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A New Synthetic Approach to α-Aminophosphonic Acids: Synthesis and NMR Characterization

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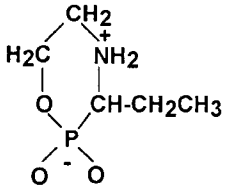
ABSTRACT: *In this article, a new synthetic approach to a 1,4,2-oxazaphosphorinane, and to α-ethyl-α-N-(hydroxyethylamino)methyl phosphonicacid and their sodium salts is described. The title compounds were characterized by NMR and FAB spectroscopy.* © 1999 John Wiley & Sons, Inc. Heteroatom Chem 10: 627–631, 1999

INTRODUCTION

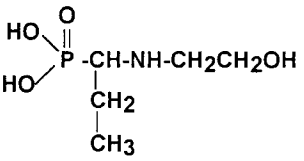
Recently, we reported on the thermal decomposition of a polyurethane phosphonate that resulted in the formation of 3-ethyl-2-hydroxy-2-oxo-1,4,2-oxazaphosphorinane **1**, a cyclic aminophosphonic acid [1].

The present interest in aminophosphonic acids and their derivatives, defined as phosphorus analogs of amino acids, is centered around the biological activities [2–5] and synthesis [6–10] of these compounds. A recent report indicated that the herbicide glyphosate (*N*-phosphonomethyl glycine) is effective in inhibiting test-tube growth of *Plasmodium falciparum,* the parasite that causes malaria [11]. It has the same effect on related types of single-celled parasites that cause opportunistic infection in AIDS patients [12].

In this article, we describe the synthesis of **1** and of α-ethyl-α-*N*-(hydroxyethylamino)methylphosphonic acid **2** and their sodium salts:



1



2

RESULTS AND DISCUSSION

3-Ethyl-2-hydroxy-2-oxo-1,4,2-oxazaphosphorinane **1** was obtained by heating various phosphonic acid diesters with a hydroxyalkylcarbamate mixture (Scheme 1) in a molar ratio of 1:1. During the first stage of the reaction at 135°C, transesterification oc-

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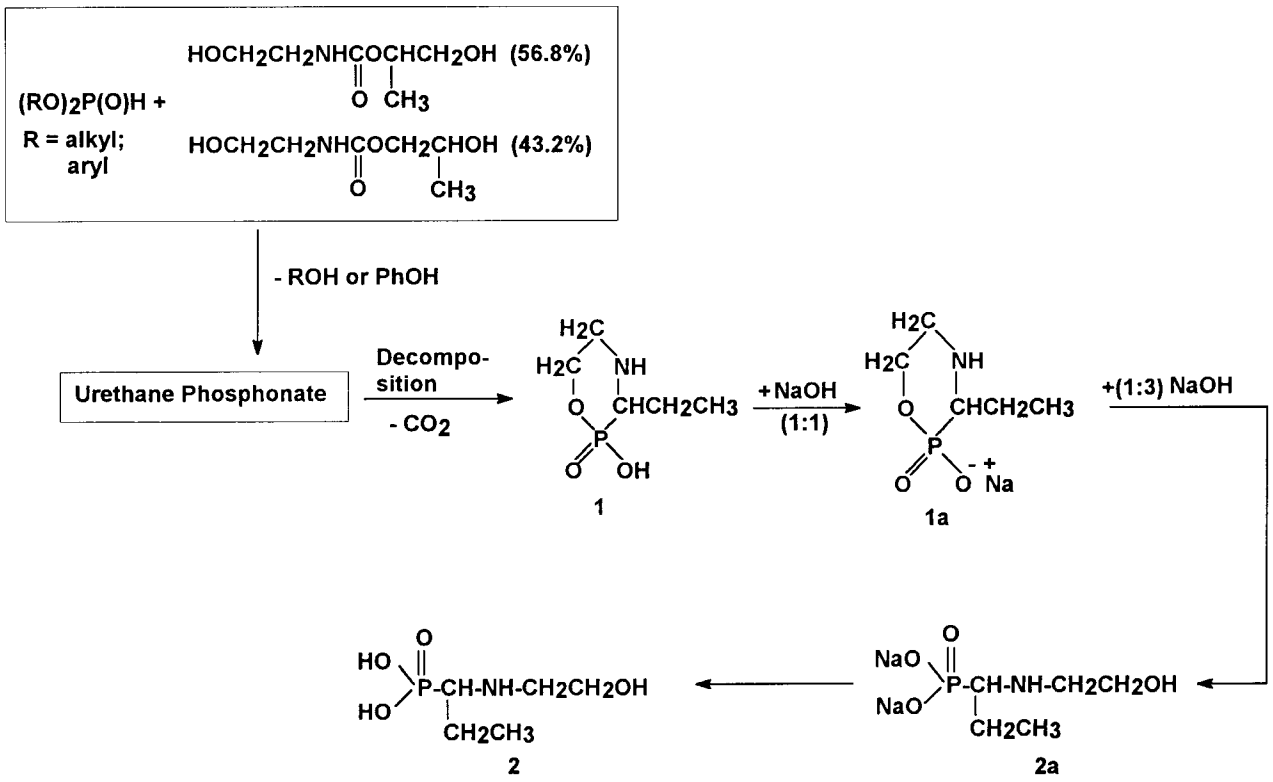


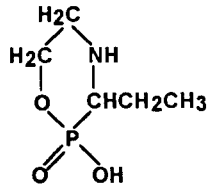
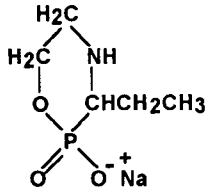
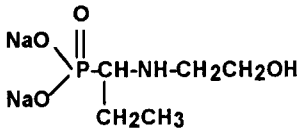
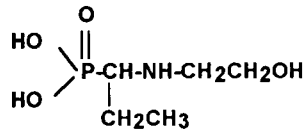
SCHEME 1

curred to give the urethane phosphonates. In the second stage of the reaction at 170°C, thermal decomposition of the urethane phosphonates led to the selective isolation of **1** in low yield. The structure of compound **1** was established by elemental analysis, IR, and ^{1}H, ^{31}P, and ^{13}C NMR spectroscopy (Table 1). The NMR data (Table 1) confirm the structure of **1**. The $^{1}H\{^{31}P\}$ NMR spectrum showed two multiplets at 1.64–1.77 and 1.83–1.97 ppm, which appear as quintets that can be assigned to the $CHCH_2CH_3$ protons and correspond to the signal at 21.4 ppm in the ^{13}C NMR spectrum. A HETCOR experiment revealed that the signal for the CH_3 group at $\delta_H = 1.04$ ppm in the ^{1}H NMR spectrum correlates with the signal at $\delta_C = 10.1$ ppm in the ^{13}C NMR spectrum. The signals at $\delta_C = 3.16$–3.36 ppm that appear as a triplet (3.22 ppm) (from the $^{1}H\{^{31}P\}$ NMR) and the multiplet (3.27–3.38 ppm) in the ^{1}H NMR spectrum correlate with the corresponding signals at $\delta_C = 55.9$ ppm and at $\delta_C = 44.7$ ppm in the ^{13}C NMR spectra, that is, the CH and CH_2N protons. The signal at $\delta_C = 4.18$–4.36 ppm (a multiplet) in the ^{1}H NMR spectrum correlates with the signal at $\delta_C = 63.1$ ppm in the ^{13}C NMR spectrum, that is, the $POCH_2$ protons. The $^{13}C\{^{1}H\}$DEPT spectrum shows that the signals correspond to the following groups: $\delta_C = 10.1$ ppm, the CH_3 group; $\delta_C = 21.40$ ppm and $\delta_C = 44.7$ ppm, the two CH_2 groups; $\delta_C = 55.9$ ppm, the CH group; and $\delta_C = 63.1$ ppm, the $POCH_2$ group. The IR spectral data are in accordance with the ^{1}H NMR data. The FAB spectrum shows a signal at $MH^+ = 166.1$.

We currently know that the thermal decomposition of the urethane phosphonate is accompanied by the evolution of CO_2; the reaction is exothermic (the temperature of the reaction mixture rose from 170°C up to 185°C); the 3-ethyl-2-hydroxy-2-oxo-1,4,2-oxazaphosphorinane is formed by the decomposition of a low molecular weight alkylurethane phosphonate with a defined structure; and that the P-H group participates in the formation of **1**.

The treatment of **1** with an aqueous solution of NaOH (molar ratio 1:1) resulted in the formation of the sodium salt of 3-ethyl-2-hydroxy-2-oxo-1,4,2-oxazaphosphorinane **1a** (see Scheme 1). The structure was confirmed by ^{1}H, ^{13}C, and ^{31}P NMR spectroscopy (Table 1). It should be noted that the phosphorus chemical shift of **1a** appears at 17.7 ppm, which is shifted 7 ppm downfield with respect to compound **1**. The chemical shift of the phosphorus atom depends on the electron density around the phosphorus. The electron density of the phosphorus atom in **1a** is lower compared with **1** because of the electron

TABLE 1 Physical and NMR Data for Compounds **1, 1a, 2a** and **2**

N	Compound	MP, °C	NMR, (D_2O) $^{31}P\{H\}$, ^1H, and ^{13}C NMR, δ ,ppm, J, Hz
1		301-302, decomp.	^{31}P NMR: δ = 10.6. - ^1H NMR: δ = 4.18 - 4.36 (m, 2H, $POCH_2$); 3.27 - 3.38 (m, 2H, NCH_2); 3.16 - 3.26 (m, 1H, NCH); 1.64 - 1.97 (m, 2H, CH_2); 1.04 [t, $^3J_{HH}$ = 7.3, 3H, CH_3]. - ^{13}C NMR: δ = 63.1 [d, $^2J_{PC}$ = 4.4]; 55.9 [d, $^1J_{PC}$ = 136.8]; 44.7 [d, $^3J_{PC}$ = 2.1]; 21.4 [d, $^2J_{PC}$ = 2.3]; 10.1 [d, $^3J_{PC}$ = 7.7].
1a		74.5-76	^{31}P NMR: δ = 17.7. - ^1H NMR: δ =3.94 - 4.10 (m, 2H, $POCH_2$); 2.66 - 2.77 (m, 2H, NCH_2); 2.56 [q, $^3J_{HH}$= 8.2, 1H, NCH]; 1.30 - 1.61 (m, 2H, CH_2); 1.04 [t, $^3J_{HH}$ =7.3, 3H, CH_3]. - ^{13}C NMR: δ = 70.0 [d, $^2J_{PC}$ = 4.7]; 56.8 [d, $^1J_{PC}$ = 133.6, PC]; 44.8 [d, $^3J_{PC}$ = 2.2]; 23.3 [d, $^2J_{PC}$ = 2.4]; 11.1 [d, $^3J_{PC}$ = 8.5].
2a		339 - 341, decomp.	^{31}P NMR: δ = 21.4. - ^1H NMR: δ = 3.68 - 3.82 (m, 2H, CH_2OH); 3.10 - 3.42 (m, 3H, NCH + NCH_2);1.62 - 2.01 (m, 2H, CH_2); 0.98 [t, $^3J_{HH}$ = 7.3, 3H, CH_3]. ^{13}C NMR: δ = 61.2 (s, CH_2); 59.2 [d, $^1J_{PC}$ = 136.1]; 50.6 [d, $^3J_{PC}$ = 2.2]; 24.5 [d, $^2J_{PC}$ = 2.6];12.8 [d, $^3J_{PC}$ = 8.4].
2		105 -106	^{31}P NMR: δ = 12.8. - ^1H NMR: δ = 3.74 - 3.93 (m, 2H, CH_2OH); 3.10 - 3.38 (m, 3H, NCH +NCH_2); 1.68 - 2.06 (m, 2H, CH_2); 0.98 [t, $^3J_{HH}$ = 7.3, 3H, CH_3]. ^{13}C NMR: δ = 56.8 [s, CH_2; 57.2 [d, $^1J_{PC}$ = 136.1]; 47.4 [d, $^3J_{PC}$ = 5.1]; 20.6 [d, $^2J_{PC}$ = 2.3];10.6 [d, $^3J_{PC}$ = 8.9].

withdrawing character of the NH_2^+ group of the zwitterion.

Compound **1** was quantitatively converted into the disodium salt of α-ethyl-α-*N*-(hydroxyethylamino)methyl phosphonic acid **2a** (see Scheme 1) when heated with an excess of aqueous solution of NaOH. The data from the NMR study (Table 1) confirms the structure of **2a**.

The disodium salt **2a** was quantitatively converted into the α-ethyl-α-*N*-(hydroxyethylamino)-methyl phosphonic acid **2** through treatment with Dowex 50WX8-200 (See Scheme 1). The structure

was confirmed by NMR spectroscopy (Table 1). The phosphorus chemical shift δ_P of **2** appears at high-field (12.8 ppm) compared with that of the sodium salt (21.4 ppm).

EXPERIMENTAL

Materials

Propylene carbonate, Fluka, was used without further purification; dimethyl phosphonate, diethyl phosphonate, dibutyl phosphonate, diisopropyl phosphonate, diphenyl phosphonate and 2-aminoethanol, Fluka, were distilled before use. Dowex 50WX8-200 ion-exchange resin, strongly acidic cation, 8% crosslinking, 100–200 mesh was obtained from Aldrich Chemical Co.

^{1}H, ^{13}C, and ^{31}P NMR spectra were recorded on an OMEGA 250, 300, and 400 MHz spectrometers, in D_2O solvent. The IR spectra were determined on a Mattson Cygnus 100 FTIR spectrometer. FAB mass spectra were taken on a Ktatos Concept ^{1}H spectrometer, which placed the samples into glycerol alcohol matrices.

Preparation of Hydroxyalkyl Carbamates from Propylene Carbonate and 2-Aminoethanol

A two-necked flask equipped with a stirrer, condenser, and thermometer was charged with 33.6 g (0.55 mol) of 2-aminoethanol. Then, 54.04 g (0.5 mol) of propylene carbonate was added dropwise at 10 to 12°C. The reaction mixture was allowed to stand at 45°C for 7 hours. The excess of 2-aminoethanol was removed under vacuum (0.2 mm Hg) at 65°C. The hydroxyalkyl carbamates obtained in theoretical yield were a mixture of two isomers: 1-methyl-2-hydroxyethyl-*N-2′-hydroxyethylcarbamate (56.8%) and 2-methyl-2-hydroxyethyl-N-2′*-hydroxyethylcarbamate (43.2%).

3-Ethyl-2-hydroxy-2-oxo-1,4,2oxazaphosphorinane (**1**) *using Different Substituted Phosphonate Esters*

Dimethyl Phosphonate **(A).** The hydroxyalkylcarbamates (11.1 g, 0.068 mol) and dimethyl phosphonate (7.49g, 0.068 mol) were put into a three-necked flask equipped with a condenser, magnetic stirrer, and capillary inert gas outlet. The transesterification was performed at 135°C. At 50% completion of the reaction (monitored by the amount of methanol evolved), the evolution of methanol ceased. The reaction mixture was then heated at 170°C for 6 hours. The reaction mixture was dissolved in 40 mL of absolute methyl alcohol. A white precipitate formed, which was filtered off and washed several times with methyl alcohol, and then dried at 80°C. The yield was 2.14 g (13.0%). Cacld. for $C_5H_{12}NO_3P$ (165): C, 36.36; H, 7.27; N, 8.48; P. 18.79; found: C, 35.01; H, 7.36; N, 8.13; P, 18.23. The NMR data are given in Table 1.

The same procedure was followed for all other phosphonate esters (**B–E**).

Diethyl Phosphonate (**B**). Hydroxyalkylcarbamates 18.7 g (0.115 mol) and diethyl phosphonate 15.72 g (0.114 mol) were placed into a three-necked flask, and the transesterification was performed as previously described. When the evolution of ethanol ceased, the reaction mixture was heated at 170°C for 3 hours. Yield: 3.01 g (10.1 %), Calcd. for $C_5H_{12}NO_3P$ (165): C, 36.36; H, 7.27; N, 8.48; P, 18.79; found: C, 36.08; H, 7.19; N, 8.50: P, 18.54.

Dibutyl Phosphonate (**C**). The procedure was the same as for **B**. Hydroxyalkylcarbamates 16.33 g (0.1 mol); dibutyl phosphonate 19.9 g (0.1 mol). Yield: 1.83 g (6.5 %). Calcd. for $C_5H_{12}NO_3P$ (165): C, 36.36; H, 7.27; N, 8.48; P, 18.79; found: C, 36.21; H, 7.26; N, 8.30; P, 18.68.

*Diisopropyl Phosphonate (***D***).* The procedure was the same as for **B**. Hydroxyalkylcarbamates 12.46 g (0.076 mol); diisopropyl phosphonate 12.79 g (0.077 mol). Yield: 1.67 g (13.0%). Calcd. for $C_5H_{12}NO_3P$ (165): C, 36.36; H, 7.27; N, 8.48; P, 18.79; found: C, 36.35; H, 7.39; N, 8.48; P, 18.78.

Diphenyl Phosphonate (**E**). 6.1 g (0.037 mol) of hydroxyalkylcarbamates and 9.01 g (0.038 mol) diphenyl phosphonate were used. The transesterification was performed at 90°C for 45 minuntes to 95% completion (monitored by the amount of phenol evolved). The reaction mixture was than heated at 170°C for 3 hours. Yield: 0.21 g (2.1 %). Calcd. for $C_5H_{12}NO_3P$ (165): C, 36.36; H, 7.27; N, 8.48; P, 18.79; found: C, 35.58; H, 7.25; N, 8.64; P, 18.60.

Sodium Salt of 3-Ethyl-2-hydroxy-2-oxo-1,4,2-oxazophosphorinane (**1a**). A flask was charged with 0.65 g (0.004 mol) of **1,** 5 ml of water, and 0.16 g (0.004 mol) of sodium hydroxide. The reaction mixture was heated under reflux at 80°C for 2 hours. The water was removed by vacuum distillation at 60°C to give 0.74 g (100% yield) of a white powder. The NMR data for **1a** are given in Table 1.

Disodium Salt of α-Ethyl-α-N-(hydroxyethylamino)methylphosphonic Acid (**2a**). A flask equipped with a stirrer was charged with 2.06 g (0.011 mol) of compound **2**, 0.90 g (0.022 mol) of sodium hydroxide, and 10 mL of water. The water was removed at

80°C to give 2.55 g (100% yield) of a light brown powder. The NMR data for **2a** are given in Table 1.

α-Ethyl-α-N-(hydroxyethylamino)methylphosphonic Acid (**2**) To 2.72 g (0.0165 mol) of compound **1,** contained in a flask equipped with a reflux condenser and stirrer, 30 mL 25% of sodium hydroxide solution was added. The reaction mixture was heated at 115°C for 30 hours. Subsequently, the reaction mixture was treated with Dowex 50WX8-200 in order to exchange the sodium cations by hydrogen-ion exchange. The water was removed under vacuum to give 2.91g (96.5% yield) of a light brown powder. The NMR data for **2** are given in Table 1.

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