Heteroatom Chemistry
Volume 19, Number 2, 2008

Novel Routes to Aminophosphonic Acids: Interaction of Dimethyl H-Phosphonate with Hydroxyalkyl Carbamates

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Received 28 April 2006; revised 15 December 2006

ABSTRACT: *It was found that the reaction of dimethyl H-phosphonate (**1**) with 2-hydroxyalkyl-N-2′-hydroxyalkyl carbamates at 135°C includes several chemical reaction steps: (i) chemical transformations of 1-methyl-2-hydroxyethyl-N-2′-hydroxyethyl carbamate (**2**) and 2-methyl-2-hydroxyethyl-N-2′-hydroxyethyl carbamate (**3**); (ii) transesterification of dimethyl H-phosphonate with **2** and **3**, and with secondary hydroxyl-containing compounds that are formed during the course of the chemical transformation of 2-hydroxyalkyl-N-2′-hydroxyalkyl carbamates; (iii) hydrolysis of **1** and dialkyl H-phosphonates, formed via transesterification of **1** with secondary hydroxyl-containing compounds. The interaction was studied by means of ^{1}H, ^{13}C, ^{31}P NMR, and FAB mass spectroscopy.* © 2008 Wiley Periodicals, Inc. Heteroatom Chem 19:119–124, 2008; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.20404

INTRODUCTION

Recently, it has been reported that the reaction of phosphonic acid diesters **1** [$(RO)_2P(O)H$, R = CH_3, C_2H_5, C_3H_7, i-C_3H_7, C_4H_9, and C_6H_5] with a mixture of 1-methyl-2-hydroxyethyl-*N*-2′-hydroxyethyl carbamate **2** and 2-methyl-2-hydroxyethyl-*N*-2′-hydroxyethyl carbamate **3** at elevated temperatures (>160°C) resulted in 3-ethyl-2-hydroxy-2-oxo-1,4,2-oxazaphosphorinane (**8**), a hitherto nondescribed cyclic α-aminophosphonic acid (Scheme 1) [1–3].

Obviously, **8** cannot be obtained directly from diesters of H-phosphonic acids **1** and the mixture of **2** and **3.** It is produced via the reaction of diesters of H-phosphonic acids with secondary compounds that in turn are formed as a result of the chemical transformations of **2** and **3**. It results from the addition of the P—H group of H-phosphonic acids to the C=N double bond (from Schiff bases).

It was shown [4] that ′**2** and ′ **3** undergo several chemical transformations, resulting in the formation of several secondary compounds (Scheme 2).

We describe the continuation of our efforts to prove the mechanism of the formation of **8**. In this communication, we report results from studying the interaction of dimethyl H-phosphonate (**1**, R = CH_3) with a mixture of **2** and **3**.

RESULTS AND DISCUSSION

Studies by FAB spectroscopy of the reaction mixture obtained after heating **1** with **2** and **3** at 135°C revealed that during the heating several new compounds were formed (Fig. 1).

Besides the peaks of the starting compounds *m/z* 111.0 for **1** and 164.1 for **2** and **3**, additional new peaks were detected (Table 1).

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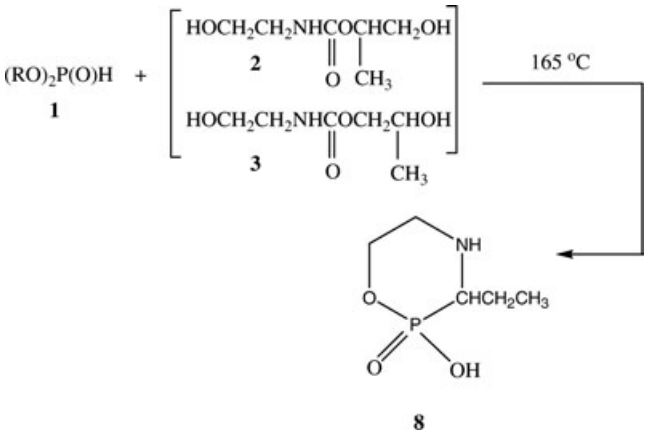
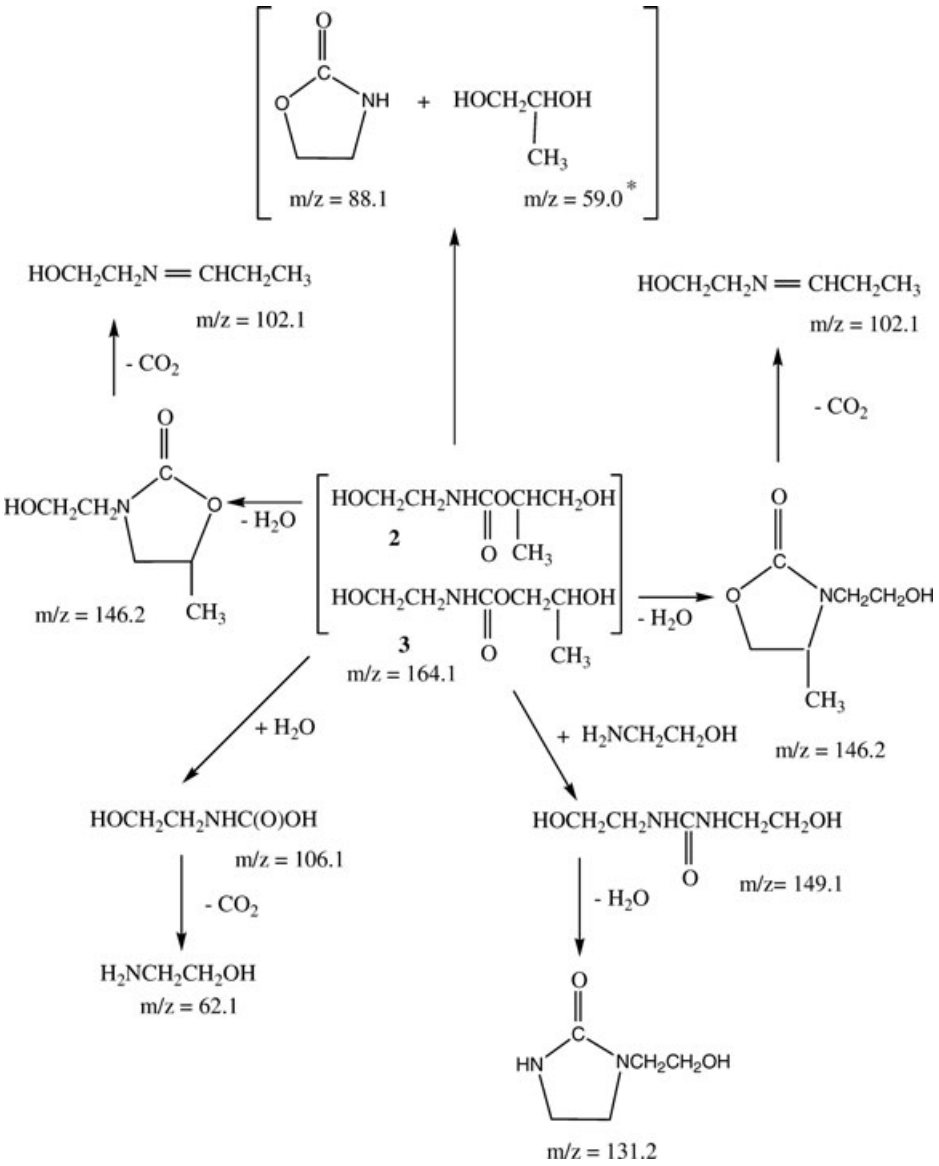
Contract grant sponsor: Bulgarian Academy of Sciences.
Contract grant sponsor: Deutsche Forschungsgemeinschaft.



SCHEME 1 Synthesis of 3-ethyl-2-hydroxy-2-oxo-1,4,2-oxazaphosphorinane **8**.

The main peak with $m/z = 146$ can be assigned to 5-methyl-3-(2-hydroxyethyl)-2-oxazolidinone **4**, which is formed by dehydration of **2** (Scheme 2) [4]. The decarboxylation of **4** furnished the Schiff base **5** (m/z 102.1). The experimental results show that decarboxylation proceeds at 135°C. The lower temperature of decarboxylation [5,6] could be explained with the acidity of the reaction mixture. Under these conditions, the reaction mixture contained the monomethyl ester of phosphonic acid $CH_3OP(O)(H)OH$ (**11**) (m/z 97.0) and phosphonic acid **12** (H_3PO_3) (m/z 83.0), which initiate the decarboxylation of 5-methyl-3-(2-hydroxyethyl)-2-oxazolidinone (**4**). $^{31}P\{H\}$ NMR spectra (Fig. 2) of the reaction mixture showed signals in the range from 11.83 to 6.38 ppm. From 11.61 to 10.68 ppm,



SCHEME 2 Chemical transformation of **2** and **3**.

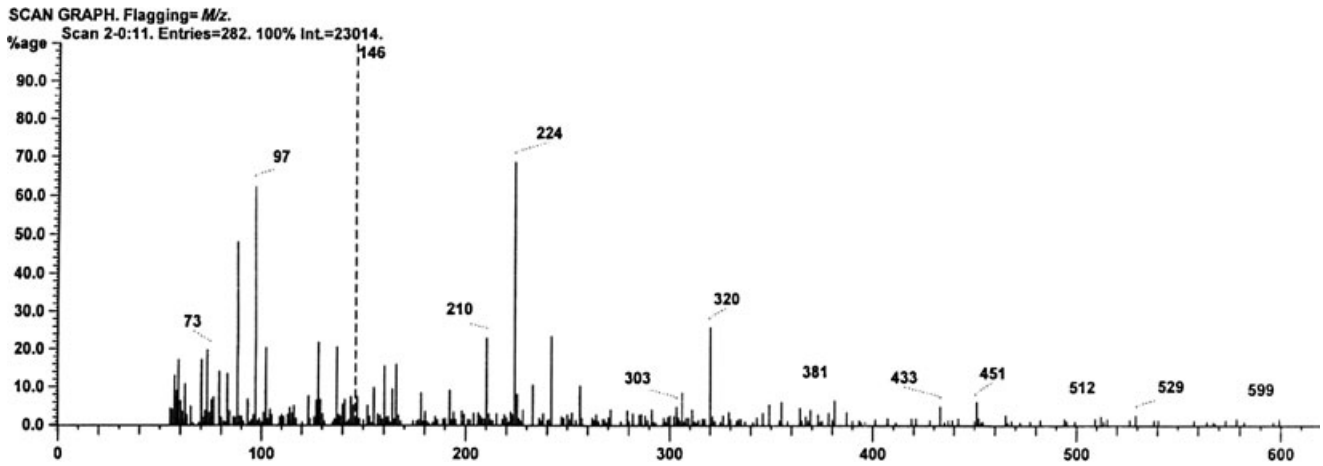
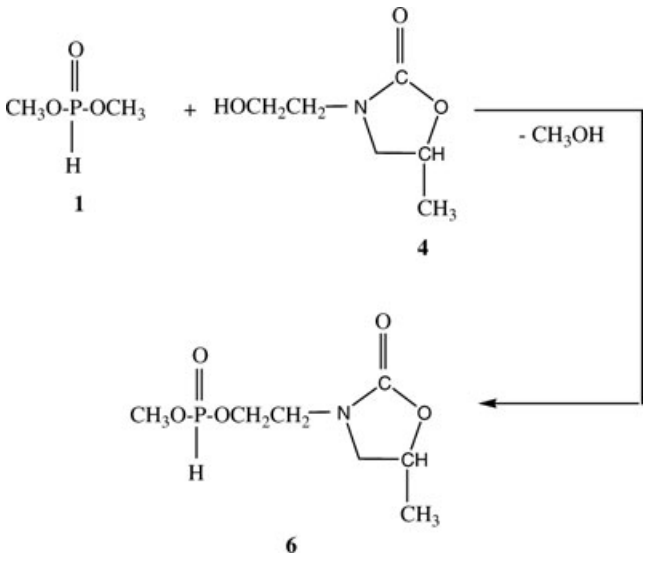


FIGURE 1 FAB spectrum of the reaction mixture obtained after heating of **1** with **2** and **3**.

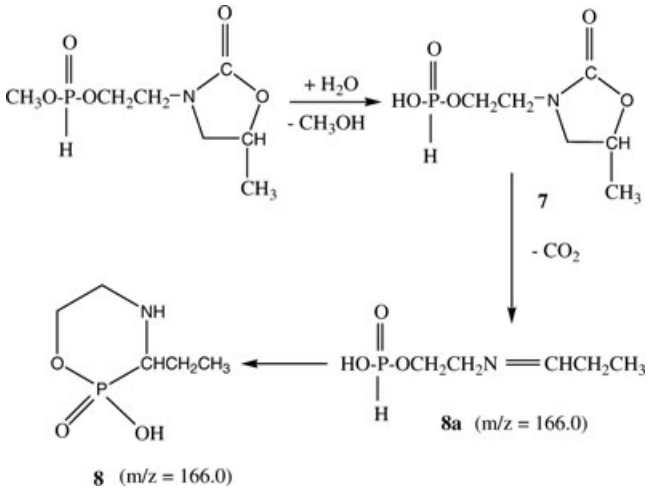
there were four signals that can be assigned to the phosphorus atoms of the products **6, 9, 10**, and **13**, respectively.

Product **6** is formed by transesterification of **1** with **4** (Eq. (1)).



(1)

The corresponding signal at $\delta_P = 11.05$ ppm, which represents a doublet of sextets with $^1J_{PH} = 705.3$ Hz and $^3J_{PH} = 11.5$ Hz, can be assigned to the phosphorus atom of **6**. The hydrolysis of **6** (Eq. (2)) furnished product **7** with $m/z = 210$ and the signal at $\delta_P = 7.24$ ppm, which is a doublet of triplets with $^1J_{PH} = 665.6$ and $^3J_{PH} = 7.7$ Hz.



(2)

TABLE 1 FAB-MS Spectral Data of the Reaction Products Obtained by the Interaction of **1** with the Mixture of **2** and **3**

Product	*$[M + H]^+$*	*Product*	*$[M + H]^+$*
1	111.0 (2.4)	**11**	97.0 (62.4)
2, **3**	164.1 (9.6)	**12**	83.0 (13.7)
4	146.1 (100)	**13**	155.1 (10.0)
5	102.1 (20.5)	**14**	123.1 (7.9)
6	224.0 (68.8)	**15**	88.1 (48.2)
7	210.1 (23.1)	**16**[a]	59.0 (17.3)
8	166.0 (16.1)	**17**[a]	137.1 (20.7)
9	242.0 (23.4)	**18**[a]	128.1 (21.9)
10	320.0 (25.9)		

Peak intensities are given in parenthesis.
[a]The marked $(M + H)^+$ is formed under FAB conditions after dehydratation.

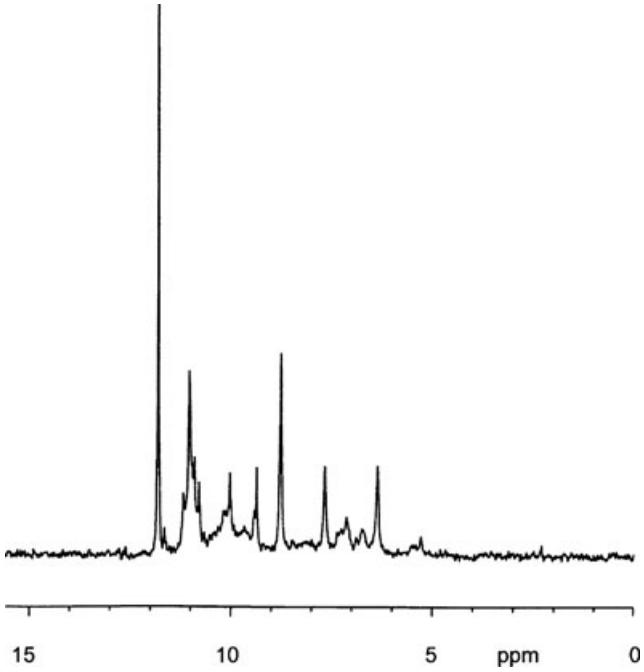
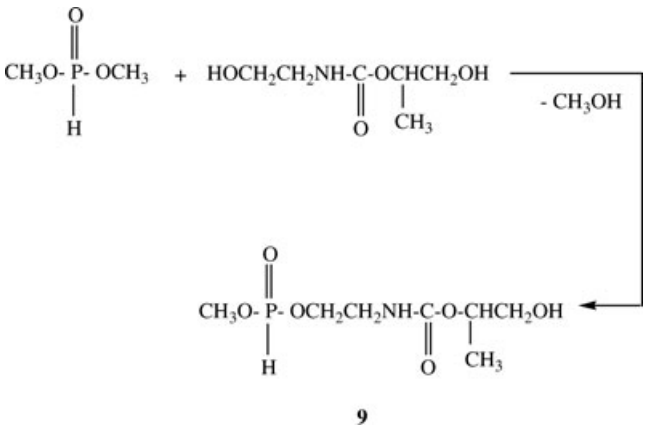


FIGURE 2 $^{31}P\{H\}$ NMR spectrum of the reaction mixture obtained after heating of **1** with **2** and **3**.

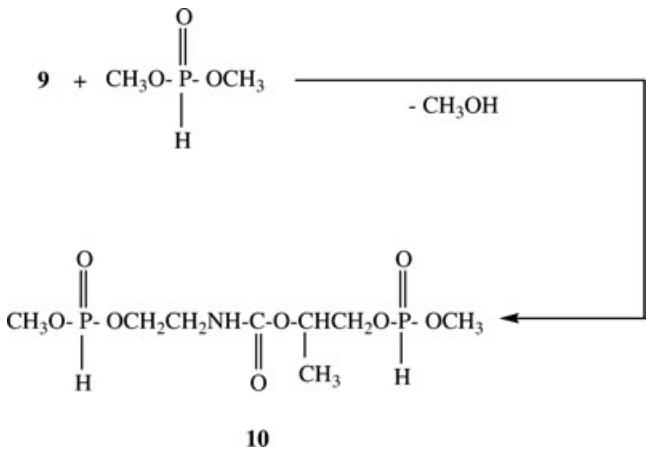
A FAB spectrum shows a peak at m/z 166 (16.1%), which can be assigned to **8a** or **8**. We assume that the thermal decarboxylation of **7** results in the formation of the Schiff base **8a**. Addition of the P—H group to the C=N double bond then furnishes **8**.

The transesterification of **1** with **2** or **3** (Eq. (3)) leads to the formation of product **9** with $m/z = 242$.



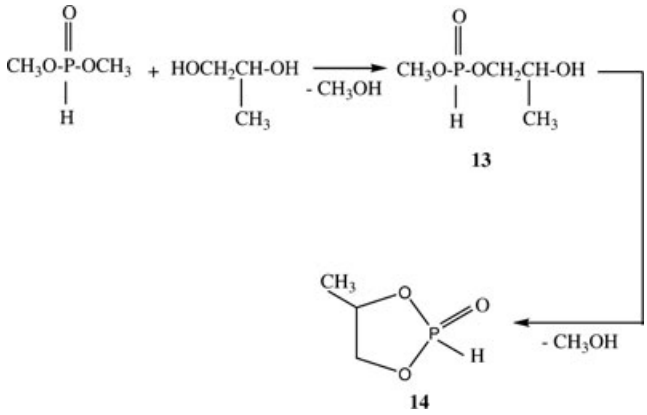
(3)

The signal at $\delta_P = 10.92$ ppm can be assigned to the phosphorus atom of product **9**. The transesterification of **9** with **1** (Eq. (4)) resulted in the formation of product **10** with $m/z = 320$.



(4)

The intramolecular transesterification [7] of **2** or **3** yielded 2-oxazolidinone **15** ($m/z = 88$) and 1,2-propanediol **16***($m/z = 59.0$) (Scheme 2) [4]. 1,2-Propanediol participates in a transesterification reaction with **1** to yield methyl-2-hydroxypropyl H-phosphonate (**13**). The peak with $m/z = 155.1$ can be assigned to **13.** The subsequent intramolecular transesterification of **13** (Eq. (5)) resulted in 4-methyl-1,3,2-dioxaphospholane (**14)** with $m/z = 123.1$.



(5)

The resulting **13** undergoes an intramolecular transesterification yielding **14**. The intramolecular transesterification is favored because **13** represents an α-hydroxy-ethyl ester of phosphonic acid [8–11]. The structure of **14** was verified by ^{1}H, ^{13}C, and ^{31}P NMR and FAB spectroscopy. Since 4-methyl-1,3,2-dioxaphospholane **13** contains a chiral center in the molecule, it is expected to exist as a mixture of diastereomers (having the methyl functions either cis or trans with respect to the P=O function). NMR data confirm this assumption. $^{31}P\{H\}$ NMR (Fig. 3a) shows two signals at $\delta_P = 23.92$ and $\delta_P = 23.10$ ppm at an intensity ratio of 1:1. ^{1}H-coupled ^{31}P NMR

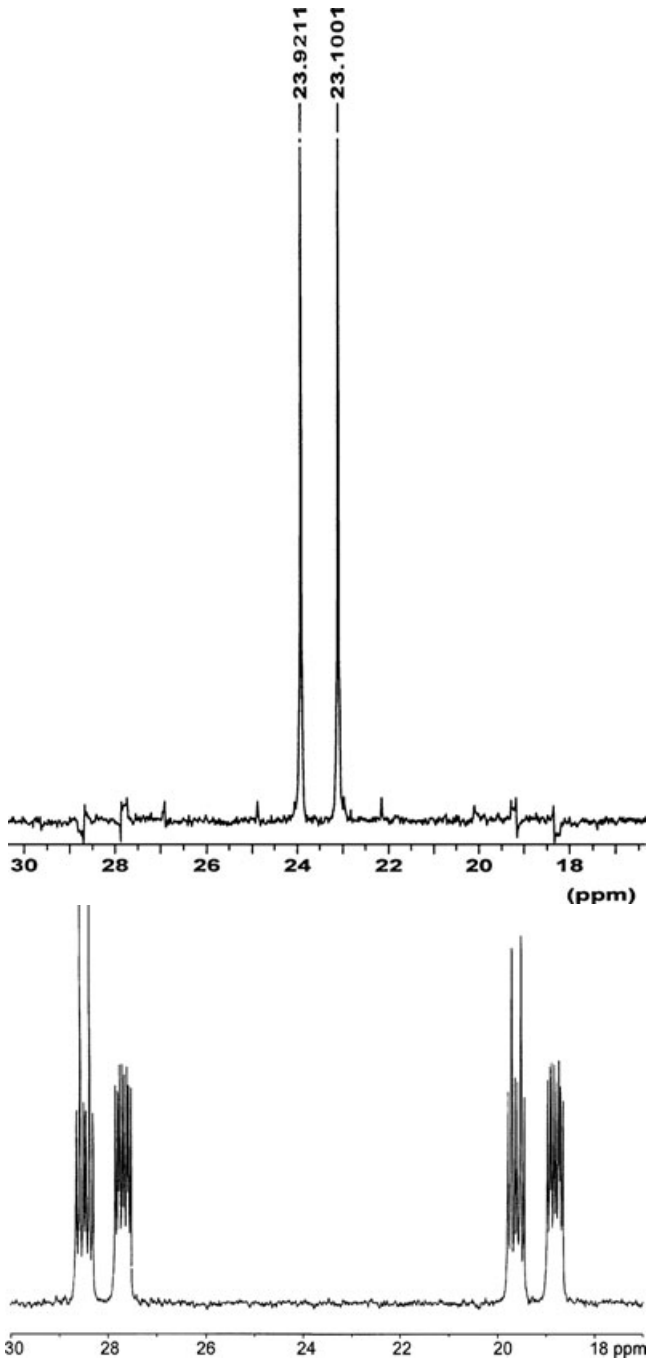
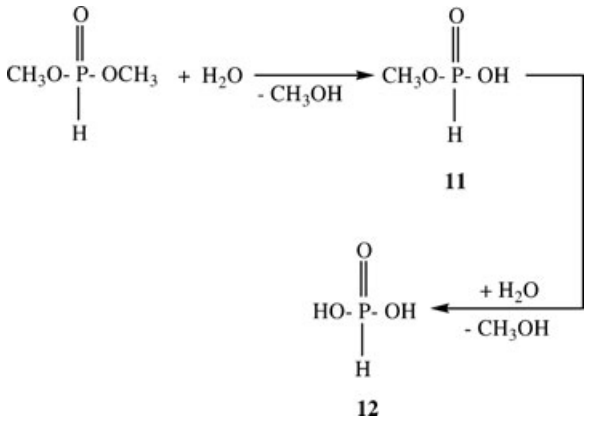


FIGURE 3 (a) ^{1}H-decoupled ^{31}P{H} NMR spectrum of **14**. (b) ^{1}H-coupled-^{31}P NMR spectrum of **14**.

(Fig. 3b) unequivocally confirms the skeleton of **14**. More detailed results from structural studies on **14** will be published separately.

Hydrolysis of **1** (Eq. (6)) furnished monomethyl H-phosphonate **11** ($m/z = 97$) and H-phosphonic acid **12** ($m/z = 83$).



(6)

The ^{31}P NMR signal at $\delta_P = 8.79$ ppm is a doublet of quartets with $^{1}J_{PH} = 666.03$ Hz and $^{3}J_{PH} = 12.1$ Hz, which can be assigned to the phosphorus atom of **11**. The signal at $\delta_P = 6.39$ ppm characterizes the phosphorus atom of the phosphonic acid **12**.

Heating of the above-mentioned reaction mixture to 160°C yielded **8**. This cyclic aminophosphonic acid **8** appears as an insoluble white solid product at the surface of the reaction mixture, which can be isolated via treatment of the reaction mixture with absolute methanol.

To sum up, the interaction of **1** with the mixture of **2** and **3** at 135°C includes several chemical reactions: (i) chemical transformations of **2** and **3**; (ii) transesterification of dimethyl H-phosphonate with **2** and **3**, and with secondary hydroxyl-containing compounds which are formed as a result of the chemical transformation of 2-hydroxyalkyl-*N*-2′-hydroxyalkyl carbamates; (iii) intramolecular transesterification of methyl-2-hydroxypropyl H-phosphonate; (vi) hydrolysis of **1** and dialkyl H-phosphonates, formed via transesterification of **1** with secondary hydroxyl-containing compounds.

At 135°C, 1,2-propanediol, 2-oxazolidinone, and **8** were isolated by vacuum distillation. At 165°C, 3-ethyl-2-hydroxy-2-oxo-1,4,2-oxazaphosphorinane **8** was obtained.

EXPERIMENTAL

Materials

Dimethyl H-phosphonate **1** was purchased from Aldrich, manufactured by Fluka AG, CH-9470 Buchs, Switzerland and purified by distillation prior to use. A mixture of **2** and **3** was synthesized by reacting propylene carbonate and ethanolamine as described in [1]. NMR spectra were measured using a Bruker 500 MHz spectrometer. Solutions were

made in $CDCl_3$, using TMS as internal and 85% H_3PO_4 as external standards. FAB spectra from compounds in glycerol were measured using a Varian MAT 8200 spectrometer.

Reaction of Dimethyl H-Phosphonate with a Mixture of **2** *and* **3**. *Heating at 135°C.* Dimethyl H-phosphonate **1** (30.8 g, 0.28 mol) and the mixture of **2** and **3** (45.5 g, 0.28 mol) were put into a three-necked flask equipped with a condenser, magnetic stirrer, and thermometer. The reaction was performed at 120°C–128°C. Evolution of methanol began. After 35 min, the evolution of methanol ceased and 7.4 g (48%) of methanol was evolved. The reaction mixture was kept at 135°C for 30 min. Subsequently, the reaction mixture was cooled to room temperature and subjected to vacuum distillation to furnish the following:

1,2-Propanediol [2.3 g, 0.03 mol, 10,7%), bp 34°C, 4×10^{-2} mmHg]; ^{1}H NMR ($CDCl_3$), δ_H (ppm): 1.13 (d, $^3J_{HH}$) = 6.6 Hz, 3H, CH_3), 3.22–3.49 (m, 2H, CH_2), 3.70–3.80 (m, 1H, CH), 4.24 (br s, OH). ^{13}C{^{1}H} NMR ($CDCl_3$), δ_C (ppm): 19.11 (CH_3), 68.19 (CH_2), 68.63 (CH).

4-methyl-1,3,2-dioxaphospholane **14** yield 11.6 g (33.9%); bp 56°C (2×10^{-2} mmHg); ^{1}H NMR ($CDCl_3$), δ_H (ppm): 1.37 (d, 3H, $^3J_{HH}$ = 6.3 Hz, CH_3), 1.46 (d, 3H, $^3J_{HH}$ = 6.3 Hz, CH_3), 3.81–3.86 and 4.23–4.32 (m, 2H, $POCH_2$), 3.98–4.02 and 4.45–4.53 (m, 2H, $POCH_2$), 4.64–4.69 (m, 1H, POCH), 4.77–4.81 (m, 1H, POCH), 7.25 (d, 1H, $^1J_{PH}$ = 717.54 Hz, PH), 7.28 (d, 1H, $^1J_{PH}$ = 715.02 Hz, PH). ^{31}P{H} NMR ($CDCl_3$), δ_P (ppm): 23.92, 23.10; ^{31}P NMR ($CDCl_3$), δ_P (ppm): 23.92, dd t, 23.10, eight lines from dddd; ^{13}C{H} NMR ($CDCl_3$), δ_C (ppm): 76.1 (C4), 72.5 (C5), 19.8 (d, $^3J_{POCC}$ = 6.1 Hz, CH_3): 75.4 (C4), 71.7 (C5), 19.4 (d, $^3J_{POCC}$ = 4.9 Hz, CH_3).

2-Oxazolidinone yield 7.9 g (0.09 mol, 32.4%), bp 89°C (4×10^{-2} mmHg); ^{1}H NMR (CD_3Cl) δ_H (ppm): 3.64 (t, $^3J_{HH}$ = 8.2 Hz, 2H, N–CH_2), 4.46 (m, 2H, OCH_2), 6.68 (br s, 1H, NH). ^{13}C{H} NMR ($CDCl_3$), δ_C (ppm): 41.0 (C4), 65,5 (C5), 161.5 (C2).

Heating at 165°C. Eleven grams of the reaction mixture obtained after separation of the abovementioned compounds was heated to and then kept at 165°C for 6 h. Subsequently, the reaction mixture was allowed to cool to room temperature and than extracted with absolute methyl alcohol. The white precipitate formed was filtered off and washed several times with absolute methyl alcohol and dried at 80°C to yield 1.4 g (12.7%) of 3-ethyl-2-hydroxy-2-oxo-1,4,2-oxazaphosphorinane. ^{1}H NMR (D_2O), δ_H (ppm): 1.03 (t, 3H, $^3J_{HH}$ = 7.3 Hz, CH_3); 1.64–1.80 (m, 1H, CH_2—CH_3), 1.83–1.97 (m, 1H, CH_2—CH_3); 3.16–3.37 (m, 3H, CH_2 and CH)), 4.18–4.36 (m, 2H, $POCH_2$). ^{13}C{H} NMR (D_2O), δ_C (ppm): 10.11 (CH_3), 21.4 (CH_2), 44.7 (CH_2), 55.92 (d, $^1J_{PC}$ = 136.7 Hz, CH), 64.42 (CH_2). ^{31}P{H} NMR (D_2O), δ_P (ppm): 10.21.

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