Heteroatom Chemistry
Volume 11, Number 3, 2000

Reactions of N-Phthalylamino Acid Chlorides with Trialkyl Phosphites

Zyta Ziora,[1] Alina Maly,[1] Barbara Lejczak,[1] Pawel Kafarski,[1] Jolanta Holband,[2] and Grażyna Wójcik[2]

[1]*Institute of Organic Chemistry, Biochemistry and Biotechnology, Wrocław University of Technology, Wybrzeże Wyspiańskiego 27, 50-370 Wrocław, Poland*

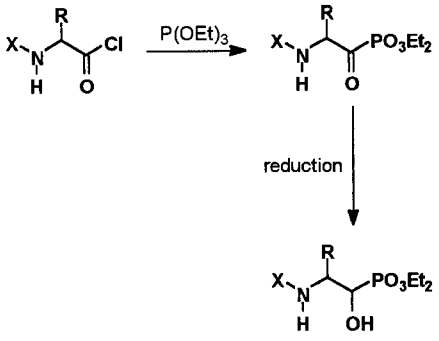
[2]*Institute of Physical and Theoretical Chemistry, Wrocław University of Technology, Wybrzeże Wyspiańskiego 27, 50-370 Wrocław, Poland*

Received 22 October 1999; revised 27 December 1999

ABSTRACT: *Reaction of commercially available trialkyl phosphites with N-phthalylamino acids gave mixtures of seven products, whereas the same reaction carried out with pure triethyl phosphite yielded only the desired 2-(N-phthalylamino)-1-oxoalkanephosphonates. These compounds underwent rearrangement to the same types of products that were obtained with the commercial phosphites. This latter series of reactions was promoted by the presence of dialkyl phosphites.* © 2000 John Wiley & Sons, Inc. Heteroatom Chem 11:232–239, 2000

INTRODUCTION

2-Amino-1-hydroxyalkanephosphonic acids may be considered analogs of the potent protease inhibitor and immunoregulator bestatin, which was recently shown to significantly decrease HIV infection by inhibiting leucine aminopeptidase activity [1]. Moreover, these acids are analogs of a non-terpenoid fragment of a promising anticancer agent, paclitaxel [2]. Preliminary studies have shown that some representatives of this class of compounds act as selective inhibitors against proteolytic enzymes, such as renin and HIV protease [3]. Stereocontrolled synthesis of these compounds is still a matter of challenge, although there are several reports dealing with their preparation and stereochemistry [3,4]. We assumed that the reduction of α-ketophosphonates, obtained by the previously described action of trialkyl phosphites with N-protected amino acid chlorides [5], might provide alternative substrates for the preparation of 2-amino-1-hydroxyalkanephosphonic acids.



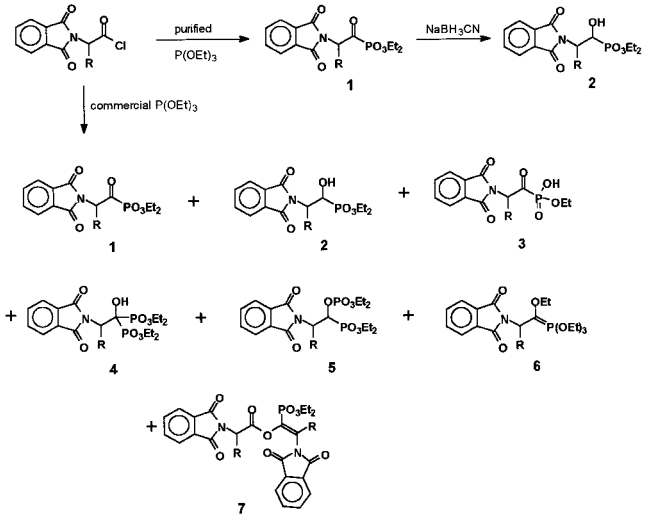
Quite surprisingly, the use of N-phthalylamino acid chlorides and commercially available trialkyl phosphites afforded complex mixtures of products instead of the desired ketophosphonates. In this article, we describe the determination of the structures of these compounds.

Correspondence to: Zyta Ziora.
Contract Grant Sponsor: Komitet Badań Naukowych.
Contract Grant Number: 3 T09A 135 10
Contract Grant Sponsor: Komitet Badań Naukowych.
Contract Grant Number: 341 701.

RESULTS AND DISCUSSION

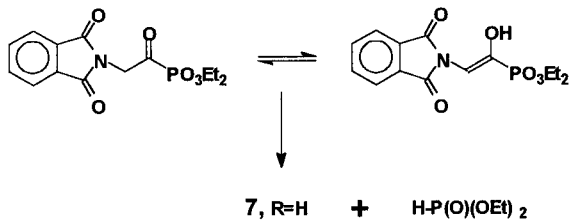
Reactions of commercially available triethyl phosphite with chlorides of phthalylglycine, *N*-phthalyl-L-alanine, *N*-phthalyl-L-valine, *N*-phthalyl-L-leucine and *N*-phthalyl-L-phenylalanine afforded complex mixtures of several products. This could be avoided by use of triethyl phosphite that has been purified by distillation from sodium, and this resulted in the formation of the corresponding diethyl 1-oxo-2-(*N*-phthalylamino)alkanephosphonates (compounds **1**) with satisfactory yields and purity. Their reduction with sodium cyanoborohydride afforded the desired diethyl 1-hydroxy-2-(*N*-phthalylamino)-alkanephosphonates (compounds **2**). However, they were contaminated by many side-products, most probably products of decomposition of substrate **1**. We have also noticed that, upon storage or in some cases upon attempted chromatographic purification, compounds **1** underwent spontaneous conversion to mixtures nearly identical to those obtained in the reactions with commercial triethyl phosphite. We have also found that this conversion is promoted by the addition of diethyl phosphite to the solutions of compounds **1**.

As seen from the scheme, the formation of seven compounds was observed upon reaction of nonpurified triethyl phosphite with *N*-phthalylamino acid chlorides.



Examinations of the ^{31}P NMR spectra of the crude reaction mixtures have shown the same type of products in each case, suggesting a standard reaction course. The quantitative composition of the mixture varied with the structure of the amino acid used and depended on the reaction conditions (for example, being different when the reaction was carried out in benzene as against toluene). Using fractional crystallization and chromatographic techniques, we were able to isolate some of these compounds. Their structures were then established by means of X-ray and NMR studies: The desired ketophosphonates **1** gave a ^{31}P NMR signal at around $\delta = -2$ and appeared usually in minute amounts (*enol* forms not being detected among these compounds). Interestingly, monoethyl ketophosphonates (compounds **3**, signal around $\delta = 5$) were produced in slightly larger quantities. The presence of hydroxyphosphonates **2** (as diastereomeric mixtures with ^{31}P NMR signals appearing at **δ** = 22–25) is not surprising if we consider the fact that trialkyl phosphites are known to reduce α-ketoacids [6]. Formation of bisphosphonates **4** (signals around $\delta = 20$, in some cases overlapping with those derived from compound **5**) might also be expected since the addition of diethyl phosphite to α-ketophosphonates is one of the known preparative methods of compound **4** [7,8]. Also, the reaction of ketophosphonates **1** with trialkyl phosphites yielding compounds **5** has been recently described [8,9]. Although it was reported that this reaction requires the presence of an acidic or basic catalyst, namely under conditions that are unlikely in our case, their formation was unambiguously proven by NMR studies. ^{31}P NMR spectra of compounds **5** consist of two sets of signals (one around $\delta = 0$–2 and the second at 18–20). In the case of glycine (R = H) only two doublets (AB-spectrum) were observed, whereas in other cases (when reactions were carried out starting from amino acids of defined configuration) two sets of doublets (two AB spectra) derived from non-equimolar mixtures of diastereomers were observed (see Experimental). ^{31}P-^{31}P COSY spectra have proven the presence of two coupled phosphorus atoms in the molecule.

We were successful in isolation of compound **6** (^{31}P NMR signal at around $\delta = 70$) only when the derivative of leucine [R = $CH_2CH(CH_3)_2$] was used as a substrate. The chemical structure of this product was proposed only on the basis of ^{31}P NMR spectra and is therefore somewhat speculative. The structure of compound **7**, R = H (^{31}P NMR signal at $\delta =$ 10), a product of the reaction of phthalylglycine chloride with triethyl phosphite, was found from X-ray studies. It crystallized from an ethyl acetate solution of the crude reaction mixture upon addition of hexane, and if appeared to be a product of acylation of compound **1** with phthalylglycine or condensation of two molecules of α-ketophosphonate **1**. In the latter case, the hydroxylic group of the *enol* form of this compound attacks the carbonyl carbon atom of its *keto* form yielding compound **7** and diethyl phosphite.



Because this reaction is accompanied by release of diethyl phosphite, it is most likely involved in the promotion of the decomposition of pure compound **1**. There is a possibility of formation of two geometrical isomers in this reaction (*E* and *Z* isomers). Because compound **7**, R = H, is of the *E* configuration, we assumed that the signal of its *Z* isomer appears in its ^{31}P NMR spectra at $\delta = 11$. Thus, we undertook efforts to isolate this compound. It was isolated by direct crystallization from the reaction mixture if toluene was used as solvent. Recrystallization from chloroform-hexane gave crystals which, quite surprisingly, appeared to be crystals of the polymorphic form (compound **7a**) of the *E* isomer and its NMR spectra were identical with those found for compound **7**, R = H, (with the ^{31}P NMR signal appearing now at $\delta = 10$). Thus, it is possible that the *Z* isomer underwent isomerization upon crystallization.

The molecular structures and atom numbering of conformers **7**, R = H, and **7a** are given in Figures 1 and 2, respectively. The two molecules differ in their conformation. The main difference consists in the mutual orientation of two phthalyl rings in the crystal. In compound **7**, their planes are parallel (within 1.8°), while in **7a**, they are approximately perpendicular (the angle between ring planes being 89.8°). Also, although the orientation of the phosphonate fragment of the molecule is different, nevertheless the ethoxy groups lie along the direction approximately perpendicular to the alkyl chain that joins the two phthalyl rings. The two ester moieties are nonequivalent because they are involved in different weak C-H···O intermolecular hydrogen bondings to the oxygens from the phthalyl rings. The large values of the thermal vibration amplitudes of the ethoxy group atoms (larger for **7a** than 7) indicate the possibility of a structural disorder. The larger values of thermal vibration amplitudes of **7a** and its smaller density and lower melting point suggest that it is a less stable polymorph at room temperature, and this supports the suggestion that it might be a product of isomerization of the *Z* isomer.

In order to find out if the observed reaction is general, we also studied the reaction of phthalylglycine chloride with trimethyl phosphite, tri-n-butyl phosphite, diethyl benzyl phosphite and diethyl phenylphosphonite. In all the cases, complex mixtures of products were obtained and their ^{31}P NMR spectra were very similar to those obtained when triethyl phosphite was used as the substrate. In all of these spectra, we were able to detect products analogous to those described above.

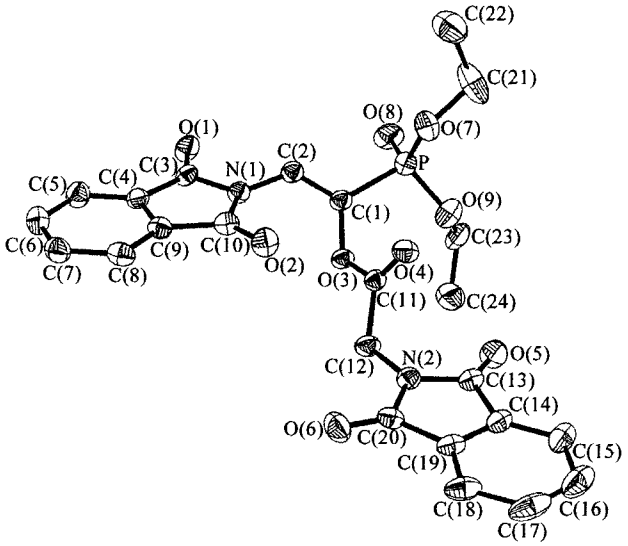


FIGURE 1. Crystal structure of diethyl (E)-1-(N-phthalylglycyloxy)-2-(N-phthalylamino)-ethenephosphonate (compound 7, R = H).

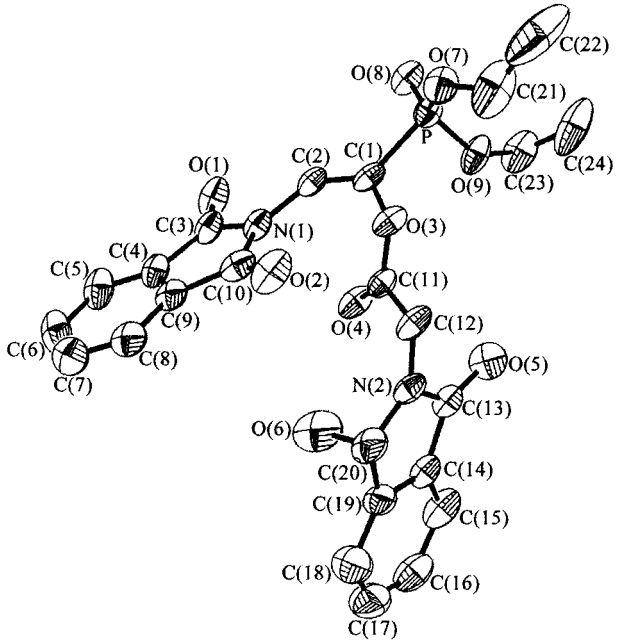


FIGURE 2. Crystal structure of diethyl (E)-1-(N-phthalylglycyloxy)-2-(N-phthalylamino)-ethenephosphonate (compound 7a).

EXPERIMENTAL

Materials

N-Phthalylamino acids were obtained according to standard procedures. Triethyl phosphite was purchased from Merck (Darmstadt, Germany) or Aldrich (Milwaukee, USA), trimethyl phosphite was purchased from Merck, and diethyl benzyl phosphite was purchased from Aldrich. Tri-*n*-butyl phosphite was a generous gift from Hoechst (Frankfurt/Main, Germany), and diethyl phenylphosphonite was prepared according to a standard procedure.

NMR Measurements

Proton, phosphorus, and carbon NMR spectra were recorded in deuterated DMSO, D_2O, and $CDCl_3$ on a Bruker DRX spectrometer operating at 300.13 MHz for ^1H, 121.50 MHz for ^{31}P, and 75.47 MHz for ^{13}C. Chemical shifts are given in relation to $SiMe_4$, 85% H_3PO_4, and the central peak of the deuterated chloroform triplet, respectively. All downfield shifts are denoted as positive. Structures of the isolated compounds were deduced from the combination of their $^1H\{^{31}P\}$, ^1H-^{13}C HMQC, and ^1H-^{31}P HMQC spectra and supported by means of IR spectroscopy and elemental analyses.

Crystallography

The diffraction data were collected on a KUMA KM4 computer-controlled four-circle diffractometer with graphite-monochromated Mo Kα radiation. In the case of compound **7**, we used a conventional scintillation detector, whereas the data collection for compound **7a** was performed using a plate detector, that is, a CCD camera produced by KUMA Diffraction Ltd. (Wroclaw, Poland). Both structures were solved by a direct method with SHELXS 86 [10] and refined on F^2 by full-matrix least-squares methods using SHELXL 93 with anisotropic thermal parameters for non-hydrogen atoms [11]. The hydrogen atom parameters with isotropic thermal parameters were included in the final cycles of refinement. No absorption corrections were applied. Detailed structures and discussion of the source and character of thermal vibration amplitudes will be published in a separate article. Crystallographic data were deposited at the Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW, United Kingdom.

Preparation of Diethyl 1-oxo-2-(N-phthalylamino)alkanephosphonates (*Compounds* **1**)

These compounds were obtained by a modification of a previously described procedure [5]. Thus, *N*-phthalylamino acid (0.01 mol) was dissolved in hot toluene (30–60 mL), and thionyl chloride was added dropwise (7.0 mL, 0.09 mol). The mixture was stirred at 50°C, using a Dean Stark apparatus, cooled to room temperature, and the volatile components of the reaction mixture removed under reduced pressure. Then the crude chloride was dissolved in toluene (10–40 mL), cooled to −5° C, and freshly distilled triethyl phosphite was added dropwise (1.8 g, 0.01 mol). The mixture was then stirred until it reached room temperature. It was purified by means of column chromatography on silica-gel 60 (70–230 mesh ASTM) yielding an oily product of satisfactory purity. (Because of their instability and moderate purities elemental analyses for these compounds were not performed.)

Diethyl (S)-1-oxo-2-(N-phthalylamino) propanephosphonate ($R = CH_3$)

This compound was purified using ethyl acetate: benzene (1:1) as eluent. It was obtained as a dense, colorless oil. Yield, 80%; purity, 83%; ^{31}P NMR ($CDCl_3$)δ: −2.4. ^1H NMR ($CDCl_3$)δ: 1.15 and 1.21 (t, J = 6.9 Hz, 3H each, OCH_2CH_3), 1.75 (d, J = 7.0 Hz, 3H, CH_3CH), 4.0–4.15 (m, 4H, OCH_2), 4.1 (dq, J = 7.0 Hz, 1H, $CHCH_3$), 7.65–7.7 and 7.8–7.85 (m, 2H each, C_6H_4).

Diethyl (S)-1-oxo-2-(N-phthalylamino)-3-methylbutanephosphonate [R = CH(CH$_3$)$_2$)]

This compound was purified using ethyl acetate: methylene chloride (1:1) as eluent and obtained as a dense colorless oil. Yield, 83%; purity, 84%; ^{31}P NMR ($CDCl_3$) δ: −2.6. ^1H NMR ($CDCl_3$)δ: 0.55 and 0.77 (d, J = 6.8 Hz, 3H each, $CHCH_3$), 0.90 and 0.96 (t, J = 7.1 Hz, 3H each, OCH_2CH_3), 2.40 (dhep, J = 6.8, 8.1 Hz, 1H, $CHCH_3$), 4.45–4.5 (m, 4H, OCH_2CH_3), 4.48 and 4.50 (d, J = 8.1 Hz, 0.5H each, $NCHCO$), 7.53 and 7.58 (dd, J = 5.3, 3.0 Hz; 2H each, C_6H_4).

Diethyl (S)-1-oxo-2-(N-phthalylamino)-4-methylpentanephosphonate [R = CH$_2$CH(CH$_3$)$_2$)]

This compound was purified using ethyl acetate: benzene (1:1) as eluent and obtained as a colorless oil. Purity, 73%; yield, 81%; ^{31}P NMR ($CDCl_3$) δ: −2.3. ^1H NMR ($CDCl_3$) δ: 0.86 and 0.91 (d, J = 6.6 Hz, 3H each, $CHCH_3$), 1.18 and 1.22 (t, J = 7.1 Hz, 3H each,

OCH_2CH_3), 1.45–1.50 (m, 2H, CH_2CHCH_3), 2.02–2.30 (m, 1H, CH_2CHCH_3), 4.07 and 4.10 (dq, $J = J_{PH} =$ 7.1 Hz, 2H each, OCH_2CH_3), 5.10 and 5.14 (t, $J = 8.1$ Hz, 0.5H each, NCHCO), 7.68 and 7.80 (dd, $J = 5.3$, 3.0 Hz; 2H each, C_6H_4).

A Representative Example of the Reduction of α-Ketophosphonates **1***: Diethyl* (*S*)*-1-hydroxy-2-*(*N-phthalylamino*)*-3-methylbutanephosphonate* **2** *[R = CH(CH$_3$)$_2$)]*

Diethyl (*S*)-1-oxo-2-(*N*-phthalylamino)-3-methylbutanephosphonate (0.64 g, 1.7 mmol) was dissolved in anhydrous THF, followed by addition of $NaBH_3CN$ (0.33g, 5.2 mmol). The mixture was then stirred at room temperature for 24 hours, then 30 mL of water was added, and the solution was neutralized by addition of acetic acid. The aqueous phase was extracted with chloroform (3 × 20 ml) and dried over anhydrous magnesium sulphate. The crude product contained approximately 65% of hydroxyphosphonate **2** as a non-equimolar mixture of isomers (85:15) with ^{31}P NMR signals at $\delta = 22.2$ and 24.9. A colorless oily product that separated on silica-gel chromatography using ethyl acetate:methylene chloride (1:1) as the eluent appears to be a single diastereoisomer but contained around 20% of phthalyl-L-valine. ^{31}P NMR ($CDCl_3$) δ: 22.3. ^{1}H NMR ($CDCl_3$) δ: 0.75 and 0.77 (d, $J = 6.7$ Hz, 3H each, $CHCH_3$), 1.09 and 1.11 (t, $J = 7.2$ Hz, 3H each, OCH_2CH_3), 2.45–2.60 (m, 1H, $CHCH_3$), 3.93 (dq, $J = J_{PH} = 7.2$ Hz, 2H, OCH_2CH_3), 3.98 and 3.99 (dq, $J = J_{PH} = 7.2$ Hz, 2H, OCH_2CH_3), 4.17 (dd, $J_{PH} = 10.8$, $J = 4.2$ Hz, 1H NCH), 4.28 (dbd, $J = 14.3$, 4.2 Hz, 1H, CHP), 5.00 (bs, 1H, OH), 7.6–7.65 and 7.75–7.80 (m, 2H each, C_6H_4). ^{13}C NMR ($CDCl_3$) δ: 16.0 ($J = 9.6$ Hz, OCH_2CH_3), 16.2 ($J = 6.2$ Hz, OCH_2CH_3), 19.36 and 19.40 ($CHCH_3$), 26.7 ($J = 9.6$ Hz, $CHCH_3$), 58.2 (NCH), 62.6 and 63.2 ($J = 7.5$ Hz, 1C each, OCH_2), 68.9 ($J = 166.7$ Hz, CHP), 123.3 and 134.3 (phthalyl CH), 131.4 (phthalyl *C*), 170.0 (CO). Because of the moderate purity of this compound, its elemental analyses were not determined.

Diethyl 1-hydroxy-2-(*N-phthalylamino*)*-3-phenylylpropanephosphonate* **2** *(R = CH$_2$C$_6$H$_5$)*

Isolation of this compound in a pure form was the only successful isolation of compound **2** from the reaction mixture. It was isolated when trying to separate products of the reaction of triethyl phosphite with *N*-phthalyl-L-phenylalanine by means of column chromatography on silica-gel using ethyl acetate as eluent. ^{31}P NMR ($CDCl_3$) δ: 22.0 (major isomer 91%) and 23.8 (minor isomer, 9%). ^{1}H NMR given only for major isomer (DMSO) δ: 1.33 (t, $J =$ 7.1 Hz, 6H, OCH_2CH_3), 3.25–3.40 (m, 3H, $CH_2C_6H_5$ and OH), 4.16 and 4.19 (dq, $J = J_{PH} = 7.1$ Hz, 2H each, OCH_2CH_3), 4.35–4.45 (m, CHP), 4.45–4.70 (m, 1H, NCH), 7.05–7.20 (m, 4H, C_6H_4), 7.80–7.85 (m, 5H, C_6H_5). ^{1}H NMR given only for major isomer ($CDCl_3$) δ: 1.15 and 1.16 (t, $J = 7.1$ Hz, 3H each, OCH_2CH_3), 3.19 (ABX system, $J = 7.8$, 8.6, 13.5 Hz, 2H, $CH_2C_6H_5$), 4.02 and 4.08 (dq, $J = J_{PH} = 7.1$ Hz, 2H each, OCH_2CH_3), 4.07 (multiplet overlapping with OCH_2, $J = 4.5$, $J_{PH} = 12.7$ Hz, CHP), 4.80–4.85 (m, $J = 4.5$ Hz, 1H, NCH), 7.10–7.15 and 7.60–7.65 (m, 2H each, C_6H_4), 7.05–7.15 (m, 5H, C_6H_5). ^{13}C NMR (DMSO) δ: 14.36 and 14.44 ($J = 6.6$ Hz, 1C each, OCH_2CH_3), 32.5 ($CH_2C_6H_5$), 52.6 ($J = 12.7$ Hz, NCH), 59.9 and 60.7 ($J = 7.0$ Hz, OCH_2), 64.4 ($J =$ 162.0 Hz, CHP), 126.4 and 126.5 (phthalyl CH), 121.4 and 132.8 (phenyl CH), 124.5 (phenyl *C*), 135.2 (phthalyl *C*), 165.9 (CO). Elemental analyses calculated for $C_{21}H_{24}NO_4P$ (385.40): 3.63% N, 8.04% P; found: 3.34% N, 7.91% P.

Ethyl (*S*)*-1-oxo-2-*(*N-phthalylamino*)*-3-phenylylpropanephosphonate* **3** *(R = CH$_2$C$_6$H$_5$)*

Isolation of this compound in a pure form was once more the only successful isolation of compound **3** from the reaction mixture. It was isolated when trying to separate products of the reaction of triethyl phosphite with *N*-phthalyl-L-phenylalanine by means of column chromatography on silica-gel using ethyl acetate: chloroform as eluent. ^{31}P NMR ($CDCl_3$) δ: 4.8. ^{1}H NMR ($CDCl_3$) δ: 1.19 and 1.21 (t, $J =$ 7.0 Hz, 1.5H each, OCH_2CH_3), 3.69 (d, $J = 8.3$ Hz, 2H, $CH_2C_6H_5$), 4.01 and 4.14 (dq, $J = J_{PH} = 7.1$ Hz, 1H each, OCH_2CH_3), 4.07 (multiplet overlapping with OCH_2, $J = 4.5$, $J_{PH} = 12.7$ Hz, CHP), 5.38 (t, $J =$ 8.3 Hz, 1H, NCH), 7.15–7.25 (m, 5H, C_6H_5), 7.65–7.85 (m, 4H, C_6H_4), 7.80 (bs, OH). ^{13}C NMR ($CDCl_3$) δ (ppm): 15.95 and 16.00 ($J = 6.8$ Hz, 0.5C each, OCH_2CH_3), 34.4 ($CH_2C_6H_5$), 53.1 (NCH), 63.4 ($J =$ 4.5 Hz, OCH_2), 64.4 ($J = 162.0$ Hz, CP), 128.5 and 128.8 (phthalyl CH), 123.5, 127.0, and 131.8 (phenyl CH), 129.6 (phenyl *C*), 135.2 (phthalyl *C*), 134.0 ($J =$ 160.8 Hz, CP), 166.4 (phthalyl CO). Elemental analyses calculated for $C_{17}H_{18}NO_4P$: 4.23% N, 9.35% P; found: 4.35% N, 9.07% P.

Tetraalkyl 1-Hydroxy-2(*N-phthalylamino*)*ethylenebisphosphonates* **4**

A chemically pure compound **4** was isolated only when N-phthalylglycine chloride was used as the

substrate. Thus, to the solution of *N*-phthalylglycine chloride (2.24 g, 0.01 mole) in benzene, trialkyl phosphite was added dropwise, and the mixture was stirred with cooling for 2 hours. After removal of the volatile reagents, products were isolated either by crystallization or by means of column chromatography.

Tetramethyl 1-hydroxy-2(N-phthalylamino)ethylene-1,1-bisphosphonate (*R* = *H*).

This compound crystallized directly from the reaction mixture and was obtained in 10% yield. m.p. 155–161°C, ^{31}P NMR ($CDCl_3$)δ:20.8. ^{1}H NMR ($CDCl_3$) δ: 3.82, 3.84, and 3.86 (d, J_{PH} = 12.5 Hz, totally 12H, OC*H*$_3$), 4.37 (dd, J = 7.6, J_{PH} = 10.8 Hz, 2H, NC*H*$_2$), 5.57 (t, J_{PH} = 11.3 Hz, 1H, O*H*), 7.90–8.00 (m, 4H, C_6H_4). ^{13}C NMR ($CDCl_3$) δ: 54.5 and 54.6 (J = 18.8 Hz, 1C each, OCH_3), 54.5 (J = 18.6 Hz, OCH_3), 67.2 (J = 168.5 Hz, *C*P), 123.8 and 131.7 (phthalyl *C*H), 134.4 (phthalyl *C*), 169.2 (phthalyl *C*O). IR (KBr) ν (cm^{-1}): 3351 (OH), 1773 and 1694 (C=O), 1265 and 1243 (P=O), 1068, 1043 and 1021 (POC). Elemental analyses calculated for $C_{14}H_{19}NO_9P_2$ (407.23): 3.44% N, 15.21% P; found: 3.58% N, 15.01% P.

Tetraethyl 1-Hydroxy-2(N-phthalylamino) ethylene-1,1-bisphosphonate (*R* = *H*)

This compound was isolated from the reaction mixture after crystallization of compound **7** by means of column chromatography using ethyl acetate: methylene chloride (3:5) as eluent (this resulted in the mixture of products) and then acetone. Acetone fractions contained the pure, oily compound **4**. Yield, 11%; ^{31}P NMR ($CDCl_3$) δ:18.9. ^{1}H NMR ($CDCl_3$) δ: 1.22 and 1.30 (t, J = 7.1 Hz, 3H each, $OCH_2C\underline{H}_3$), 1.25 (t, J = 7.1 Hz, 6H, OCH_2CH_3), 4.18 and 4.20 (dq, J = J_{PH} = 7.1 Hz, 2H each, OCH_2CH_3), 4.19 (dq, J = J_{PH} = 7.1 Hz, 4H, OCH_2CH_3), 4.43 (dd, J = 7.5, J_{PH} = 10.5 Hz, 2H, NC*H*$_2$), 5.53 (t, J_{PH} = 11.43 Hz; 1H, O*H*), 7.72 (dd, J = 3.0, 6.0 Hz, 2H, C_6H_4), 7.84 (dd, J = 3.0, 6.0 Hz, 2H, C_6H_4). IR (film) ν (cm^{-1}): 3400 (OH), 1723 and 1639 (C=O), 1219 (P=O). 1054 and 957 (POC). Elemental analyses calculated for $C_{14}H_{19}NO_9P_2$ (407.23): 3.44% N, 15.21% P; found: 3.58% N, 15.01% P.

Tetraalkyl 1-Phosphonoxy-2-(N-phthalylamino)alkanephosphonates **5**

Compounds 5 were isolated directly from the crude reaction mixtures by precipitation or column chromatography.

Tetramethyl 1-phosphonoxy-2-(N-phthalylamino)ethanephosphonate (R = H). This compound was obtained directly from the reaction mixture by dissolving it in ethyl acetate and then careful precipitation with hexane. Yield 20%. m.p. 102–103°C. ^{31}P NMR ($CDCl_3$) δ: 2.6 (d, J_{PP} = 20.0 Hz) and 19.8 (d, J_{PP} = 20.0 Hz). ^{1}H NMR ($CDCl_3$) δ: 3.51 and 3.72 (d, J = 11.3 Hz, 3H each, OC*H*$_3$), 3.92 (d, J_{PH} = 10.7 Hz, 6H, OCH_3), 3.98 (ddd, J = 14.5, 3.0, J_{PH} = 4.9 Hz, 1H, NC*H*$_2$), 4.28 (ddd, J = 14.5, 10.5, J_{PH} = 6.9 Hz, 1H, NC*H*$_2$), 5.08 (ddd, J = 10.5, 3.0, J_{PH} = 20.5 Hz, 1H, C*H*), 7.73 and 7.86 (dd, J = 3.0, 6.0 Hz, 2H, C_6H_4).^{13}C NMR ($CDCl_3$) δ: 38.3 (dd, J = 8.3, 2.3 Hz, NC), 53.8 (J = 6.8 Hz, OCH_3), 54.6 (J = 5.7 Hz, OCH_3), 54.7 (J = 15.9 Hz, OCH_3), 69.6 (dd, J = 7.2, 167.5 Hz, *C*P), 123.2 and 132.0 (phthalyl CH), 134.0 (phthalyl *C*), 167.8 (phthalyl *C*O). Elemental analyses calculated for $C_{14}H_{19}NO_9P_2$ (407.23): 3.44% N, 15.21% P; found: 3.42% N, 15.17% P.

Tetraethyl 1-phosphonoxy-2-(N-phthalylamino)propanephosphonate (R = CH_3). This compound was isolated chromatographically as an oily mixture of diastereomers (1:1) using ethyl acetate:methylene chloride (5:3) as eluent. Yield, 9%; ^{31}P NMR ($CDCl_3$) δ: major isomer: −0.1 (d, J_{PP} = 13.3 Hz) and 18.4 (d, J_{PP} = 13.3 Hz), minor isomer: −0.1 (d, J_{PP} = 16.1 Hz) and 18.7 (d, J_{PP} = 16.1 Hz). ^{1}H NMR ($CDCl_3$) δ: 0.840, 0.837, and 1.19, and 1.135, 1.138, and 1.21 (t, J = 7.1 Hz, 1H each, OCH_2CH_3), 1.274, 1.278, 1.288, 1.295, and 1.319, 1.323 (t, J = 7.1 Hz, 1H each, OCH_2CH_3), 1.595 and 1.589 (d, J = 6.9 Hz, 1.5H each, $CHCH_3$), 3.55–3.80 and 3.90–4.15 (m, J = J_{PH} = 7.1 Hz, 1H each, OCH_2CH_3), 3.97 (dq, J = J_{PH} = 7.1 Hz, 2H, OCH_2CH_3), 4.13 and 4.16 and 4.18 and 4.20 (dq, J = 7.1, 1H each, OCH_2CH_3), 4.6–4.75 (m, 1H, NC*H*), 5.05–5.30 (m, 1H, CHP), 7.60–7.65 and 7.70–7.75 (m, 4H, C_6H_4). Elemental analyses calculated for $C_{15}H_{21}NO_9P_2$ (421.28): 3.32% N, 14.70% P; found: 3.29% N, 15.66% P.

Tetraethyl 1-Phosphonoxy-2-(N-phthalylamino)-3-phenylpropanephosphonate (R = $CH_2C_6H_5$). This compound was isolated chromatographically as an oily mixture of diastereomers (1:2) using ethyl acetate as the eluent. Yield, 11%. ^{31}P NMR ($CDCl_3$) δ: major isomer: −0.1 (d, J_{PP} = 16.1 Hz) and 18.4 (d, J_{PP} = 16.1 Hz), minor isomer: 0.0 (d, J_{PP} = 12.7 Hz) and 18.8 (d, J_{PP} = 12.7 Hz). ^{1}H NMR ($CDCl_3$) δ: 0.823 and 0.826 and 1.11 and 1.20 (t, J = 7.1 Hz, 1H each, OCH_2CH_3), 1.140 and 1.143 (d, J = 6.9 Hz, 1H each, OCH_2CH_3), 1.302 and 1.305 (t, J = 7.1 Hz, 3H each, OCH_2CH_3), 3.45–3.50 (m, 2H, $CH_2C_6H_5$), 3.50–3.80 (dq, J = J_{PH} = 7.1 Hz, 2H, OCH_2CH_3), 3.95–4.25 (m, 2H, OCH_2CH_3), 4.15 (minor isomer, dq, J = J_{PH} =

7.1 Hz, 1.33H, OCH_2CH$_3$), 4.20 (major isomer, dq, $J = J_{PH}$ = 7.1 Hz, 2.67H, OCH_2CH$_3$), 4.70–4.90 (m, 1H, NC*H*), 5.20–5.50 (m, 1H, C*H*P), 6.90–7.05 (m, 5H, C$_6H_5$), 7.50–7.60 and 7.60–7.70 (m, 4H, C$_6H_4$). ^{13}C NMR ($CDCl_3$) δ (ppm): 14.90 and 15.16 and 15.42 and 15.48 and 15.52 (J = 6.8 Hz, OCH$_2$*C*H$_3$), 32.5 (*C*H$_2$C$_6$H$_5$), 34.0 (minor isomer, J = 11.2 Hz, OCH$_2$*C*H$_3$), 62.58 and 62.58 and 63.15 and 63.47 (J = 6.2 Hz, O*C*H$_2$), 52.3 and 53.4 (N*C*H), 70.8 (minor isomer, J = 166.6 Hz, CP), 71.5 (major isomer, J = 160.0 Hz, CP), 122.0 and 132.7 (phthalyl *C*H), 125.6, 127.4 and 127.8 (phenyl *C*H), 128.0 (phenyl *C*), 135.9 (phthalyl *C*), 167.0 (phthalyl *C*O), 122.1, 130.7, 132.8 and 144.0 (minor isomer, phthalyl and phenyl *C*). Elemental analyses calculated for $C_{21}H_{25}NO_9P_2$ (497.38): 2.82% N, 12.45% P; found: 2.79% N, 12.37% P.

Compound **6**

We were able to isolate this compound only once from the reaction mixture obtained when the reaction was carried out with the chloride of *N*-phthalyl-L-leucine. After extraction of the reaction mixture with water, the product was isolated by means of column chromatography using ethyl acetate:methylene chloride (5:3) as the eluent. ^{31}P NMR ($CDCl_3$) *δ:* 68.8. ^{1}H NMR ($CDCl_3$) *δ:* 0.85 and 0.87 (d, J = 6.7 Hz, 6H, CHC*H*$_3$), 1.15 (t, J = 7.1 Hz, 3H, COCH$_2$C*H*$_3$), 1.25 (t, J = 6.9 Hz, 9H each, POCH$_2$C*H*$_3$), 1.35–1.50 (m, 1H, C*H*CH$_3$), 1.70–1.90 (m, J = 4.4 Hz, 1H, CHC*H*$_2$), 2.22 (t-t, J = 4.4, 7.0 Hz, 1H, NCHC*H*$_2$), 4.08 (dq, $J = J_{PH}$ = 6.9 Hz, 6H, POC*H*$_2$CH$_3$), 4.11 (q, J = 7.1 Hz, 2H, COC*H*$_2$CH$_3$), 4.86 (dd, J = 4.4, J_{PH} = 11.6 Hz, 1H, NC*H*), 7.65–7.68 and 7.78–7.80 (m, 4H, C$_6H_4$). ^{13}C NMR ($CDCl_3$) *δ:* 13.1 (COCH$_2$*C*H$_3$), 14.9 (J = 7.5 Hz, POCH$_2$*C*H$_3$) 20.0 and 22.1 (CH*C*H$_3$), 24.1 (CH*C*H$_3$), 49.8 (CH*C*H$_2$), 60.77 (CO*C*H$_2$), 63.1 (J = 5.3 Hz, PO*C*H$_2$), 122.5 and 133.1 (phthalyl *C*H), 130.8 (phthalyl *C*), 167.8 (J = 147.9 Hz, CP), 172.6 (phthalyl CO).

Diethyl (*E*)*-1-*(*N-phthalylglycyloxy*)*-2-*(*N-phthalylamino*)*ethenephosphonate* **7**

After the reaction of *N*-phthalylglycine chloride with triethyl phosphite had been carried out in benzene, the solvent was removed under reduced pressure, and the oily mixture was dissolved in ethyl acetate and products precipitated by careful addition of hexane. This crystallization afforded ethyl *N*-phthlalylglycinate, which crystallized first, followed by the compound **7.** Yield, 10%; m.p., 182–183°C. When the reaction was carried out in toluene, compound **7a** crystallized spontaneously from the reaction mixture. It was recrystallized from an ethyl acetate:hexane mixture. Yield, 10%; m.p., 172–173°C.

Both compounds gave the same spectral data. ^{31}P NMR ($CDCl_3$) *δ:* 9.8. ^{1}H NMR ($CDCl_3$) *δ:* 1.37 (t, J = 7.0 Hz, 6H, OCH$_2$C*H*$_3$), 4.19 (dq, $J = J_{PH}$ = 7.0 Hz, 4H, OC*H*$_2$CH$_3$), 4.66 (s, 2H, NC*H*$_2$), 7.39 (d, J_{PH} = 9.0 Hz, C = C*H*), 7.73 and 7.81 and 7.85 and 7.95 (dd, J = 3.0, 6.0 Hz, 2H each, C$_6H_4$). ^{13}C NMR ($CDCl_3$) *δ:* 16.5 (J = 7.5 Hz, POCH$_2$*C*H$_3$), 39.1 (NC*H*$_2$), 63.7 (J = 5.3 Hz, PO*C*H$_2$), 120.8 (J = 41.0 Hz, C = *C*H), 124.0 and 127.7 and 134.6 and 135.4 (phthalyl CH), 131.9 and 132.3 (phthalyl C), 129.6 (J = 229.0 Hz, HC=CP), 164.8 and 167.4 (phthalyl CO). IR (KBr) ν (cm^{-1}): 2993, 2939, and 2908 (CH); 1770, 1741, and 1722 (C=O); 1156 (P=O); 1054 and 1028 (POC). Elemental analyses calculated for $C_{24}H_{31}N_2O_9P$ (522.49): 5.36% N, 5.93% P; found: 5.31% N, 6.08% P.

CONCLUSION

It is well established that dialkyl 1-oxoalkanephosphonates are quite unstable and readily undergo decomposition when stored either as pure compounds or in various solutions. The pathways and products of these decompositions have not been defined so far. Studying the reaction of triethyl phosphite with phthalylamino acids, we have shown that a variety of phosphorus-containing compounds are formed in these reactions, and we have established the chemical structures of all the products. Moreover, we have shown that the decomposition of 1-oxoalkanephosphonates to similar mixtures of products is promoted by the presence of diethyl phosphite. The condensation of two molecules of α-ketophosphonate seems to be a primary source of diethyl phosphite. The second source could be the reaction of a ketophosphonate with a trace amount of ethanol present in some of the solvents used for crystallization and chromatography. We reached this conclusion from the fact that the final mixtures of products in many cases also contained small quantities of ethyl esters of *N*-phthalylamino acids.

ACKNOWLEDGMENTS

The authors are greatly indebted to Prof. Z. Gałdecki from the Technical University of Łódź for his help in the crystal structure determinations.

REFERENCES

[1] (a) Beninga, J.; Rock, K. L.; Goldberg, A. L. J Biol Chem 1998, 273, 18734–18742; (b) Pulido-Cejudo, G.;

Conway, B.; Proulx, P.; Brown, R.; Izaguirre, C. A. Antivir Res 1997, 36, 167–177.
[2] (a) Wan, M. C.; Taylor, H. L.; Wall, M. E.; Coggon, P.; McPhail, A. T. J Am Chem Soc 1971, 93, 2325–2327; (b) Nicolaou, K. C.; Dai, W. M.; Guy, R. K. Angew Chem Int Ed 1994, 33, 15–44.
[3] (a) Patel, D. V.; Rielly-Gauvain, K.; Ryono, D. E. Tetrahedron Lett 1990, 31, 5587–5590; (b) Stowasser, B.; Budt, K.-H.; Jian-Qi, L.; Peyman, A.; Ruppert, D. Tetrahedron Lett 1992, 33, 6625–6628; (c) Yokomatsu, T.; Yamagishi, T.; Shibuya, S. Tetrahedron Asymmetry 1993, 4, 1401–1404; (d) Wester, R. T.; Chambers, T. J.; Green, M. D.; Murphy, W. R. Bioorg Med Chem Lett 1994, 4, 2005–2008.
[4] (a) Dellaria, J. F. Jr.; Maki, R. Tetrahedron Lett 1986, 27, 2337–2340;(b) Heisler, A.; Rabiller, C. Phosphorus Sulfur Silicon 1995, 101, 273–280; (c) Zygmunt, J.; Gancarz, R.; Lejczak, B.; Wieczorek, P.; Kafarski, P. Bioorg Med Chem Lett 1996, 6, 2989–2992; (d) Wróblewski, A. E.; Piotrowska, D. G. Tetrahedron 1998, 54, 8123–8132; (e) Wiemer, D. F. Tetrahedron 1997, 53, 16609–16644.
[5] Oshikawa, T.; Yamashita, M. Bull Chem Soc Jpn 1990, 63, 2728–2730.
[6] Saegusa, T.; Kobayashi, S.; Kimura, Y.; Yokohama, T. J Org Chem 1977, 42, 2797–2798.
[7] (a) Ruel, R.; Bouvier, J.-P.; Young, R. N. J Org Chem 1995, 60, 5209–5213; (b) Benech, J. M.; Coindet, M.; El Manouni, D.; Leroux, Y. Phosphorus Sulfur Silicon 1997, 123, 377–383.
[8] (a) Griffith, D. V.; Hughes, J. M.; Brown, J. W.; Cesar, J. S.; Swetnam, S. P.; Cumming, A.; Kelly, J. D. Tetrahedron 1997, 53, 17815–17822; (b) Mitchell, M. C.; Kee, T. P. Coord Chem Rev 1997, 158, 359–383.
[9] (a) Griffiths, D. V.; Griffiths, P. A.; Karim, K.; Whitehead, B. J. J Chem Soc Perkin Trans 1 1996, 555–561; (b) Griffiths, D. V.; Karim, K.; Harris, J. E. J Chem Soc Perkin Trans 1 1997, 2539–2544; (c) Griffiths, D. V.; Harris, J. E.; Whitehead, B. J. J Chem Soc Perkin Trans 1 1997, 2545–2548.
[10] Sheldrick, G. M. Acta Crystallogr A 1990, 46, 467–473.
[11] Sheldrick, G. M. SHELXL 93. Program for Refinement of Crystal Structures, University of Göttingen: Göttingen, Germany, 1993.