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Linear and Cyclic Aminomethanephosphonic Acid Esters Derived from Benzaldehyde Derivatives, 3-Aminopropanol, and Diethyl Phosphite

Jenny Zamorano-Octaviano, Arely Hernández-Martínez, Armando Ortega-Guevara, Irma Linzaga-Elizalde, and Herbert Höpfl

Centro de Investigaciones Químicas, Universidad Autónoma del Estado de Morelos, Av. Universidad 1001, Cuernavaca, Mor. CP 62210, México

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ABSTRACT: *A series of four diethyl {[(3-hydroxypropyl)amino](aryl)methyl}phosphonates have been prepared and characterized. In one case, the phosphonate was transformed to a seven-membered 1,4,2-oxazaphosphepane heterocycle through a one-pot intramolecular esterification. The analogous reaction with formaldehyde gave the six-membered diethyl (1,3-oxazinan-3-ylmethyl)phosphonate, which could be transformed in a posterior reaction to the corresponding aminomethanephosphonic acid.* © 2006 Wiley Periodicals, Inc. Heteroatom Chem 17:75–80, 2006; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.20178

INTRODUCTION

Aminomethanephosphonic acid derivatives **1** are phosphonic acid analogues of α-amino acids and have been extensively studied due to their applications in agrochemistry as plant growth regulators and herbicides [1]. Some derivatives have also promising properties as neuroinhibitors [2], HIV protease [3], and human collagenase inhibitors [4], antithrombotic agents [5], or are useful substrates for the synthesis of phosphanopeptides and phosphanopeptide nucleic acids [6].

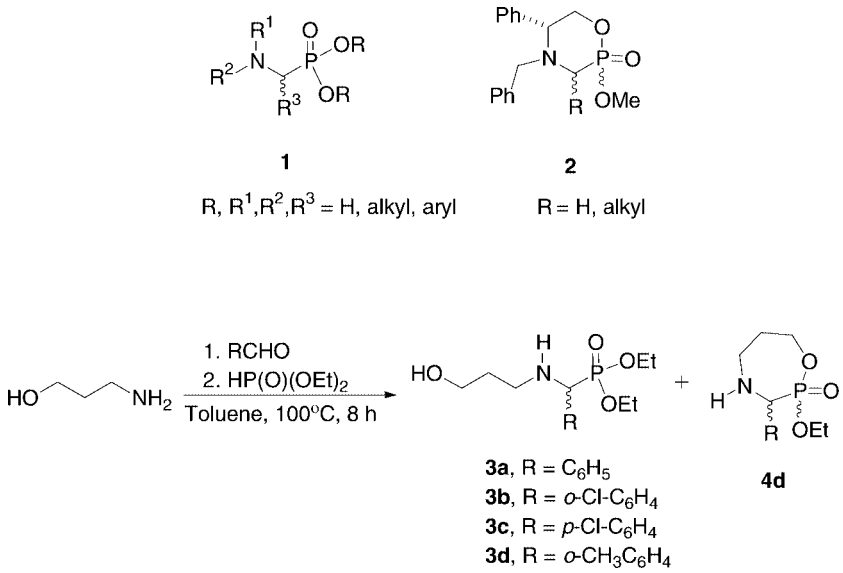
It has been shown recently that aminomethanephosphonic acid derivatives of chiral 2-aminoethanol substrates give rise to six-membered heterocyclic 1,4,2-oxazaphosphinanes **2** that are interesting starting materials for the preparation of enantiopure phosphonic acid analogues of α-amino acids [7–9]. Herein, we describe procedures for the preparation of a series of four (3-hydroxypropylamino)(aryl)methylphosphonates **3a–3d**, a seven-membered 1,4,2-oxazaphosphepane **4d**, diethyl(1,3-oxazinan-3-ylmethyl)phosphonate **5**, and {[(3-hydroxypropyl)amino]methyl}phosphonic acid **6**. The four structure types permitted a comparison of their ^{1}H, ^{13}C, and ^{31}P NMR data.

RESULTS AND DISCUSSION

Diethyl {[(3-hydroxypropyl)amino](aryl)methyl}phosphonates **3a–3d** have been prepared in yields ranging from 72 to 75% by the Kabachnik–Fields reaction [10], realizing a three-component combination of a benzaldehyde (benzaldehyde and *o*-chloro, *p*-chloro as well as *o*-tolualdehyde), 3-aminopropanol, and diethyl phosphite in toluene (Scheme 1) [11].

Compounds **3a–3d** have similar IR and NMR spectroscopic data. The molecular structures are

Correspondence to: Irma Linzaga-Elizalde; e-mail: linzaga@ciq.uaem.mx.



SCHEME 1

evidenced by absorptions in the IR spectra, which are characteristic for the NH (3365–3420 cm^{-1}), OH (3262–3331 cm^{-1}), P═O (1234–1241 cm^{-1}), and P—OEt (1019–1027 cm^{-1}) vibrations. The P—OEt groups are diastereotopic due to their proximity to a stereogenic center and give rise to ABM_3X spin systems. In the ^1H NMR spectra, the signal for the CHP hydrogen atom is a sharp doublet at $\delta \approx 4.0$–4.7 ppm with $^2J_{HP} \approx 18$–21 Hz; similar values have been reported for other aminomethanephosphonates [12]. The absence of a coupling with the NH proton is common and may in this particular case also be the result of the formation of a hydrogen bond between the nitrogen atom and the hydroxyl group in γ-position via a six-membered cyclic structure [13]. In accordance with the ^1H NMR data, the ^{13}C NMR spectra show two doublets for the P—OEt methyl groups at $\delta \approx 15.9$–16.6 ppm with $^3J_{CP} \approx 5.0$–6.6 Hz (with exception of **3c** that gives a singlet at 16.2 ppm). The methylene groups can be observed as singlets at 62.7 and 63.2 ppm for **3b** and **3c**, as doublet for **3d** at 62.7 ppm, $^2J_{CP} = 7.6$ Hz, and as doublets for **3a** at 63.0 and 63.2 ppm, $^2J_{CP} = 6.9$ Hz. The signals for the NCH_2 groups have chemical shifts of δ 46.5–47.5 ppm with $^3J_{CP} \approx 15.2$–15.9 Hz. The doublets at $\delta \approx 55.4$–60.8 ppm with $^1J_{CP} \approx 153$–155.5 Hz evidence that the P—C bonds have been formed. The ^{31}P NMR shifts range from $\delta = 23.5$–24.4 ppm.

The derivative prepared from *p*-chlorobenzaldehyde **3c** crystallized in the form of crystals suitable for X-ray crystallography, so that the geometry adopted in the solid state could be analyzed [14]. The values found for the P═O, P—O, and P—C bond lengths are 1.4703(16), 1.5715(16)/1.5743(16), and 1.819(2) Å, respectively. The C—P—OEt, C—P═O, EtO—P═O, and EtO—P—OEt bond angles have values of 104.94(10)/106.38(10), 112.61(10), 115.95(9)/116.42(9), and 99.03(8)°, respectively. These data agree with those observed for other aminoarylmethylphosphonates [15]. As it can be seen from Fig. 1a, the 3-hydroxypropylene group can indeed be bent in such a way that an intramolecular O—H···N hydrogen bridge is formed (O—H···N 2.11 Å, 149.4°; O···N 2.82 Å). Furthermore, the NH hydrogen atoms participate in intermolecular N—H···O_P hydrogen bonds (N—H···O 2.30 Å, 161.3°; O···N 3.03 Å), thus forming a hydrogen-bonded dimer, which is shown in Fig. 1b.

Interestingly, when the reaction shown in Scheme 1 was carried out in the presence of *o*-tolualdehyde, a mixture of the diethyl {[(3-hydroxypropyl)-amino](2-methylphenyl) methyl} phosphonate **3d** and the 1,4,2-oxazaphosphepane derivative **4d** was obtained that could be separated by column chromatography (isolated yields: 62% for **3d** and 7% for **2d**).

In comparison to its precursor **3d**, 1,4,2-oxazaphosphepane **4d** gives bands with higher NH and P═O frequencies in the IR spectra (3407, 1234 $cm^{-1} \leftrightarrow$ 3453, 3313, 1247 cm^{-1}). The formation of the seven-membered C_4NOP heterocycle is proved by ^1H NMR spectroscopy, since now all three methylene groups are diastereotopic. The HNCHP fragment is identified by a doublet for the CHP hydrogen atom at $\delta = 4.14$ ppm ($^2J_{HP} = 10$ Hz), and in this case the NH hydrogen can be observed at $\delta = 2.71$ ppm.

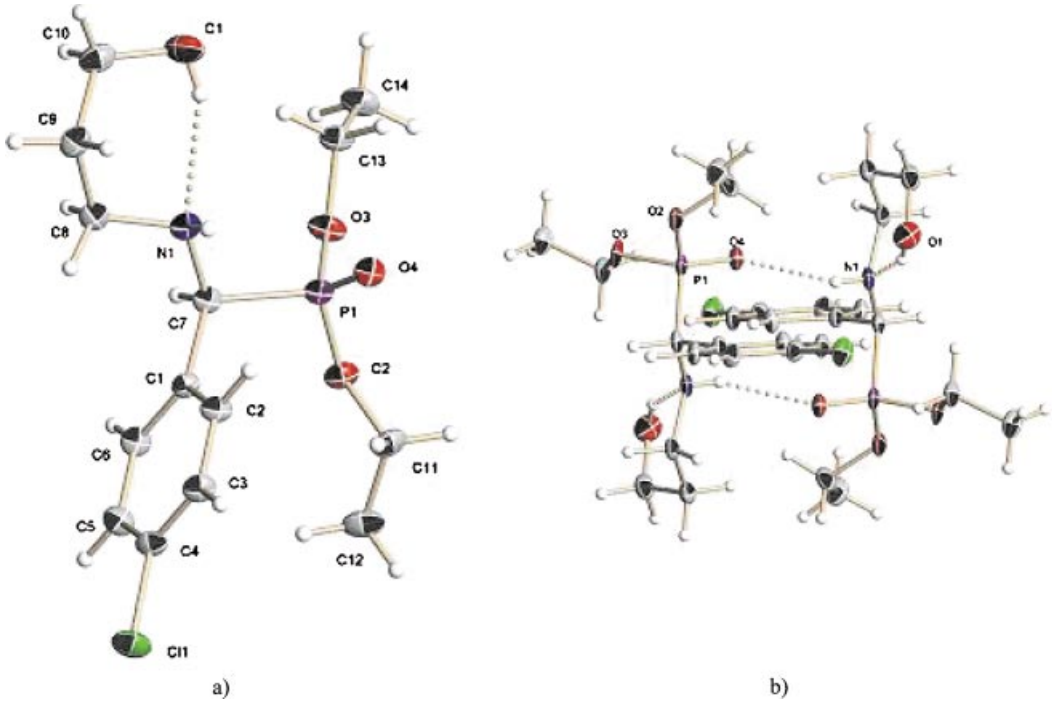


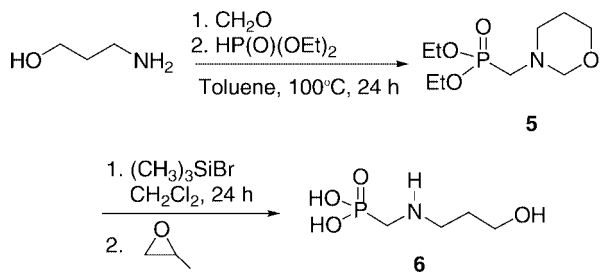
FIGURE 1 (a) Perspective view of the molecular structure of compound **3c**. (b) A fragment of the crystal lattice showing the intermolecular N–H···O hydrogen-bonding interactions.

The ^{13}C–^{31}P coupling constant with the central carbon atom is inferior to that for **3d** (138 ↔ 153.8 Hz), and the carbon signal is shifted to higher frequencies (57.8 ↔ 55.4 ppm). The $CH_2OP(O)OCH_2$— skeleton is identified by doublets at $\delta = 62.2$ ppm ($^2J_{CP} = 7.6$ Hz) and $\delta = 65.2$ ppm ($^2J_{CP} = 3$ Hz). As far as to the ^{31}P NMR data, the chemical shift is more positive for the 1,4,2-oxazaphosphepane **4d** when compared to **3d**, $\delta = 28.3 \leftrightarrow 24.4$ ppm.

When formaldehyde was used instead of a benzaldehyde for the reaction shown in Scheme 1, diethyl (1,3-oxazinan-3-ylmethyl)phosphonate **5** was isolated with 30% yield. The yield could be increased to 59% when 2 mol of formaldehyde was used instead of 1 mol. A related 1,3-oxazolidine derivative has already been reported by Royer et al. using formaldehyde and phenylglycinol as starting materials [8,16,17]. The molecular structure of **5** was evidenced by characteristic IR-absorptions of the P=O (1230 cm^{-1}) and POCC (1033 cm^{-1}) bands. In the ^1H NMR spectrum, a doublet at $\delta = 3.1$ ppm ($^2J_{HP} = 11$ Hz) for the —CH_2P— methylene group and a singlet at $\delta = 4.39$ ppm for the —OCH_2N— α-amino ether group make the difference when compared to the other derivatives discussed so far. The chemical shift measured in the ^{31}P NMR spectrum is $\delta = 26.1$ ppm.

The diethyl (1,3-oxazinan-3-yl-methyl)phosphonate **5** can be transformed to the aminomethanephosphonic acid **6** through a hydrolysis reaction with bromotrimethylsilane and propylene oxide (Scheme 2). In comparison to compounds **3a–3d, 4d**, and **5**, the IR spectrum now shows bands at 2837 and 1232 cm^{-1}, which are characteristics for P—OH groups. Accordingly, in the ^1H and ^{13}C NMR spectra, the signals corresponding to the POEt groups are missing; the doublet for the CH_2P is at 3.1 ppm with $^2J_{HP} = 12.8$ Hz. The signal in the ^{31}P NMR spectrum is shifted to lower fields, $\delta = 12.3$ ppm.

In conclusion, this contribution has shown that diethyl {[(3-hydroxypropyl)amino](aryl)methyl}phosphonates can be prepared by hydrophosphonylation reactions from benzaldehyde derivatives and 3-aminopropanol. These aminomethylphosphonates are characterized by the presence of an



SCHEME 2

intramolecular hydrogen bond. It has been shown that benzaldehydes with electrodonating groups also generate seven-membered 1,4,2-oxazaphosphepane heterocycles via an intramolecular esterification. With a nonaromatic aldehyde like formaldehyde, a diethyl (1,3-oxazinan-3-ylmethyl)phosphonate derivative is obtained, which can be hydrolyzed to the corresponding {[(3-hydroxypropyl)amino]-methyl}phosphonic acid.

EXPERIMENTAL

General Comments

Materials were obtained from commercial suppliers and were used without further purification. Melting points are uncorrected. NMR studies were carried out with Varian Gemini 200 and Varian Inova 400 instruments. Standards were TMS (internal, ^{1}H, ^{13}C) and H_3PO_4 (external, ^{31}P). Chemical shifts are stated in parts per million; they are positive, when the signal is shifted to higher frequencies than the standard. COSY and HETCOR experiments have been carried out in order to assign the ^{1}H and ^{13}C spectra completely. IR spectra have been recorded on a Bruker vector 22 FT spectrophotometer. Mass spectra were obtained on HP 5989A and Jeol JMS 700 equipments. X-ray diffraction studies were performed on a Bruker-APEX diffractometer with a CCD area detector at 100 K ($\lambda_{Mo K\alpha} = 0.71073$ Å, monochromator: graphite).

General Procedure for the Synthesis of Compounds **3a–3d, 4**, *and* **5**

A 1:1 mixture of benzaldehyde and 3-aminopropanol was heated to reflux in toluene using a Dean–Stark trap. When the calculated amount of H_2O has been separated, one equivalent of diethyl phosphite was added to the resulting imine, whereupon the mixture was heated to 100°C for 8 h. After cooling to room temperature, the remaining solvent was evaporated and the crude of the reaction was purified by column chromatography (dichloromethane: methanol = 98: 2).

Diethyl {[(3-hydroxypropyl)amino](phenyl)methyl}phosphonate **3a**. According to the general procedure, 3-amino-1-propanol (0.500 g, 6.7×10^{-3} mol) was treated with benzaldehyde (0.706 g, 6.7×10^{-3} mol) and diethyl phosphite (0.925 g, 6.7×10^{-3} mol) in 25 mL of toluene. Column chromatography afforded **3a** as a colorless liquid. 1.51 g, yield: 75%. IR (film) ν 3417, 3331, 1239, 1054, 1025 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.09 (t, 3H, $J = 7.2$ Hz) and 1.24 (t, 3H, $J = 7.2$ Hz), 1.55–1.63 (m, 1H), and 1.66–1.76 (m, 1H), 2.65 (ddd, 1H, $J = 4.5$, 6.6, 11.4 Hz), 2.73 (ddd, 1H, $J = 4.3$, 8.0, 12.2 Hz), 3.03 (bs, 2H), 3.70–3.78 (m, 2H), 3.88–3.94 (m, 2H), 398–4.06 (m, 2H), 4.00 (d masked, 1H, $^{2}J_{HP} = 18$ Hz), 7.27–7.37 ppm (m, 5H). ^{13}C ($CDCl_3$, 100 MHz) δ 16.4 (d, $^{3}J_{CP} = 5.1$ Hz), 16.6 (d, $^{3}J_{CP} = 5.1$ Hz), 31.0, 47.5 (d, $^{3}J_{CP} = 15.4$ Hz), 60.8 (d, $^{1}J_{CP} = 153.8$ Hz), 63.0 (d, $^{2}J_{CP} = 6.9$ Hz), 63.2 (d, $^{2}J_{CP} = 6.9$ Hz), 63.5, 128.3, 128.4, 128.6, 128.7, 135.2 ppm (d, $^{2}J_{CP} = 3.4$ Hz). ^{31}P ($CDCl_3$, 161.8 MHz) δ 24.2 ppm. MS (FAB) *m/z* 302, 164, 165, 91.

Diethyl {(2-chlorophenyl)[(3-hydroxypropyl)amino]methyl}phosphonate **3b**. According to the general procedure, 3-amino-1-propanol (0.500 g, 6.7×10^{-3} mol) was treated with *o*-chlorobenzaldehyde (0.936 g, 6.7×10^{-3} mol) and diethyl phosphite (0.925 g, 6.7×10^{-3} mol) in 25 mL of toluene. Column chromatography afforded **3b** as a colorless liquid. Yield: 68%. IR (KBr) ν 3420, 1237, 1027 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.06 (t, 3H, $J = 7$ Hz), 1.29 (t, 3H, $J = 7$ Hz), 1.56–1.61 (m, 1H), 1.67–1.71 (m, 1H), 2.63 (ddd, 1H, $J = 4.7$, 6.9, 11.6 Hz), 2.70 (ddd, 1H, $J = 4.5$, 7.9, 12.4 Hz), 2.86 (bs, 2H), 3.68–3.78 (m, 2H), 3.86–3.92 (m, 2H), 4.09–4.15 (m, 2H), 4.71 (d, 1H, $^{2}J_{HP} = 21.2$ Hz), 7.18–7.60 ppm (m, 5H). ^{13}C ($CDCl_3$, 100 MHz) δ 16.3 (d, $^{3}J_{CP} = 5.7$ Hz), 16.5 (d, $^{3}J_{CP} = 5.7$ Hz), 31.2, 47.0 (d, $^{3}J_{CP} = 15.9$ Hz), 55.7 (d, $^{1}J_{CP} = 155.5$ Hz), 63.1, 127.4, 129.2, 129.6, 133.8, 134.9, 135.1 ppm. ^{31}P ($CDCl_3$, 161.8 MHz) δ 23.7 ppm. MS (FAB) *m/z* 338, 337, 336, 200, 199, 198, 125.

Diethyl {(4-chlorophenyl)[(3-hydroxypropyl)amino]methyl}phosphonate **3c**. According to the general procedure, 3-amino-1-propanol (3.0 g, 0.04 mol) was treated with *p*-chlorobenzaldehyde (5.6 g, 0.04 mol) and diethyl phosphite (5.5 g, 3.98×10^{-2} mol) in 75 mL of toluene. Column chromatography afforded **3c** as a colorless crystalline solid. Yield: 70%. mp 62–65°C. IR (KBr) ν 3419, 1238, 1026 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.17 (t, 3H, $J = 7$ Hz), 1.28 (t, 3H, $J = 7$ Hz), 1.60–1.67 (m, 1H), 1.69–1.79 (m, 1H), 2.64–2.74 (m, 3H), 3.75 (t, 2H, $J = 5.4$ Hz), 3.84–3.92 (m, 2H), 3.96–4.10 (m, 2H), 4.00 (d masked, $^{2}J_{HP} = 20.4$ Hz), 7.3 ppm (s, 4H). ^{13}C ($CDCl_3$, 50 MHz) δ 16.2, 31.1, 47.0 (d, $^{3}J_{CP} = 15.9$ Hz), 60.2 (d, $^{1}J_{CP} = 153.0$ Hz), 62.9, 128.7, 129.6, 129.7, 133.9 ppm. ^{31}P ($CDCl_3$, 161.8 MHz) δ 23.5 ppm. MS (FAB) *m/z* 338, 337, 336, 200, 199, 197, 125.

Diethyl {[(3-hydroxypropyl)amino](2-methylphenyl)methyl}phosphonate **3d** *and 2-Ethoxy-3-phenyl-1,4,2-oxazaphosphepane 2-oxide* **4d**. According to

the general procedure, 3-amino-1-propanol (0.50 g, 6.7×10^{-3} mol) was treated with *o*-tolualdehyde (0.80 g, 6.7×10^{-3} mol) and diethyl phosphite (0.925 g, 6.7×10^{-3} mol) in 25 mL of toluene. Column chromatography afforded **3d** and **4d** as colorless liquids.

3d: Yield: 62%. IR (film) ν 3408, 3338, 1234, 1047, 1025 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ 1.09 (t, 3H, $J = 7.2$ Hz), 1.29 (t, 3H, $J = 7.2$ Hz), 1.57–1.68 (m, 1H), 1.69–1.8 (m, 1H), 2.38 (s, 3H), 2.62 (ddd, 1H, $J = 5.0$, 6.6, 11.6 Hz), 2.73 (ddd, 1H, $J = 4.8$, 7.4, 12.2 Hz), 3.2 (bs, 2H), 3.67–3.74 (m, 2H), 3.86–4.96 (m, 2H), 4.03–4.13 (m, 2H), 4.36 (d, 1H, $^1J_{HP} = 20.8$ Hz), 7.3–7.4 ppm (m, 4H). ^{13}C ($CDCl_3$, 100 MHz) δ 15.9 (d, $^3J_{CP} = 6.1$ Hz), 16.1 (d, $^3J_{CP} = 6.0$ Hz), 19.5, 31.0, 46.5 (d, $^3J_{CP} = 15.2$ Hz), 55.4 (d, $^1J_{CP} = 153.3$ Hz), 62.5, 62.7 (d, $^2J_{CP} = 7.6$ Hz), 126.1, 126.8, 127.4, 130.2, 133.3, 137.0 ppm. ^{31}P ($CDCl_3$, 161.8 MHz) δ 24.4 ppm. MS (FAB) *m/z* 317, 316, 179, 178, 176, 105.

4d: Yield: 7%. IR (film) ν 3453, 3313, 1486, 1464.8, 1439, 1247, 1039, 1022 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ 1.07 (t, 3H, $J = 7.2$ Hz), 2.0–2.1 (m, 1H), 2.28–.40 (m, 1H), 2.40 (s, 3H), 2.71 (bs, 1H), 2.86 (ddd, 1H, $J = 2.5$ Hz, $J = 10.4$ Hz, $J = 12.8$ Hz), 3.49 (ddd, 1H, $J = 3.3$ Hz, $J = 5.5$ Hz, $J = 8.8$ Hz), 3.71–3.81 (m, 1H), 3.89–4.08 (m, 1H), 4.14 (d, 1H, $J_{HP} = 10$ Hz), 4.37–4.44 (m, 1H), 7.14–7.61 ppm (m, 4H). ^{13}C ($CDCl_3$, 100 MHz) δ 16.0 (d, $^3J_{CP} = 6.1$ Hz), 19.7, 32.6, 48.4, 57.8 (d, $^1J_{CP} = 138.2$ Hz), 62.2 (d, $^2J_{CP} = 7.6$ Hz), 65.2 (d, $^2J_{CP} = 3$ Hz), 126.5 (d, $J = 3$ Hz), 127.7 (d, $J = 3.1$ Hz), 128.0 (d, $J = 4.6$ Hz), 130.2, 134.7, 135.6 ppm (d, $^2J_{CP} = 7.5$ Hz). ^{31}P ($CDCl_3$, 161.8 MHz) δ 28.4. MS (FAB) *m/z* 271, 270, 160.

Diethyl(1,3-oxazinan-3-ylmethyl)phosphonate **5**. According to the general procedure, 3-amino-1-propanol (1.0 g, 1.33×10^{-2} mol) was treated with formaldehyde (0.80 g, 2.66×10^{-2} mol) and diethyl phosphite (1.84 g 1.33×10^{-2} mol) in 25 mL of toluene. Column chromatography afforded **5** as a colorless liquid. Yield: 59%. IR (KBr) ν 3471, 1230, 1033 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ 1.33 (t, 6H, $J = 7.0$ Hz), 1.66–1.68 (m, 2H), 3.08 (t, 2H, $J = 5.6$ Hz), 3.12 (d, 2H,$^2J_{HP} = 11.2$ Hz), 3.84 (t, 2H, $J = 5.4$ Hz), 4.11–4.19 (m, 4H), 4.34 ppm (s, 2H). ^{13}C ($CDCl_3$, 100 MHz) δ 16.4 (d, $^3J_{CP} = 6.1$ Hz), 21.5, 47.4 (d, $^1J_{CP} = 167.8$ Hz), 51.5 (d, $^3J_{CP} = 7.6$ Hz), 62.0 (d, $^2J_{CP} = 6.9$ Hz), 67.7, 85.7 ppm (d, $^3J_{CP} = 10.6$ Hz). ^{31}P ($CDCl_3$, 161.8 MHz) δ 25.9 ppm. MS EI *m/z* 237, 100.

{[(3-Hydroxypropyl)amino]methyl}phosphonic Acid **6**. To a cold solution of **5** (0.20 g, 8.8×10^{-4} mol) in anhydrous dichloromethane (0.5 mL) trimethylsilylbromide (0.40 g, 2.6×10^{-3} mol) was added. After stirring the mixture at room temperature for 24 h, the solvents were removed under reduced pressure and water (5 mL) was added to the residue. After 24 h, the water was evaporated under reduced pressure and propylene oxide (3 mL) was added. After stirring the mixture at room temperature for 1 h, the solvents were evaporated and the product was recrystallized from methanol to give **6** as a white solid. Yield: 93%. mp = 215–218°C. IR (KBr) ν 3316, 3024, 2837, 1572, 1463, 1232, 1183, 1080, 1046 cm^{-1}. ^1H NMR (D_2O, 400 Hz) δ 1.86–1.93 (m, 2H), 3.1 (d, 2H, $^2J_{HP} = 12.8$ Hz), 3.2 (t, 2H, $J = 7.4$ Hz), 3.7 ppm (t, 2H, $J = 6.0$ Hz). ^{13}C (D_2O, 100 MHz) δ 27.8, 44.2 (d, $^1J_{CP} = 138.2$ Hz), 47.5 (d, $^3J_{CP} = 7.6$ Hz), 59.1 ppm. ^{31}P ($CDCl_3$, 161.8 MHz) δ 12.3 ppm.

REFERENCES

[1] (a) Hamm, P. (to Monsanto), US Patent 3 556 762, 1971; (b) Irani, R. R. (to Monsanto), US Patent 3 455 675, 1969.

[2] Oleksyszyn, J. In Aminophosphonic and Aminophosphinic Acids; Kukhar, V. P.; Hudson, H. R. (Eds.); Wiley: New York, 2000; pp. 537ff.

[3] Camp, N. P.; Hawkins, P. C. D.; Hitchcock, P. B.; Gani, D. Bioorg Med Chem Lett 1992, 2, 1047.

[4] Bird, J.; De Mello, R. C.; Harper, G. P.; Hunter, D. J.; Karran, E. H.; Markwell, R. E.; Miles-Williams, A. J.; Rahman, S. S.; Ward, R. W. J Med Chem 1994, 37, 158.

[5] Green, D.; Patel, G.; Elgendy, S.; Baban, J. A.; Skordalakes, E.; Husman, W.; Goodwin, C. A.; Scully, M. F.; Kakkar, V. V.; Deadman, J. Phosphorus Sulfur Silicon 1996, 109–110, 533.

[6] Kafarski, P.; Lejczak, B. In Aminophosphonic and Aminophosphinic Acids; Kukhar, V. P.; Hudson, H. R. (Eds.); Wiley: New York, 2000; pp. 173ff.

[7] Linzaga, I.; Escalante, J.; Muñoz, M.; Juaristi, E. Tetrahedron 2002, 58, 8973.

[8] Maury, C.; Gharbaoui, T.; Royer, J.; Husson, H.-P. J Org Chem 1996, 61, 3687.

[9] Cristau, H.-J.; Monbrun, J.; Tillard, M.; Pirat, J.-L. Tetrahedron Lett 2003, 44, 3188.

[10] (a) Kabachnik, M. I.; Medved, T. Y. Dokl Akad Nauk SSSR 1952, 83, 689; (b) Kabachnik, M. I.; Medved, T. Y. Izb Akad Nauk SSSR Ser Khim 1954, 1024.

[11] Fields, E. K. J Am Chem Soc 1952, 74, 1528.

[12] Failla, S.; Finocchiaro, P.; Consiglio, G. D. Heteroat Chem 2000, 11, 493.

[13] Hägele, G. In Aminophosphonic and Aminophosphinic Acids; Kukhar, V. P.; Hudson, H. R. (Eds.); Wiley: New York, 2000; pp. 217ff.

[14] Crystal data for $C_{14}H_{23}ClNO_4P$ (**3c**), $M_r = 335.75$ $gmol^{-1}$, $0.37 \times 0.41 \times 0.54$ mm^3, triclinic, space group $P\bar{1}$, $a = 7.9013(14)$, $b = 9.7613(18)$, $c = 10.726(2)$ Å, $\alpha = 91.207(3)$, $\beta = 102.227(3)$, $\gamma = 90.002(3)°$, $V = 808.3(3)$ $Å^3$, $Z = 2$, $\rho_{calcd} = 1.380$ gcm^{-3}, $\theta_{max} = 25°$, 2834 independent reflections, $R_1 = 0.048$ for 2550 reflections with $I > 2\sigma(I)$ and $wR_2 = 0.1331$ for

all data, 199 parameters. Crystallographic data for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-249365.

[15] (a) Choi, N.; McPartlin, M. In Aminophosphonic and Aminophosphinic Acids; Kukhar, V. P.; Hudson, H. R. (Eds.); Wiley: New York, 2000; pp. 327ff; (b) Mironov, V. F.; Gubaidullin, A. T.; Ivkova, G. A.; Litvinov, I. A.; Buzykin, B. I.; Burnaeva, L. M.; Konalova, I. V. Russ J Gen Chem 2001, 71, 457.

[16] (a) Marco, J. L.; Royer, J.; Husson, H.-P. Tetrahedron Lett 1985, 26, 3567; (b) Maury, C.; Royer, J.; Husson, H.-P. Tetrahedron Lett 1992, 33, 6127.

[17] Dimukhametov, M. N.; Bayandina, E. V.; Davydov, E. Yu.; Zyablikova, T. A.; Dobrynin, A. B.; Litvinov, I. A.; Alfonsov, V. A. Russ Chem Bull 2001, 2357.