Synthesis of phosphinic and phosphonic analogs of aromatic amino acids

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The reaction of aryl and aralkyl aldoximes with hypophosphorous acid resulted in aminophosphinic acids, which were oxidized into the corresponding aminophosphonic acids.

Key words: amino acids, phosphorus analogs of amino acids; α-aminoaralkylphosphinic acids, oxidation; α-aminoaralkylphosphonic acids.

Phosphonic analogs of aromatic amino acids (1, R is aryl or aralkyl) and their *N*-acyl derivatives, including peptides, as well as the corresponding esters are some of the most studied compounds among phosphorus analogs of amino acids. A considerable number of works and reviews are devoted to their synthesis and properties.[1—4] Being structural analogs of amino acids, α-aminophosphonic acids compete with them for active enzyme centers and receptors. As inhibitors of various metabolic transformations of amino acids, α-aminophosphonic acids exhibit antibacterial and antitumor activity, are neuroactive, and have herbicide properties (see Refs. 1, 5, and 6).

Phosphinic analogs of aromatic amino acids (2, R is aryl or aralkyl) have not been adequately studied. One known procedure of their synthesis is based on addition of hypophosphorous acid to *N*-substituted Schiff's bases obtained from aldehydes with subsequent elimination of the protection. However, the yields of phosphinic analogs of Phe, Tyr, and Trp, synthesized by this procedure, are low (5—22%). The replacement of H_3PO_2 by bis(trimethylsilyloxy)phosphine allowed one to increase markedly the yield in the case of phosphinic analog of Phe.[8] This reagent was used to synthesize the same Phe analog from *N*-(trityl)benzylideneimine.[9]

Some aryl-substituted phosphinic analogs of phenylglycine were obtained by amidoalkylation of hypophosphorous acid with *N,N'*-arylidenebis(acetamides) followed by hydrolysis in 40—70% yields. But this method is not convenient for phosphinic analogs of the amino acids which differ from phenylglycine. Phosphinic analogs of proteinogenic aromatic amino acids were obtained in satisfactory yields by a rather complicated way from substituted imine of ethyl aminomethyl(diethoxymethylene)phosphinite.[11]

The first general method for the synthesis of α-aminoalkylphosphinic acids consisted in interaction of aldoximes with hypophosphorous acid, leading in one stage to phosphinic analogs of Ala, Val, Met, and Glu.[12] Although the reaction of oximes with H_3PO_2 remained hitherto poorly studied, the limits of their applications were unclear, and the search for the optimal conditions required additional experiments. The simplicity and mild conditions of the synthesis determined the choice of the oxime variant for obtaining phosphinic analogs of aromatic amino acids (Scheme 1).

Earlier,[12,15,16,18] we demonstrated the possibility of preparing α-aminophosphinic acids by interaction of oximes of aliphatic aldehydes and ketones with H_3PO_2. The formation of N^{α}-hydroxy-α-aminophosphinic acids was not observed, but was observed in the case of acetaldoxime, acetone oxime, and benzaldoxime.[13,14]

However, it is possible that N^{α}-hydroxy-α-aminophosphinic acids are intermediates in the reaction similarly to the known cases of the addition of H_3PO_2 at the C=N double bonds of imines and hydrazones. The reduction of oxime to α-aminophosphinite could proceed through formation of intermediate ester of H_3PO_2 possessing an N^{α}-hydroxy group, similarly to the transformation of oximes into imines with the participation of dialkylchlorophosphites, which was described earlier.[17] Another possibility consisting in a direct reduction of the N—O bond under the action of H_3PO_2 seems less probable because it requires, according to our data, more drastic conditions for other hydroxylamine derivatives.

It should be noted that small amounts of the corresponding α-aminophosphonates are always formed in this reaction, although the process is carried out in the atmosphere of an inert gas and in the presence of an

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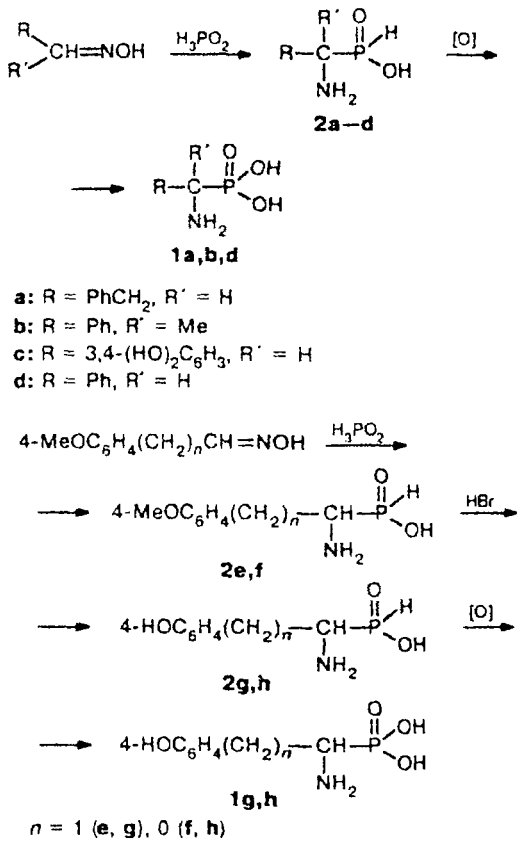
Scheme 1



excess of a strong reducing agent such as H_3PO_2. At present, various explanations of the indicated side reaction are considered in connection with our study of the mechanism of interaction of oximes with H_3PO_2.

It was first demonstrated in this work that oximes of aromatic and aliphatic-aromatic aldehydes and ketones could be transformed into the corresponding α-aminophosphinic acids under the action of H_3PO_2. The yields of the target aminophosphinic acids depend on the reaction conditions. Thus, isopropyl alcohol that is usually used as a solvent was unsuitable in the case of oximes of phenylacetaldehyde and *p*-methoxyphenylacetaldehyde, because the yields of the corresponding aminophosphinic acids did not exceed several per cent. When the reaction was carried out in methanol, the yields were several times higher, which is not yet adequately explained up to now, as is the necessity of using a considerable (tenfold) excess of H_3PO_2 and the exclusion of the solvent in the case of benzaldoxime.

The necessity of boiling for a long time a solution of acetophenone oxime in alcohol with H_3PO_2 suggests that in this case the rate-limiting stage is the addition of H_3PO_2 at the C=N bond, and not the reduction of the N—O bond.

One of the problems of synthesis of functionally substituted acids **2** consists in the fact that heating with strong acids is used to eliminate protective groups, though the instability of *N*-substituted derivatives **2** under these conditions has been reported earlier.[19] However, it turned out that in our case the hydrolysis of compounds of the type **2** was not accompanied by pronounced product decomposition.

The availability of α-aminophosphinic acids makes it possible to use their oxidation as a method for the synthesis of α-aminophosphonates, which is also justified completely for their aromatic analogs. Application of such oxidants as Br_2 in acid media, $HgCl_2$ and SO_2Cl_2 in glacial AcOH, or I_2 in HI leads, in the case of acids **2**, to the corresponding α-aminophosphonic acids (Table 1) in about 80% yields. The most suitable reagents being Br_2 or I_2 in acid media.

Experimental

Thin-layer chromatography was performed on Merck Kieselgel $60F_{254}$ plates in two systems: Pr^iOH—25% NH_4OH—H_2O, 7 : 2 : 1 (*A*) and AcOH—H_2O—acetone—Pr^iOH, 2.0 : 5.0 : 7.5 : 5.5 (*B*); the development of the substances was carried out by color reactions with ninhydrin and ammonium molybdate. Ion-exchange chromatography was performed on a Dowex 50X8 sulfocationite (100—200 mesh) in the H^+ form (BioRad, USA). Melting points were determined on an Electrothermals instrument (UK); the corresponding values (m.p.) are given uncorrected and with decomposition. ^1H NMR spectra were recorded on a Varian XL-100-15 instrument with Bu^tOH as the internal standard; the chemical shifts are given with respect to $SiMe_4$. Mass spectra were

Table 1. The characteristics of α-aminoaralkylphosphonic acids synthesized

Compound	R_f (*A*)	M.p./°C	^1H NMR (0.2 *N* NaOD), δ
1a	0.23	254[a]	2.35—3.25 (m, 3 H, CH_2CH); 6.95—7.08 (m, 5 H, H(Ar))
1b	0.20	205[b]	1.56 (d, 3 H, CH_3, J = 12 Hz); 6.80—7.20 (m, 5 H, H(Ar))
1f	0.18	268	3.70 (s, 3 H, CH_3); 3.63 (d, 1 H, CHP, J = 15 Hz); 6.55—7.10 (m, 4 H, H(Ar))
1g	0.13	277	2.15—3.05 (m, 3 H, CH_2CH); 6.18—6.72 (m, 4 H, H(Ar))
1h	0.09	[c]	3.56 (d, 1 H, CHP, J = 15 Hz); 6.20—6.84 (m, 4 H, H(Ar))

[a] Ref. 21: m.p. 247—249 °C. [b] Ref. 22: m.p. 237 °C. [c] Decomposes without melting at T > 230 °C.

obtained by the plasma desorption method on a MSBKh instrument (Ukraine).

1-Amino-2-phenylethylphosphinic acid (2a). A solution of oxime of phenylacetaldehyde (10.0 g, 74 mmol) in 50 mL of MeOH was added with stirring in an atmosphere of nitrogen in 30 min to a boiling solution of H_3PO_2 (9.77 g, 148 mmol) in 25 mL of MeOH and refluxed for an extra 4 h. The reaction mixture was concentrated to 1/3 of the initial volume, and 50 mL of Pr^{i}OH was added. Then triethylamine was added to pH 5, and the mixture was allowed to stand overnight at 20 °C. The precipitate that formed was filtered off and washed with ethanol. White crystals of compound **2a** (4.2 g, 30.7%) were obtained, m.p. 224—225 °C (H_2O—Pr^{i}OH) (*cf.* Ref. 7: m.p. 227—228 °C), R_f 0.70 (*A*), 0.75 (*B*). ^{1}H NMR (D_2O), δ: 2.65—3.55 (m, 3 H, CH_2CH); 7.04 (dd, 1 H, PH, J_1 = 526 Hz, J_2 = 1.5 Hz); 7.33—7.45 (m, 5 H, H(Ar)). MS, *m/z*: 184.1 $[M-1]^+$.

1-Amino-1-phenylethylphosphinic acid (2b). Acetophenone oxime (2.7 g, 20 mmol) was added with stirring in an atmosphere of nitrogen in 30 min to a boiling solution of H_3PO_2 (2.64 g, 40 mmol) in 8 mL of Pr^{i}OH and refluxed for an extra 24 h. The reaction mixture was cooled, poured into 15 mL of H_2O, and twice extracted with EtOAc. The aqueous layer was concentrated, and the residue was dissolved in 10% Pr^{i}OH. The product was isolated by ion-exchange chromatography with 10% Pr^{i}OH as the eluent. White crystals of compound **2b** (1.28 g, 34.6%) were obtained, m.p. 230 °C (H_2O—EtOH), R_f 0.65 (*A*), 0.74 (*B*). ^{1}H NMR (0.2 *N* NaOH), δ: 1.85 (d, 3 H, CH_3, J = 14 Hz); 6.89 (d, 1 H, PH, J = 524 Hz); 7.35—7.50 (m, 5 H, H(Ar)). 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-1-(3,4-dihydroxyphenyl)methylphosphinic acid (2c). A solution of oxime of 3,4-dihydroxybenzaldehyde (15.3 g, 100 mmol) in 50 mL of Pr^{i}OH was added with stirring in an atmosphere of nitrogen in 30 min to a boiling solution of H_3PO_2 (13.2 g, 200 mmol) in 50 mL of Pr^{i}OH and refluxed for an extra 4 h. The reaction mixture was cooled, and the precipitate that formed was filtered off and washed on the filter with ethanol. White crystals of compound **2c** (6.30 g, 31%) were obtained, which decompose without melting at T > 230 °C, R_f 0.69 (*B*). ^{1}H NMR (0.5 *N* DCl), δ: 4.40 (d, 1 H, CHP, J = 13 Hz); 6.90—7.30 (m, 4 H, H(Ar))*. Found (%): C, 41.11; H, 4.78; N, 6.62. $C_7H_{10}NO_4P$. Calculated (%): C, 41.39; H, 4.96; N, 6.90. MS, *m/z*: 203.2 $[M]^+$.

1-Amino-1-phenylmethylphosphinic acid (2d). Benzaldoxime (0.36 g, 3.0 mmol) was added with stirring in an atmosphere of nitrogen at 20 °C in 30 min to H_3PO_2 (1.98 g, 30 mmol), and the reaction mixture was allowed to stand for 72 h. The product was isolated by ion-exchange chromatography, and white crystals of compound **2d** (0.29 g, 56.5%) were obtained, m.p. 207—209 °C (H_2O—EtOH) (*cf.* Ref. 10: m.p. 242—243 °C), R_f 0.67 (*A*), 0.75 (*B*). ^{1}H NMR (D_2O), δ: 3.90 (dd, 1 H, CHP, J_1 = 13 Hz, J_2 = 1 Hz); 6.78 (dd, 1 H, PH, J_1 = 509 Hz, J_2 = 1.5 Hz); 7.2—7.4 (m, 5 H, H(Ar)). Found (%): C, 49.31; H, 5.63; N, 8.01. $C_7H_{10}NO_2P$. Calculated (%): C, 49.13; H, 5.89; N, 8.19. MS, *m/z*: 171.0 $[M-1]^+$.

1-Amino-2-(*p*-methoxyphenyl)ethylphosphinic acid (2e). Oxime of *p*-methoxyphenylacetaldehyde[20] (13.0 g, 78.8 mmol) was added with stirring in an atmosphere of nitrogen in 30 min to a boiling solution of H_3PO_2 (10.43 g, 158 mmol) in 300 mL of MeOH and refluxed for extra 15 h. The reaction mixture was concentrated to 1/5 of the initial volume, and the residue was dissolved in H_2O. The product was isolated by ion-exchange chromatography with H_2O as the first eluent and 1% NH_4OH as the second. The fractions containing acid **2e** were concentrated, and white crystals of compound **2e** (4.38 g, 25.9%) were obtained, m.p. 210—211 °C (H_2O), R_f 0.69 (*A*), 0.74 (*B*). ^{1}H NMR (0.2 *N* NaOH), δ: 2.40—3.20 (m, 3 H, CH_2CH); 3.83 (s, 3 H, CH_3); 6.74 (dd, 1 H, PH, J_1 = 501 Hz, J_2 = 1.5 Hz); 6.85—7.30 (m, 4 H, H(Ar)). Found (%): C, 50.09; H, 6.71; N, 6.66. $C_9H_{14}NO_3P$. Calculated (%): C, 50.23; H, 6.56; N, 6.51. MS, *m/z*: 215.1 $[M]^+$.

1-Amino-1-(*p*-methoxyphenyl)methylphosphinic acid (2f). A solution of oxime of *p*-methoxybenzaldehyde (13.2 g, 87.3 mmol) in 40 mL of Pr^{i}OH was added with stirring in an atmosphere of nitrogen in 30 min to a boiling solution of H_3PO_2 (11.55 g, 175 mmol) in 60 mL of Pr^{i}OH and refluxed for an extra 4 h. The reaction mixture was allowed to stand overnight at 20 °C. The precipitate that formed was filtered off and washed with ethanol. White crystals of compound **2f** (4.90 g, 28%) were obtained, m.p. 206—208 °C (H_2O—EtOH) (*cf.* Ref. 10: m.p. 237—238 °C), R_f 0.66 (*A*), 0.75 (*B*). ^{1}H NMR (0.2 *N* NaOH), δ: 3.80 (d, 1 H, CHP, J = 13 Hz); 3.80 (s, 3 H, CH_3); 6.75 (dd, 1 H, PH, J_1 = 509 Hz, J_2 = 1.5 Hz); 6.90—7.30 (m, 4 H, H(Ar)). Found (%): C, 47.52; H, 6.22; N, 6.71. $C_8H_{12}NO_3P$. Calculated (%): C, 47.76; H, 6.01; N, 6.96. MS, *m/z*: 200.3 $[M-1]^+$.

1-Amino-2-(*p*-hydroxyphenyl)ethylphosphinic acid (2g). A solution of compound **2e** (2.54 g, 11.8 mmol) and NaH_2PO_2 (0.05 g, 0,6 mmol) in 22 mL of 48% HBr was refluxed in an atmosphere of nitrogen for 45 min. and evaporated to dryness. The residue was dissolved in 15% Pr^{i}OH, and the product was isolated by ion-exchange chromatography with 15% Pr^{i}OH as the eluent. White crystals of compound **2g** (2.27 g, 96%) were obtained, m.p. 226—227 °C (H_2O—Pr^{i}OH) (*cf.* Refs. 7 (235 °C) and 11 (252 °C for monohydrate)), R_f 0.61 (*A*), 0.78 (*B*). ^{1}H NMR (0.2 *N* NaOH), δ: 2.20—3.13 (m, 3 H, CH_2CH); 6.55—7.13 (m, 4 H, H(Ar)); 6.75 (dd, 1 H, PH, J_1 = 499 Hz, J_2 = 1.5 Hz). MS, *m/z*: 199.2 $[M-2]^+$.

1-Amino-2-phenylethylphosphonic acid (1a). Br_2 was added dropwise with stirring at 20 °C to a solution of compound **2a** (1.17 g, 6.3 mmol) in 5 mL of 2.0 *N* HCl until a stable yellow color appeared, and then stirred for extra 30 min. The reaction mixture was evaporated to dryness, the residue was dissolved in ethanol, and propylene oxide was added. A crude product (1.38 g) was recrystallized from aqueous ethanol. White crystals of compound **1a** (1.11 g, 87%) were obtained (see Table 1).

In a similar manner, the corresponding aminophosphonate **1b** was synthesized from aminophosphinic acid **2b**, yield 76% (see Table 1). 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.

1-Amino-2-(*p*-hydroxyphenyl)ethylphosphonic acid (1g). A 1 *N* solution of I_2 (10.5 mL) in EtOH was added dropwise with stirring at 20 °C to a solution of compound **2g** (0.20 g, 1.0 mmol) in a mixture of 0.5 mL of conc. HI and 3 mL of EtOH. The reaction mixture was stirred for an extra 1 h and then evaporated to dryness. The residue was dissolved in 15% Pr^{i}OH, and the product was isolated by ion-exchange chromatography with 15% Pr^{i}OH as the eluent. The fractions containing acid **1g** were concentrated, and the residue was recrystallized from aqueous Pr^{i}OH. White crystals of compound **1g** (0.18 g, 83%) were obtained.

In a similar manner, aminophosphonic acid **1f** (see Table 1) was synthesized from aminophosphinic acid **2f** (in 58% yield). Found (%): C, 44.39; H, 5.71; N, 6.29. $C_8H_{12}NO_4P$. Calculated (%): C, 44.25; H, 5.57; N, 6.45.

* The >P—H proton is exchanged for deuterium and does not appear in the spectrum.

1-Amino-1-(*p*-hydroxyphenyl)methylphosphonic acid (1h). A solution of compound **2f** (1.00 g, 5.0 mmol) and NaH_2PO_2 (0.05 g, 0,6 mmol) in 8 mL of 48% HBr was kept in an atmosphere of nitrogen at 100 °C for 7 h and evaporated to dryness. The residue was dissolved in H_2O, and the product was isolated by ion-exchange chromatography with H_2O as the eluent. White crystals of compound **2h** (0.26 g, 28%) were obtained, m.p. 192—194 °C (H_2O—EtOH), R_f 0.58 (*A*), 0.76 (*B*). ^1H NMR (0.2 *N* NaOH), δ: 3.70 (d, 1 H, CHP, J = 16 Hz); 6.50—7.10 (m, 4 H, H(Ar)); 6.73 (dd, 1 H, PH, J_1 = 503 Hz, J_2 = 1.5 Hz). MS, *m/z*: 186.3 $[M-1]^+$. Oxidation of compound **2h** into **1h** (yield 71%) was carried out similarly to the above-mentioned synthesis of compound **1g** from **2g**. Found (%): C, 41.08; H, 5.21; N, 6.73. $C_7H_{10}NO_4P$. Calculated (%): C, 41.39; H, 4.96; N, 6.89.

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References

1. P. Kafarski and P. Mastalerz, *Betrage zur Wirkstofforschung, Heft 21*, Akademie-Industrie-Komplex Arzneimittelforschung, Academia der Wissenschaften der DDR, Berlin, 1984.
2. K. A. Petrov, V. A. Chauzov, and E. S. Erokhin, *Usp. Khim.*, 1974, **43**, 2045 [*Russ. Chem. Rev.*, 1974, **43** (Engl. Transl.)].
3. V. P. Kukhar' and V. A. Solodenko, *Usp. Khim.*, 1987, **56**, 1504 [*Russ. Chem. Rev.*, 1987, **56** (Engl. Transl.)].
4. V. P. Kukhar', N. Yu. Svistunova, V. A. Solodenko, and V. A. Soloshonok, *Usp. Khim.*, 1993, **62**, 284 [*Russ. Chem. Rev.*, 1993, **62** (Engl. Transl.)].
5. G. M. Kishore and D. M. Shah, *Ann. Rev. Biochem.*, 1988, **57**, 627.
6. P. Kafarski and B. Lejczak, *Phosp. Sulf., and Silicon*, 1991, **63**, 193.
7. E. K. Baylis, C. D. Campbell, and J. G. Dingwall, *J. Chem. Soc., Perkin Trans. 1*, 1984, 2845.
8. D. Grobelny, *Synthesis*, 1987, 942.
9. X. Jiao, C. Verbruggen, M. Borloo, W. Bollaert, A. Groot, R. Dommisse, and A. Haemers, *Synthesis*, 1994, 23.
10. R. Tyka and G. Hagele, *Phosp. Sulf., and Silicon*, 1989, **44**, 103.
11. P. P. McCleery and B. Tuck, *J. Chem. Soc., Perkin Trans. 1*, 1989, 1319.
12. R. M. Khomutov and T. I. Osipova, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1978, 1954 [*Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1978, **27**, 1722 (Engl. Transl.)].
13. N. Kreutzkamp, K. Storck, and C.Schimpfsky, *Archiv. Pharmazie.*, 1969, **302**, 554.
14. EP 63464, 1982; *Chem. Abstrs.*, 1983, **98**, P1026864.
15. Author Certificate SSSR No. 1558921; *Bull. Izobret.*, 1990, No. 15, 138 (in Russian).
16. Author Certificate SSSR No. 1571996 (in Russian).
17. Yu. L. Kruglyak, M. A. Landau, G. A. Leibovskaya, I. V. Martynov, L. I. Saltykova, and M. A. Sokal'skii, *Zh. Obshch. Khim.*, 1969, **39**, 215 [*J. Gen. Chem. USSR*, 1969, **39** (Engl. Transl.)].
18. A. R. Khomutov, *Bioorg. Khim.*, 1990, **16**, 1290 [*Sov. J. Bioorg. Chem.*, 1990, **16** (Engl. Transl.)].
19. H. Schmidt, *Chem. Ber.*, 1948, **81**, 479.
20. K. W. Rosenmund and H. Dornsaft, *Chem. Ber.*, 1919, **52**, 1734.
21. B. Leiczak, D. Dus, and P. Kafarski, *Anti-Cancer Drug Design*, 1990, **5**, 351.
22. T. Ya. Medved' and M. I. Kabachnik, *Dokl. Akad. Nauk SSSR*, 1952, **84**, 717 [*Dokl. Chem.*, 1952, **84** (Engl. Transl.)].

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