First synthesis of α-aminophosphonates from natural porphyrin derivatives by the Kabachnik—Fields reaction

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A preparative procedure is proposed for the synthesis of α-aminophosphonates of natural porphyrins by the microwave-assisted Kabachnik—Fields reaction.

Key words: natural porphyrins, α-aminophosphonates, microwave-assisted reaction.

In recent years, hemoglobin derivatives have attracted considerable interest as the starting compounds for the design of new biologically active substances with a broad spectrum of action. Photofrin II™ and Vusidyne,™ which are used, respectively, as photosensitizers for photodynamic tumor therapy and in ophthalmology,[1—4] are the most prominent examples of successful clinical application of hemoglobin derivatives. Low efficiency of Photofrin II™ and the complicated synthesis of Vusidyne™ are disadvantages of these drugs.[4] That is why the design of new biologically active compounds based on natural porphyrins is of great importance. It is also well known that α-aminophosphonates and α-aminophosphonic acids, being structural analogs of α-aminocarboxylic acids, exhibit various biological activities. Many representatives of this class possess antibacterial activity[5] and are used as cancerostatic, cytostatic, and other compounds of pharmacological importance.[6,7]

Recently, we have studied the microwave-assisted reactions of dialkyl phosphites with aldimines and ketimines in the presence of catalytic amounts of cadmium iodide[8] and demonstrated for the first time that the pharmacogenic α-aminophosphonate group can be introduced into natural porphyrins.[9] It should be noted that microwave-assisted reactions of the corresponding azomethines with diethyl phosphite are successfully used to synthesize α-aminophosphonates of natural porphyrins by condensation of substitued benzaldehydes with pyrrole. However, it appeared that porphyrin-derived azomethines are unstable, which was adversely reflected in the yields of the final products.

As part of our continuing studies aimed at introducing the pharmacogenic α-aminophosphonate group into natural porphyrins, we examined the possibility of synthesizing α-aminophosphonates starting from natural porphyrins by the Kabachnik—Fields reaction, *i.e.*, by condensation of a carbonyl compound with a primary amine and a dialkyl phosphite.

Microwave-assisted condensation of natural porphyrins **1a—f** (Scheme 1) with *tert*-butylamine and diethyl phosphite (1 : 1 : 3) in dichloroethane occurred quantitatively (^{31}P NMR spectroscopy). The necessity of using a threefold excess of diethyl phosphite is associated with the fact that it is partly evaporated in the course of the reaction performed in a microwave oven (the reactions were carried out in an open flat-bottom flask). If the reagents were used in the equimolar ratio, the yields of the final products decreased to 50—60%.

All phosphorus-substituted porphyrins were synthesized as crystalline compounds. Their structures were confirmed by ^{31}P and ^{1}H NMR spectroscopy (Table 1) and mass spectrometry. After purification, compounds **2a—f** were obtained in 87—95% yields.

The ^{31}P NMR spectra of compounds **2a—f** have singlets at δ 19.5—25.8. It should be noted that the signal of porphyrins **2c—e** in which the phosphonate group is directly bound to the macrocycle is shifted upfield (δ 19.5—21.2).

The mass spectra of porphyrin derivatives **2a,b** show the molecular ion peak $[MH]^+$ at m/z 816.1 and the daughter ion $[MH^+ - H_2O]$ at m/z 798.2 corresponding to the rearrangement of the chlorin macrocycle into the more stable porphyrin macrocycle through elimination of a water molecule. The mass spectra of aminophosphonates **2c,d** and **2e** show no peaks of molecular ions; the major ion peaks $[MH^+ - Bu^t]$ at m/z 731.0 and 777.4 result from elimination of the *tert*-butyl group of the aminophosphonate substituent. α-Aminophosphonate **2f** undergoes deeper fragmentation. The mass spectrum of the latter contains a fragment ion at m/z 624.7 corresponding to

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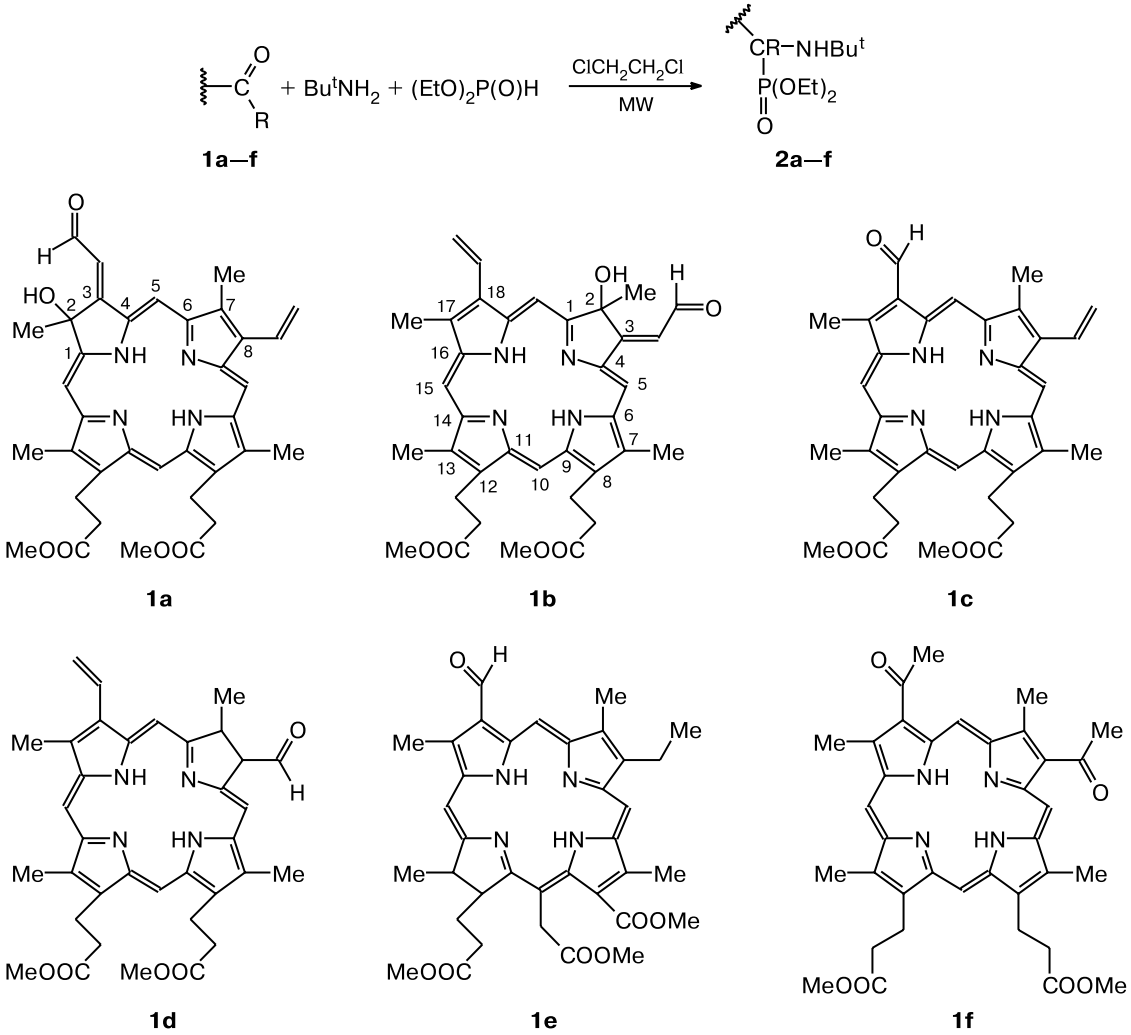
Scheme 1



R = H, Me

elimination of the Bu^t and $(EtO)_2P(O)$ groups from both α-aminophosphonate substituents.

To summarize, α-aminophosphonates of natural porphyrins can be prepared in high yields by the microwave-assisted Kabachnik—Fields reaction.

Experimental

The ^1H and ^{31}P NMR spectra (400 and 161.90 MHz, respectively) were recorded on a Varian VXR 400 instrument in C_6D_6; the chemical shifts were determined relative to the signals of the residual protons of the deuterated solvent for ^1H NMR and the signals of the external standard (85% H_3PO_4) for ^{31}P NMR. Electrospray-chemical ionization mass spectra were recorded on a Finnigan MAT-LCQ spectrometer (USA) using a chloroform—acetonitrile mixture as the carrier gas. The TLC analysis was carried out on Silufol plates using a 5 : 1 hexane—ethyl acetate system.

Commercial protohemin IX was used as the starting compound for the synthesis of α-aminophosphonates **2a,b**. It was successively transformed into aldehydes **1a,b**.[9] Formylporphyrins **1c,d** were synthesized by periodate oxidation of diols of photoprotoporphyrins.[10] Triformylchlorin e_6 trimethyl ester **1e** was prepared by oxidation of the vinyl groups of chlorin e_6 trimethyl ester with an OsO_4—$NaIO_4$ system.[11] 3,8-Diacetyl-13,17-bis(2-methoxycarbonylethyl)-2,7,12,18-tetramethylporphyrin **1f** was prepared by direct acetylation of the porphyrin ring.[12]

3-(2-*tert*-Butylamino-2-diethoxyphosphoryl)ethylidene-2-hydroxy-13,17-bis(2-methoxycarbonylethyl)-2,7,12,18-tetramethyl-8-vinylporphyrin (2a). Diethyl phosphite (21 mg, 0.15 mmol) and *tert*-butylamine (30 mg, 0.05 mmol) were added to a solution of porphyrin **1a** (30 mg, 0.048 mmol) in anhydrous dichloroethane (1.5 mL) in an open Erlenmeyer flask. The reaction was carried out in a domestic microwave oven (Daewoo, KOR-4125G, 102 W) for 2 min. The solvent and excess diethyl phosphite were evaporated *in vacuo*. The final reaction product was isolated by column chromatography on silica gel

Table 1. Parameters of the ^{31}P and ^{1}H NMR spectra of compounds **2a—f**

Compound	δ_P	δ_H (J/Hz)
2a	23.8	9.86, 9.67, 9.29, 9.22 (all s, 4 H, *meso*-H); 8.19 (dd, 1 H, 8-C<u>H</u>=CH$_2$, J_{trans} = 17.7, J_{cis} = 11.5); 7.06 (two d, 1 H, C(3)=C<u>H</u>, J_{cis} = 7.5, J_{trans} = 8.7); 6.35 (d, 1 H, *trans*-8-CH=C<u>H</u>$_2$, J_{gem} = 1.4); 6.17—6.14 (d, 1 H, *cis*-8-CH=C<u>H</u>$_2$); 5.32 (dd, 1 H, C(3)=CHC<u>H</u>, $J_{H,P}$ = 19); 4.30 (q, 4 H, P(O)(OC<u>H</u>$_2$CH$_3$)$_2$); 4.19, 4.08 (both t, 4 H each, 2 C<u>H</u>$_2$CH$_2$CO$_2$CH$_3$); 3.66, 3.64 (both s, 6 H each, 2 CH$_2$CH$_2$CO$_2$C<u>H</u>$_3$); 3.59, 3.48, 3.40 (all s, 9 H each, 3 CH$_3$); 3.21—3.14 (two overlap. t, 4 H, 2 CH$_2$C<u>H</u>$_2$CO$_2$CH$_3$); 2.35 (br.s, 1 H, N<u>H</u>); 2.14 (s, 3 H, 2 C<u>H</u>$_3$); 1.46 (s, 9 H, C(C<u>H</u>$_3$)$_3$); 1.33 (t, 6 H, P(O)(OCH$_2$C<u>H</u>$_3$)$_2$); −2.41, −2.54 (both br.s, 2 H each, 2 NH)
2b	23.8	9.87, 9.69, 9.29, 9.23 (all s, 4 H each, *meso*-H); 8.20 (dd, 1 H, 3-C<u>H</u>=CH$_2$, J_{trans} = 17.7, J_{cis} = 11.5); 7.06 (two d, 1 H, C(8)=C<u>H</u>, J_{cis} = 7.5, J_{trans} = 8.7); 6.35 (d, 1 H, *trans*-3-CH=C<u>H</u>$_2$, J_{gem} = 1.4); 6.17—6.14 (d, 1 H, *cis*-3-CH=C<u>H</u>$_2$); 5.32 (dd, 1 H, C(8)=CHC<u>H</u>, $J_{H,P}$ = 19); 4.31 (q, 4 H, P(O)(OC<u>H</u>$_2$CH$_3$)$_2$); 4.20, 4.09 (both t, 4 H each, 2 C<u>H</u>$_2$CH$_2$CO$_2$CH$_3$); 3.67, 3.65 (both s, 6 H each, 2 CH$_2$CH$_2$CO$_2$C<u>H</u>$_3$); 3.59, 3.49, 3.41 (all s, 9 H each, 3 CH$_3$ rings); 3.22—3.15 (two overlap. t, 4 H, 2 CH$_2$C<u>H</u>$_2$CO$_2$CH$_3$); 2.41 (br.s, 1 H, N<u>H</u>); 2.14 (s, 3 H, 2 C<u>H</u>$_3$); 1.46 (s, 9 H, C(C<u>H</u>$_3$)$_3$); 1.34 (t, 6 H, P(O)(OCH$_2$C<u>H</u>$_3$)$_2$); −2.38, −2.49 (both br.s, 2 H each, 2 NH)
2c	19.5	10.24, 9.99, 9.85, 9.84 (all s, 4 H, *meso*-H); 8.21 (dd, 1 H, 8-C<u>H</u>=CH$_2$, J_{trans} = 17.7, J_{cis} = 11.8); 6.35 (d, 1 H, *trans*-8-CH=C<u>H</u>$_2$, J_{gem} = 0.5); 6.20—6.16 (m, 2 H, *cis*-8-CH=C<u>H</u>$_2$ and C(3)=C<u>H</u>); 4.34—4.28 (two overlap. t, 4 H, 2 C<u>H</u>$_2$CH$_2$CO$_2$CH$_3$), 4.22—4.12 (two overlap. q, 4 H, P(O)(OC<u>H</u>$_2$CH$_3$)$_2$); 3.65, 3.65, 3.64, 3.57, 3.55, 3.52 (all s, 18 H, 2 CH$_2$CH$_2$CO$_2$C<u>H</u>$_3$ and 4 C<u>H</u>$_3$); 3.23—3.19 (two overlap. t, 4 H, 2 CH$_2$C<u>H</u>$_2$CO$_2$CH$_3$); 2.80 (br.s, 1 H, N<u>H</u>); 1.28 (t, 6 H, P(O)(OCH$_2$C<u>H</u>$_3$)$_2$); 1.24, 1.23 (both s, 9 H each, C(C<u>H</u>$_3$)$_3$); −4.21 (br.s, 2 H, 2 NH)
2d	19.5	10.26, 9.99, 9.88, 9.85 (all s, 4 H, *meso*-H); 8.24 (dd, 1 H, 3-C<u>H</u>=CH$_2$, J_{trans} = 17.7, J_{cis} = 11.8); 6.35 (d, 1 H, *trans*-3-CH=C<u>H</u>$_2$, J_{gem} = 0.5); 6.20—6.16 (m, 2 H, *cis*-3-CH=C<u>H</u>$_2$ and C(3)CH=CH$_2$), 4.34—4.28 (two overlap. t, 4 H, 2 C<u>H</u>$_2$CH$_2$CO$_2$CH$_3$); 4.20—4.12 (two overlap. q, 4 H, P(O)(OC<u>H</u>$_2$CH$_3$)$_2$); 3.65, 3.65, 3.64, 3.57, 3.55, 3.52 (all s, 18 H each, 2 CH$_2$CH$_2$CO$_2$C<u>H</u>$_3$ and 4 C<u>H</u>$_3$); 3.26—3.21 (two overlap. t, 4 H, 2 CH$_2$C<u>H</u>$_2$CO$_2$CH$_3$); 2.89 (br.s, 1 H, N<u>H</u>); 1.29 (t, 6 H, P(O)(OCH$_2$C<u>H</u>$_3$)$_2$); 1.25, 1.24 (both s, 9 H each, C(C<u>H</u>$_3$)$_3$); −4.24 (br.s, 2 H, 2 NH)
2e	21.2	10.30, 9.96, 9.85 (all s, 3 H each, *meso*-H); 8.27—8.20 (m, 2 H, 8-C<u>H</u>$_2$—CH$_3$); 6.30—6.29 (t, 1 H, 8-CH$_2$—C<u>H</u>$_3$, J = 0.5); 6.26 (m, 2 H, 8-CH$_2$—C<u>H</u>$_3$ and C(8)C<u>H</u>HMe); 4.34 (t, 2 H, C<u>H</u>$_2$CH$_2$CO$_2$CH$_3$); 4.20—4.12 (two overlap. q, 4 H, P(O)(OC<u>H</u>$_2$CH$_3$)$_2$); 3.60, 3.59, 3.57, 3.55, 3.52 (all s, 21 H each, 3 CH$_2$CH$_2$CO$_2$C<u>H</u>$_3$ and 4 C<u>H</u>$_3$); 3.24 (s, 2 H, C<u>H</u>$_2$CO$_2$CH$_3$); 2.77 (br.s, 1 H, N<u>H</u>); 1.31 (t, 6 H, P(O)(OCH$_2$C<u>H</u>$_3$)$_2$); 1.24, 1.21 (both s, 9 H each, C(C<u>H</u>$_3$)$_3$); −4.20 (br.s, 2 H, 2 NH)
2f	25.8	10.20, 10.05, 9.80, 9.79 (all s, 4 H each, *meso*-H); 4.34—4.28 (two overlap. t, 4 H, 2 C<u>H</u>$_2$CH$_2$CO$_2$CH$_3$); 4.25—4.19 (two overlap. q, 4 H, P(O)(OC<u>H</u>$_2$CH$_3$)$_2$); 3.69, 3.67, 3.64, 3.55, 3.53, 3.50 (all s, 18 H each, 2 CH$_2$CH$_2$CO$_2$C<u>H</u>$_3$ and 4 C<u>H</u>$_3$); 3.28—3.25 (two overlap. t, 4 H, 2 CH$_2$C<u>H</u>$_2$CO$_2$CH$_3$); 2.40 (br.s, 1 H, N<u>H</u>); 1.32 (t, 6 H, P(O)(OCH$_2$C<u>H</u>$_3$)$_2$); 1.21, 1.19 (both s, 9 H each, C(C<u>H</u>$_3$)$_3$), −4.13 (br.s, 2 H, 2 NH)

(acetone—dichloromethane, 1 : 20, as the eluent). After evaporation of the solvent, compound **2a** was obtained as an oil, which was dissolved in methanol and precipitated with hexane. The yield was 37 mg (95%), m.p. 204 °C (decomp.).

3-(2-*tert*-Butylamino-2-diethoxyphosphoryl)ethylidene-2-hydroxy-8,12-bis(2-methoxycarbonylethyl)-2,7,3,17-tetramethyl-18-vinylporphyrin (2b) was prepared analogously from porphyrin **1b** (30 mg, 0.048 mmol), diethyl phosphite (21 mg, 0.15 mol), and *tert*-butylamine (30 mg, 0.05 mmol); the reaction time was 2 min. The yield was 36 mg (93%), m.p. 202 °C (decomp.).

3-[(*tert*-Butylamino)diethoxyphosphoryl]methyl-13,17-bis(2-methoxycarbonylethyl)-2,7,12,18-tetramethyl-8-vinylporphyrin (2c) was prepared analogously from porphyrin **1c** (50 mg, 0.09 mmol), diethyl phosphite (37 mg, 0.27 mmol), and *tert*-butylamine (60 mg, 0.09 mmol); the reaction time was 7 min. The yield was 60 mg (89%), m.p. 212 °C (decomp.).

3-(*tert*-Butylaminodiethoxyphosphoryl)methyl-8,12-bis(2-methoxycarbonylethyl)-2,7,13,17-tetramethyl-18-vinylporphyrin (2d) was prepared analogously from porphyrin **1d** (50 mg, 0.09 mmol), diethyl phosphite (37 mg, 0.27 mmol), and *tert*-butylamine (60 mg, 0.09 mmol); the reaction time was 7 min. The yield was 61 mg (90%), m.p. 212 °C (decomp.).

3-[(*tert*-Butylamino)diethoxyphosphoryl]methyl-8-ethyl-13-methoxycarbonyl-17-(2-methoxycarbonylethyl)-15-methoxycarbonylmethyl-2,7,12,18-tetramethylporphyrin (2e) was prepared analogously from porphyrin **1e** (58 mg, 0.09 mmol), diethyl phosphite (37 mg, 0.27 mmol), and *tert*-butylamine (60 mg, 0.09 mmol); the reaction time was 8 min. The yield was 65 mg (87%), m.p. 215 °C (decomp.). Found (%): C, 63.32; H, 7.31; N, 8.44. $C_{44}H_{60}N_5O_9P$. Calculated (%): C, 63.37; H, 7.25; N, 8.40.

3,8-Bis(1-*tert*-butylamino-1-diethoxyphosphoryl)ethyl-13,17-bis(2-methoxycarbonylethyl)-2,7,12,18-tetramethylporphyrin (2f) was prepared analogously to compound **2a** from porphyrin **1f** (56 mg, 0.09 mmol), diethyl phosphite (37 mg, 0.27 mmol), and *tert*-butylamine (60 mg, 0.09 mmol); the reaction time was 4 min. The yield was 67 mg (91%), m.p. 194 °C

(decomp.). Found (%): C, 61.89; H, 7.82; N, 8.29. $C_{44}H_{60}N_5O_9P$. Calculated (%): C, 61.89; H, 7.79; N, 8.33.

For compounds **2a—d**, which were prepared by the Kabachnik—Fields reaction, the spectroscopic characteristics are identical to those reported earlier.[9]

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