benzylamine and then 1.5 ml of benzaldehyde were added. The mixture warmed up to 110°C. The mixture was stirred for 3 h at 110–120°C, then cooled to room temperature, and 15 ml of aqueous alcohol was slowly added dropwise. The mixture was evaporated in a vacuum, and the residue was dissolved in 40 ml of chloroform and washed with water (2 × 10 ml). The organic phase was dried over $MgSO_4$, the solution was concentrated and passed through a Celite bed, and the eluate was evaporated. The residue was boiled in 15 ml of 8 N HCl for 10 h, and the resulting solution was extracted with benzene (2 × 10 ml). The acidic aqueous phase was evaporated, and the residue was mixed with water, evaporated, dissolved in a minimal amount of water, and separated on Diasorb-Sulfo (H^+) weakly acidic cation exchanger. The aqueous eluate was evaporated in a vacuum, and the residue was recrystallized from an alcohol–ether mixture; 1.7 g (29% based on ammonium hypophosphite) of **Ic** was isolated, mp 187–189°C. ^{1}H NMR spectrum (D_2O + DCl), δ, ppm: 0.15 m (6H, $2CH_3$), 0.70 m (1H, C*H*Me_2), 0.83 m (2H, CH_2P), 1.43 m (2H, CH_2), 1.98 m (1H, C*H*COOH), 3.48 br.s (2H, CH_2Ph), 4.38 d (1H, CHP, J_{PH} 9 Hz), 6.74 m (10H, Ph). ^{31}P NMR spectrum, δ_P, ppm: 49.0, 48.9 (5 : 1) (D_2O + DCl, pH ~1); 39.5, 38.7 (10 : 4) (D_2O + NaOD, pH ~10) (a mixture of diastereomers). Found, %: C 64.87; 64.98; H 6.97, 7.07; P 8.11, 8.13. $C_{21}H_{28}NO_4P$. Calculated, %: C 64.77; H 7.25; P 7.95.

The ^{1}H, ^{13}C and ^{31}P NMR spectra were recorded on a Bruker DPX-200 instrument with TMS (internal) and 85% H_3PO_4 (external) references. Ion-exchange chromatography was carried out on a Dowex 50WX8-200 (H^+) (Lancaster) and Diasorb-Sulfo (H^+) (Bio-ChemMac) cation exchangers. TLC analysis of individual compounds and reaction mixtures was carried out on Merck plates with 0.2-mm silica gel UV-254 layer and on Alufol (Kavalier) plates (neutral aluminum oxide on aluminum foil); eluents for the analysis of amino acids were 1-butanol–acetic acid–water, (5–8) : 1 : 1, or chloroform–ethanol–acetic acid, (3–5) : 2 : 1.

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