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N.S. Zefirov on His 70th Anniversary

Reactions of Allenylphosphonates with 2-Aminoethanol and Amines

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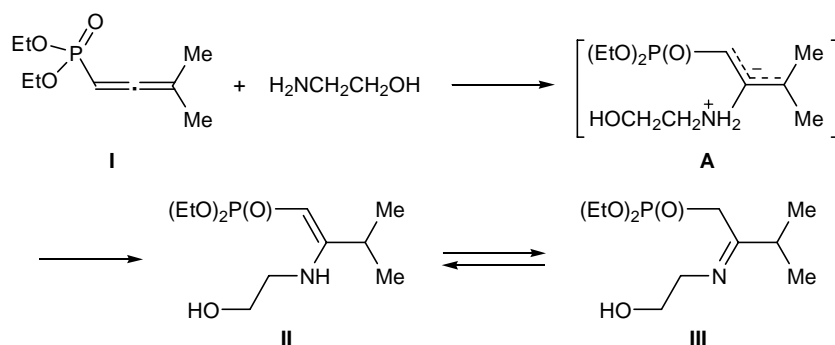
Abstract—Dialkyl 3-methyl-1,2-butadienylphosphonates take up 2-aminoethanol, butylamine, diethylamine, and morpholine in such a way that the amino nitrogen atom adds at the central carbon of the allene triad. The reactions with primary amines lead to the corresponding 1-phosphoryl-2-amino-1-butenes and isomeric 1-phosphoryl-2-iminobutanes, while secondary amines give rise to 1,2- and 2,3-enamines.

Interest in the synthesis of polyfunctional organo-phosphorus compounds originates from wide prospects in their practical application. We previously developed a convenient regio- and chemoselective method for the synthesis of new phosphorylated alkenes and alkanes having sulfur-containing groups by reactions of unsaturated four-coordinate phosphorus acid derivatives with 1,2-ethanedithiol and 2-sulfanylethanol [1, 2].

The present article reports the results of our study on reactions of allenylphosphonates with 2-aminoethanol and some primary and secondary amines. The study was aimed at synthesizing new phosphorylated alkenes having an amino group in the β -position. By reacting equimolar amounts of diethyl 3-methyl-1,2-butadienylphosphonate (**I**) with 2-aminoethanol

(Scheme 1) we obtained a crystalline product whose structure was established by the X-ray diffraction method. The chemical ionization mass spectrum of the product contained a strong peak with m/z 266, $[M + H]^+$, corresponding to the formula $C_{11}H_{24}NO_4P$. Figure 1 shows that the adduct has the enamine structure, 1-diethoxyphosphoryl-2-(2-hydroxyethyl)amino-3-methyl-1-butene (**II**), with *trans* arrangement of the phosphoryl and amino groups. Selected geometric parameters of molecule **II** are given in table. Molecules **II** in crystal are linked through intermolecular hydrogen bonds $N-H\cdots O$ and $O-H\cdots O$, giving rise to infinite chains along the $0a$ axis (Fig. 2). These hydrogen bonds are characterized by the following parameters: $N^6-H^6\cdots O^1$ ($1 + x, y, z$), N^6-H^6 0.88, $H^6\cdots O^1$ 2.18,

Scheme 1.



$N^6 \cdots O^1$ 3.024(3) Å; $\angle N^6 H^8 O^1$ 158°; $O^8 - H^8 \cdots O^1$ (1 + x , y , z), $O^8 - H^8$ 0.95, $H^8 \cdots O^1$ 1.76, $O^8 \cdots O^1$ 2.699(5), $\angle O^8 H^8 O^1$ 167°.

We detected no products which could be formed by addition to allenylphosphonate **I** of 2-aminoethanol with participation of the hydroxy group of the latter. Presumably, zwitterionic intermediate **A** arising from attack by the amine on the central carbon atom of the allene moiety in **I** stabilizes as enamine **II** with the double bond between C^1 and C^2 . According to the 1H and ^{31}P NMR data, compound **II** in benzene, toluene, or chloroform solution exists in equilibrium with imine tautomer **III** (Scheme 1). The 1H NMR spectrum of a solution of **II** in $CDCl_3$ contains a doublet signal at δ 2.92 ppm ($^2J_{PH} = 23.8$ Hz), which belongs to protons of the methylene group attached to the phosphorus atom. The absence of two doublets in the δ region 1.8–2 ppm, which are typical of protons in two nonequivalent methyl groups at sp^2 -hybridized carbon atom allowed us to rule out the structure with 2,3-double bond and confirmed the existence of enamine–imine tautomeric equilibrium displaced toward imine tautomer **III**. In the ^{31}P NMR spectrum of a solution of the product in toluene at 25°C we observed two signals at δ_P 29.0 (**II**) and 28.3 ppm (**III**) with an intensity ratio of 0.4:1. The phosphorus signals were assigned on the basis of the signal intensity ratios in the 1H and ^{31}P NMR spectra. Raising the temperature to 50°C changes the signal intensity ratio to 0.8:1 (δ_P 28.9 and 27.9 ppm, respectively). At 80°C, the ratio of the enamine and imine structures becomes equal to 1.5:1. After cooling to 25°C, the intensity of the signals at δ_P 28.9 and 27.9 ppm in the ^{31}P NMR spectrum of the solution was 0.7:1, indicating increase in the fraction of imine tautomer **III**. The observed temperature dependence of the ratio of compounds **II** and **III** in solution confirms the existence of enamine–imine equilibrium.

A mixture of enamine **IV** and imine **V** was also formed upon dissolution of the crystalline adduct obtained by reaction of allenylphosphonate **I** with butylamine (Scheme 2). The ^{31}P NMR spectrum of a solution of the adduct in chloroform contained two singlets at δ_P 30.3 and 27.4 ppm at a ratio of 0.7:1.

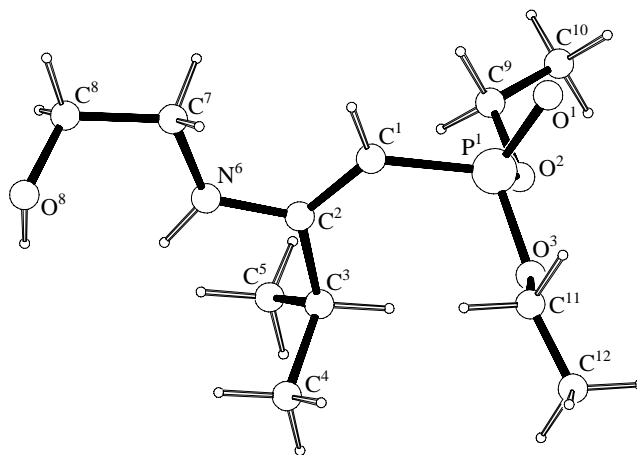
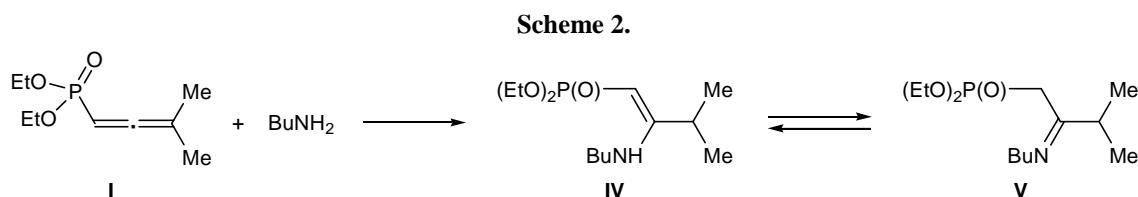


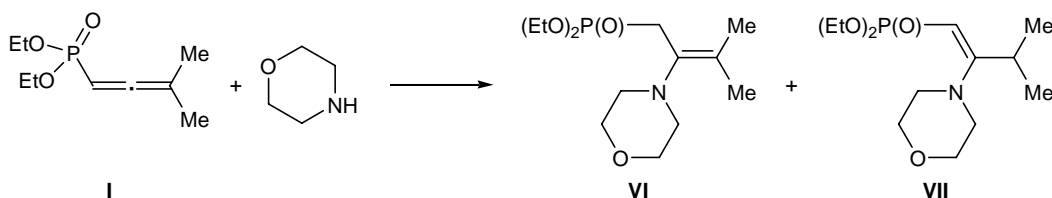
Fig. 1. Structure of the molecule of diethyl 2-(2-hydroxyethylamino)-3-methyl-1-butenylphosphonate (**II**) in crystal according to the X-ray diffraction data.

Protons of the isopropyl fragment appeared in the 1H NMR spectrum as two doublets at δ 1.11 ($^3J_{HH} = 6.6$ Hz) and 1.10 ppm ($^3J_{HH} = 6.9$ Hz). The doublet at δ 2.89 ppm ($^2J_{PH} = 23.5$ Hz) was assigned to protons of the methylene group attached to the phosphorus atom in isomer **V**. The vinyl proton in **IV** gave a doublet at δ 3.73 ppm ($^2J_{PH} = 10.2$ Hz). Methyl protons in the butyl group on the nitrogen atom give a triplet at δ 0.92 ppm. No signals from protons of methyl groups at sp^2 -hybridized carbon atom (δ 2 ppm), which could be expected for product of butylamine addition at the 1,2-double bond of allenylphosphonate **I**, were present in the 1H NMR spectrum.

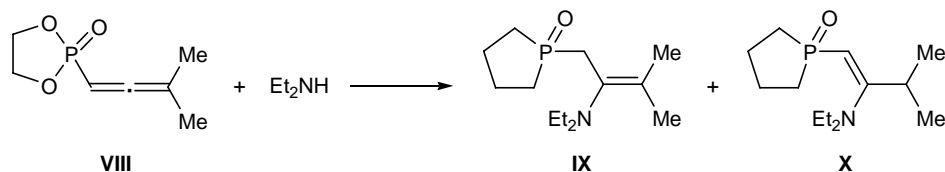
However, allenylphosphonates reacted with secondary amines, such as morpholine and diethylamine, to give adducts containing both 2,3- and 1,2-double bonds with the amino nitrogen atom linked to the central carbon atom of the allene triad. In the reaction of allenylphosphonate **I** with morpholine (Scheme 3), the ^{31}P NMR spectrum of the reaction mixture contained two signals at δ_P 28.1 and 28.0 ppm. The formation of diethyl 3-methyl-2-morpholino-2-butenylphosphonate (**VI**) follows from the presence in the 1H NMR spectrum of two doublets from protons of nonequivalent methyl groups at the sp^2 -hybridized carbon atom and of a doublet signal from protons in the methylene group at the phosphorus atom (δ 3.07 ppm, $^2J_{PH} =$



Scheme 3.



Scheme 4.



22.4 Hz). Diethyl 3-methyl-2-morpholino-1-butenylphosphonate (VII) is characterized by two doublets at δ 1.19 ($^3J_{\text{HH}} = 7.5$ Hz) and 1.08 ppm ($^3J_{\text{HH}} = 6.9$ Hz) in the ^1H NMR spectrum, which belong to methyl protons in the isopropyl fragment. Presumably, initially formed adduct VII undergoes partial isomerization to compound VI. An analogous isomerization was reported previously [3].

Likewise, 2-(3-methyl-1,2-butadienyl)-1,3,2λ⁵-dioxaphospholane 2-oxide (VIII) reacted with diethylamine to afford two isomeric addition products IX and X (Scheme 4). Both adducts have enamine structure with the nitrogen atom attached to the central carbon atom of the allene triad in VIII; they differ by the double bond position.

Thus allenylphosphonates possessing two methyl substituents at the terminal carbon atom readily react with 2-aminoethanol and primary and secondary amines; the amine attacks the central *sp*-hybridized carbon atom, in keeping with the regioselectivity typical of addition of proton-containing nucleophiles to phosphorylated unsaturated substrates [4, 5]. The primary zwitterionic adduct with a β -ammonio group

undergoes various isomerizations, depending on the amine nature, to afford either phosphorylated enamine with 1,2- or 2,3-double bond or phosphorylated imine.

EXPERIMENTAL

The IR spectra were recorded on a UR-20 spectrometer. The ^1H and ^{31}P NMR spectra were obtained on a Varian Unity 300 spectrometer operating at 300 and 121.42 MHz, respectively, from solutions in CDCl_3 ; the solvent was used as internal reference for ^1H (δ 7.24 ppm); the ^{31}P chemical shifts were measured relative to 85% H_3PO_4 as external reference. The mass spectra were run on a MAT-212 mass spectrometer (electron impact, 60 eV; emission current 0.1 mA; direct sample admission into the ion source; gradual increase of the vaporizer temperature); the exact mass values were determined by peak matching at a resolution of 10000.

X-Ray analysis of compound II. Rhombic crystals, $\text{C}_{11}\text{H}_{24}\text{NO}_4\text{P}$, with the following unit cell parameters (20°C): $a = 7.9495(6)$, $b = 13.079(2)$, $c = 14.869(3)$ Å; $V = 1546.0(4)$ Å³; $d_{\text{calc}} = 1.14$ g/cm³; $Z =$

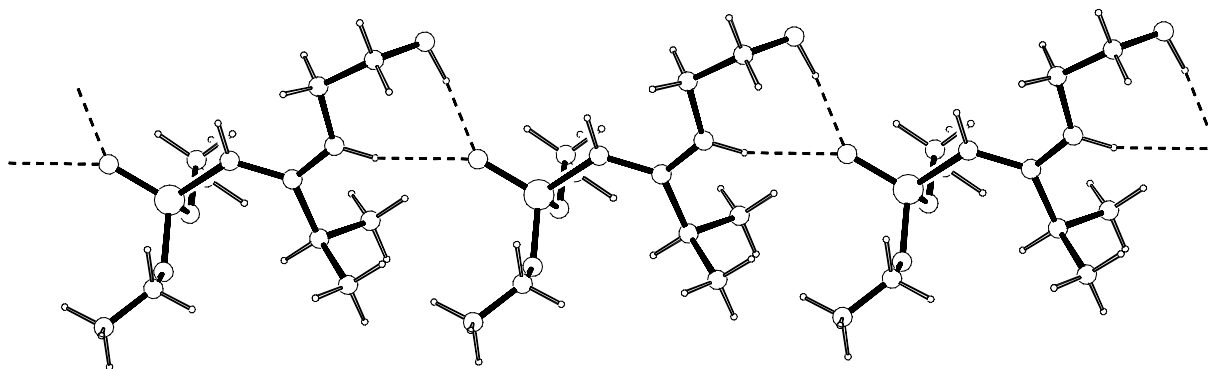


Fig. 2. Hydrogen bonds in the crystalline structure of diethyl 2-(2-hydroxyethylamino)-3-methyl-1-butenylphosphonate (II).

4, space group $P2_12_12_1$. Intensities of 1837 reflections, 1657 of which were with $I \geq 2\sigma$, were measured on an Enraf-Nonius CAD-4 automatic four-circle diffractometer ($\lambda\text{CuK}\alpha$, graphite monochromator, ω -scanning, $\theta \leq 74^\circ$). No drop in intensity of three control reflections was observed during data acquisition. The absorption was taken into account empirically ($\mu\text{Cu} = 16.2 \text{ cm}^{-1}$). The structure was solved by the direct method using SIR program [6] and was refined first in isotropic and then in anisotropic approximation using SHELX-97 program [7]. The positions of hydrogen atoms were calculated on the basis of stereochemical considerations and were refined using the rider model. The hydrogen atoms on N^6 and O^8 were localized from difference series of electron density, and their coordinates were refined in isotropic approximation at final refinement stages. The final divergence factors were $R = 0.046$, $R_w = 0.133$ (from 1626 reflections with $I \geq 2\sigma$). All calculations were performed using MoLEN [8] and WinGX software [9]. The figures were plotted, and hydrogen bonds were analyzed, using PLATON software [10].

All reactions were carried out in a stream of argon.

Diethyl 2-(2-hydroxyethylamino)-3-methyl-1-butenylphosphonate (II). *a.* Allenylphosphonate **I**, 3.72 g (1.8 mmol), was added to 1.1 g (1.8 mmol) of 2-aminoethanol. The mixture warmed up to 105°C , and crystals separated in 0.5 h. Recrystallization from benzene gave 2 g (37%) of compound **II**, mp 72°C .

b. Phosphonate **I**, 4.1 g (2 mmol), was added over a period of 10 min to a solution of 1.18 g (2 mmol) of 2-aminoethanol in 10 ml of diethyl ether under continuous stirring and cooling. The mixture was stirred for 30 min at room temperature and left overnight. A part of the solvent (25% by volume) was removed under reduced pressure, and, after 10–12 h, colorless crystals of **II** separated. Yield 1.4 g (27%), mp 72°C . Mass spectrum: m/z 266 [$M + \text{H}$] $^+$ ($I_{\text{rel}} = 100\%$).

Diethyl 2-(2-butylamino)-3-methyl-1-butenylphosphonate (IV). Butylamine, 1.41 g (1.9 mmol), was added to 3.95 g (1.9 mmol) of phosphonate **I**. The mixture warmed up to 100°C . It was then kept at room temperature until the absorption band at 1955 cm^{-1} ($\nu\text{C}=\text{C}=\text{C}$) disappeared from the IR spectrum and was distilled under reduced pressure. The distillate crystallized. Yield 4.15 g (77.4%), mp 63°C , bp $103\text{--}105^\circ\text{C}$ (0.7 mm). Found, %: C 56.78; H 10.34. $\text{C}_{13}\text{H}_{28}\text{NO}_3\text{P}$. Calculated, %: C 56.30; H 10.18.

Reaction of diethyl 3-methyl-1,2-butadienylphosphonate (I) with morpholine. Morpholine, 1.74 g (2 mmol), was added to 4.08 g (2 mmol) of phospho-

Selected bond lengths and bond angles in the molecule of diethyl 2-(2-hydroxyethylamino)-3-methyl-1-butenylphosphonate (**II**)

Bond	$d, \text{Å}$	Bond	$d, \text{Å}$
$\text{C}^1\text{--C}^2$	1.365(4)	$\text{O}^1\text{--P}^1$	1.474(3)
$\text{C}^1\text{--P}^1$	1.734(3)	$\text{O}^2\text{--P}^1$	1.564(2)
$\text{C}^2\text{--N}^6$	1.341(3)	$\text{O}^3\text{--P}^1$	1.570(2)
$\text{C}^2\text{--C}^3$	1.513(4)	$\text{C}^9\text{--O}^2$	1.431(4)
$\text{C}^7\text{--N}^6$	1.453(4)	$\text{C}^{11}\text{--O}^3$	1.443(5)
$\text{C}^8\text{--O}^8$	1.380(5)		
Angle	ω, deg	Angle	ω, deg
$\text{C}^2\text{C}^1\text{P}^1$	127.0(2)	$\text{C}^1\text{C}^2\text{C}^3$	123.1(2)
$\text{N}^6\text{C}^2\text{C}^1$	121.7(2)	$\text{C}^2\text{C}^3\text{C}^5$	111.9(3)
$\text{N}^6\text{C}^2\text{C}^3$	115.2(2)	$\text{C}^2\text{C}^3\text{C}^4$	110.9(3)
$\text{N}^6\text{C}^7\text{C}^8$	112.0(3)	$\text{C}^{10}\text{C}^9\text{O}^2$	116.3(5)
$\text{O}^8\text{C}^8\text{C}^7$	114.1(3)	$\text{C}^{12}\text{C}^{11}\text{O}^3$	113.2(5)
$\text{C}^2\text{N}^6\text{C}^7$	123.4(2)	$\text{C}^{11}\text{O}^3\text{P}^1$	118.3(3)
$\text{C}^9\text{O}^2\text{P}^1$	120.8(3)	$\text{O}^1\text{P}^1\text{O}^2$	113.4(2)
$\text{O}^1\text{P}^1\text{O}^3$	112.5(2)	$\text{O}^2\text{P}^1\text{C}^1$	111.73(15)
$\text{O}^2\text{P}^1\text{O}^3$	96.1(1)	$\text{O}^3\text{P}^1\text{C}^1$	112.0(1)
$\text{O}^1\text{P}^1\text{C}^1$	110.5(1)		

nate **I**. The mixture warmed up to 40°C . It was heated at $85\text{--}90^\circ\text{C}$ until the absorption band at 1955 cm^{-1} ($\nu\text{C}=\text{C}=\text{C}$) disappeared from the IR spectrum and was distilled under reduced pressure to isolate a mixture of diethyl 3-methyl-2-morpholino-2-butenylphosphonate (**VI**) and diethyl 3-methyl-2-morpholino-1-butenylphosphonate (**VII**). Overall yield 4.05 g (69.6%), bp $108\text{--}110^\circ\text{C}$ (0.9 mm), $n_{\text{D}}^{20} = 1.4864$.

Reaction of 1,3,2 λ^5 -dioxaphospholane 2-oxide (VIII) with diethylamine. Diethylamine, 0.85 g (1.2 mmol), was added dropwise to 2.02 g (1.2 mmol) of compound **VIII**. The mixture warmed up to 100°C . It was kept for 24 h at room temperature and repeatedly distilled under reduced pressure to isolate a mixture of compounds **IX** and **X**. Overall yield 1.86 g (64.7%), bp $123\text{--}137^\circ\text{C}$ (0.7 mm), $n_{\text{D}}^{20} = 1.5023$.

2-(3-Methyl-2-diethylamino-2-butenyl)-1,3,2 λ^5 -dioxaphospholane 2-oxide (IX). ^1H NMR spectrum (CDCl_3), δ , ppm: 0.93 t (6H, $\text{CH}_3\text{CH}_2\text{N}$, $^3J_{\text{HH}} = 7.2 \text{ Hz}$), 1.72 d.d and 1.76 d.d [3H each, $=\text{C}(\text{CH}_3)_2$, $^5J_{\text{PH}} = 4.8, 6.3 \text{ Hz}$], 2.62 q (4H, NCH_2CH_3 , $^3J_{\text{HH}} = 7.2 \text{ Hz}$), 2.80 d (2H, $\text{PCH}_2\text{C}=\text{C}$, $^2J_{\text{PH}} = 21.6 \text{ Hz}$), 4.18 m and 4.40 m (4H, $\text{OCH}_2\text{CH}_2\text{O}$). ^{31}P NMR spectrum (CDCl_3): $\delta_{\text{P}} 48.5 \text{ ppm}$.

2-(3-Methyl-2-diethylamino-1-butenyl)-1,3,2 λ^5 -dioxaphospholane 2-oxide (X). ^1H NMR spectrum

(CDCl₃), δ , ppm: 1.10 t (6H, CH₃CH₂N, ³J_{HH} = 7.1 Hz), 1.24 d [6H, (CH₃)₂CH, ³J_{HH} = 7.3 Hz], 3.21 q (4H, NCH₂CH₃, ³J_{HH} = 7.1 Hz), 3.60 d (1H, PCH=C, ²J_{PH} = 8.7 Hz), 3.69 m [1H, CH(CH₃)₂, ³J_{HH} = 7.3 Hz], 4.18 m and 4.40 m (4H, OCH₂CH₂O). ³¹P NMR spectrum (CDCl₃): δ_P 46.3 ppm.

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