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Synthesis, structure and antimicrobial activity of dialkyl [(hydroxy)(4-nitrophenyl)methyl]phosphonates

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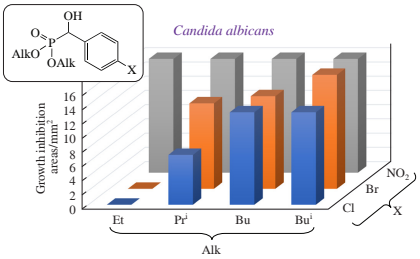
New dialkyl [(hydroxy)(4-nitrophenyl)methyl]phosphonates containing various alkyl substituents were obtained from 4-nitrobenzaldehyde and the corresponding dialkyl phosphites and demonstrated antibacterial activity against Gram-positive bacterial strains *B. cereus* and *S. aureus* and antifungal activity against *Candida albicans* fungi. The dependence of antimicrobial activity on the nature of the substituents at the carbon atom α to phosphorus has been established.



Keywords: α-hydroxy phosphonates, Abramov reaction, antibacterial activity, antifungal activity, solvent free conditions, X-ray diffraction.

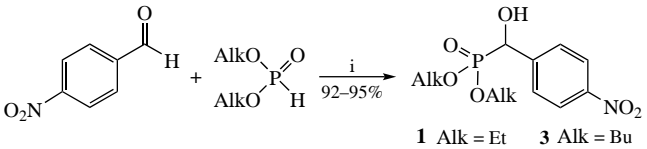
Among the known organophosphorus compounds, α-hydroxy phosphonates represent an interesting family with a wide range of properties.[1–8] The first use of a α-hydroxy phosphonate derivative as the antibiotic Fosfomycin was documented in 1969.[9] Two agents of this class are currently marketed for antiviral therapy, they are adefovir (for hepatitis B) and tenofovir (for HIV). α-Hydroxy phosphonates and their derivatives are currently used as biologically active compounds (*e.g.* phosphazinomycin A, zoledronic acid, risedronate),[10,11] enzyme inhibitors,[12] insecticides (*e.g.*, trichlorfon),[13] and antiviral, anticancer agents.[14] α-Hydroxy phosphonates are versatile building blocks to access more elaborate structures[15–20] (see Online Supplementary Materials, Figure S1). α-Hydroxy phosphonates attract attention as biologically active and valuable precursors for the synthesis of related compounds such as α-aminophosphonates, alkoxy- and acyloxyphosphonates, ketophosphonates, halophosphonates[21–23] and act as intermediates in several reactions.[16]

The most commonly used methodology to prepare α-hydroxy phosphonates is based on the addition of *H*-phosphonates (trialkyl or triaryl phosphites) to carbonyl compounds (the Abramov reaction)[24] and their derivatives (the Pudovik reaction).[25] The original Abramov reaction involved harsh conditions (heating at 70–100 °C for several hours in a sealed tube).[26] Nowadays, both the Abramov and the Pudovik reactions are performed under green conditions including microwave assisted processes to give high yields of the products.[27–33]

Earlier, we have found that α-hydroxy phosphonates containing an aromatic fragment at the α-carbon atom possess antimicrobial activities and selectivities against several some Gram-positive bacteria and *Candida albicans* fungi. We have shown that the introduction of a hexyloxy substituent to the phosphorus atom results in a notable reduction in antimicrobial activity, ultimately leading to its complete disappearance.[34,35] This work describes the synthesis and biological study of new α-hydroxy phosphonates based on 4-nitrobenzaldehyde bearing various alkoxy substituents at the phosphorus atom.

The synthesis of key α-hydroxy phosphonates **1**–**4** was achieved *via* the Abramov reaction between 4-nitrobenzaldehyde and dialkyl phosphites under solvent free conditions and with potassium phosphate as the catalyst (Scheme 1) to provide total conversion within 20 min and excellent yields of the products after crystallization. Their structures were confirmed by FTIR and NMR spectroscopy as well as X-ray diffraction analysis.

The TG/DSC analysis of compounds **1**–**4** (see Online Supplementary Materials) shows that they do not contain volatile impurities (weight loss in the range of 40–150 °C does not exceed 0.6%). For the samples **1**–**4**, the endo effect of melting is recorded with onset temperatures of 90.2, 105.3, 71.5 and 113.3 °C, respectively (the enthalpy of melting is 69.8, 67.8, 50.1 and 76.5 J g^{-1}, respectively). Heating above 150 °C leads to decomposition accompanied by exo effects. It should be noted



1 Alk = Et **3** Alk = Bu
2 Alk = Pr^i **4** Alk = Bu^i

Scheme 1 *Reagents and conditions*: i, K_3PO_4 (10 mol%), solvent free, room temperature, 20 min.

that before the onset of decomposition, no additional effects are recorded on the DSC curves, which may indicate the individuality of the compounds obtained.

In this work, we also present the crystal X-ray analysis of compounds **1**, **2** and **4** (Figure 1).† The difference between the geometry of molecules of compounds **1**, **2** and **4** is the position of the hydroxy group relative to the oxygen atom at the phosphorus atom. The torsion angles between the P=O and C–OH (O–P–C–O) bonds are –47.8, –66.7 and 70.5° for compounds **1**, **2** and **4**, respectively. In both compounds **1** and **2**, hydrogen-bonded dimers are formed and located at the inversion center for **1** [see Figure 1(*a*)] and on the two-fold axis for **2** [see Figure 1(*b*)]. The lone pair of the oxygen atom in the hydroxy group forms links between dimers, and the chains are formed *via* non-classical hydrogen C–H···O bonds. The crystal packing of compound **1** is stabilized by weak C–H···O bonds between the *O*-ethyl fragments, OH and NO_2 groups. In compound **2**, adjacent dimer chains are linked by C–H···O(N) interactions, as well as many non-classical C–H···O interactions, π–π and dipole–dipole contacts between ring-NO_2 fragments. Thus, the crystal structure in **1** is NO_2-to-tail, while in **2** there is tail-to-tail type (see Figure S2).

In compound **4**, the lone electron pair of the oxygen atom of the OH fragment participates in the formation of a dimer due to C–H···O interactions, which are also located at the inversion center [see Figure 1(*c*)]. Neighboring dimers are arranged in chains *via* hydrogen O–H···O interactions and are additionally stabilized by a hydrogen bond C–H···O between the alkyl fragment and the oxygen atom at the phosphorus atom. The crystal packing is tail-to-tail, with neighboring chains linked by multiple C–H···O contacts, including those involving the NO_2 group (Figure S3).

† *Crystal data for* **1**. $C_{11}H_{16}NO_6P$ (M = 289.22 g mol^{-1}), triclinic, space group $P\bar{1}$ at 120(2) K, a = 7.3731(18), b = 8.1700(19) and c = 10.957(3) Å, α = 79.400(7)°, β = 88.987(8)°, γ = 88.697(7)°, V = 648.5(3) Å^3, Z = 2, d_{calc} = 1.481 g cm^{-3}, μ(MoKα) = 0.235 mm^{-1}, F(000) = 304. A total of 16979 reflections were collected (3324 independent reflections and 2706 independent reflections with $I \geqslant 2(\sigma)$, R_{int} = 0.0605), GOOF 1.058, final R indices [$I \geqslant 2(\sigma)$]: R_1 = 0.0444, wR_2 = 0.0976, R indices (all data): R_1 = 0.0596, wR_2 = 0.1033.

Crystal data for **2**. $C_{13}H_{20}NO_6P$ (M = 317.27 g mol^{-1}), monoclinic, space group $C2/c$ at 120(2) K, a = 21.3820(16), b = 10.2006(8) and c = 14.9613(11) Å, β = 104.520(2)°, V = 3159.0(4) Å^3, Z = 8, d_{calc} = 1.334 g cm^{-3}, μ(MoKα) = 0.199 mm^{-1}, F(000) = 1344. A total of 34189 reflections were collected (4094 independent reflections and 3170 independent reflections with $I \geqslant 2(\sigma)$, R_{int} = 0.0640), GOOF 1.047, final R indices [$I \geqslant 2(\sigma)$]: R_1 = 0.0422, wR_2 = 0.0866, R indices (all data): R_1 = 0.0625, wR_2 = 0.0933.

Crystal data for **4**. $C_{15}H_{24}NO_6P$ (M = 345.32 g mol^{-1}), triclinic, space group $P\bar{1}$ at 120(2) K, a = 4.9287(6), b = 11.2254(13) and c = 16.460(2) Å, α = 75.912(4)°, β = 84.868(4)°, γ = 87.548(4)°, V = 879.53(18) Å^3, Z = 2, d_{calc} = 1.304 g cm^{-3}, μ(MoKα) = 0.185 mm^{-1}, F(000) = 368. A total of 18375 reflections were collected (4534 independent reflections and 3160 independent reflections with $I \geqslant 2(\sigma)$, R_{int} = 0.0799), GOOF 1.098, final R indices [$I \geqslant 2(\sigma)$]: R_1 = 0.0615, wR_2 = 0.1395, R indices (all data): R_1 = 0.1024, wR_2 = 0.1642.

The X-ray diffraction data for the single crystals were collected on a Bruker AXS D8 Venture diffractometer according to recommended strategies employing an ω/φ-scan mode. The programs used: APEX3 for data collection, SAINT for data reduction, SADABS for multi-scan absorption correction, SHELXT for structure solution, SHELXL for structure refinement by full-matrix least-squares against F^2. All non-hydrogen atoms were refined anisotropically. Hydrogen atoms at carbon atoms were placed into calculated positions and refined as riding atoms.

CCDC 2375061–2375063 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* https://www.ccdc.cam.ac.uk.

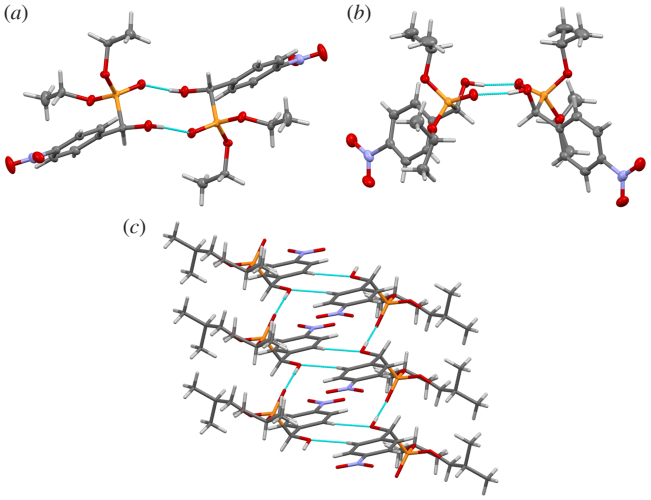


Figure 1 Geometry of dimers in compounds (*a*) **1**, (*b*) **2** and (*c*) **4**. Hydrogen bonds are shown as blue dotted lines. Thermal ellipsoids are drawn at the 50% probability level.

The *in vitro* antibacterial activities of compounds **1**–**4** against the Gram-positive and Gram-negative bacterial strains were evaluated (Table 1, Figure 2). Naftifine hydrochloride and benzalkonium chloride were examined as the control substances. According to the obtained data, α-hydroxy phosphonates **1**–**4** act selectively against Gram-positive bacteria *B. cereus, S. aureus* and are not active against Gram-negative bacteria *Ps. aeruginosa* and *E. coli.*

The fungicidal activity of the compounds was also measured in a 1% ethanol solution. Compounds **1**–**4** exhibit good antifungal activity: the diameter of growth inhibition zone is comparable to that of the reference naftifine hydrochloride. It has been shown that varying the substituents on the phosphorus atom does not affect its antifungal activity.

We also compared the obtained data with the antimicrobial activity of previously obtained dialkyl [(4-halogenophenyl)-(hydroxy)methyl]phosphonates (see Figure 2).[34,35] In contrast to chloro- and bromo-derivatives, the nitro group in the *para* position of the benzene ring leads to the emergence of antimicrobial activity in compound **1**. The nitro group in the *para* position leads to increase in fungicidal activity against *Candida* fungi [see Figure 2(*c*)]. For compound **4**, compared to its structural analog, a slight decrease in activity against bacteria *B. cereus* and *S. aureus* is observed [see Figure 2(*a*),(*b*)].

Table 1 Antimicrobial activity of dialkyl [(hydroxy)(4-nitrophenyl)-methyl]phosphonates **1**–**4** (1% in DMSO) and reference compounds.

Compound	Diameter of growth inhibition zone, *d*/mm				
	Gram-negative		Gram-positive		Fungi
	E. coli	*Ps. aeruginosa*	*B. cereus*	*S. aureus*	*C. albicans*
1	–[a]	–	9	8	16/12[b]
2	–	–	10	8	16/13
3	–	–	13	11	16/12
4	–	–	8	7	16/13
DMSO	–	–	7	7	10
EtOH	–	–	–	–	8
Benzalkonium chloride	8	11	15	13	10
Naftifine hydrochloride[c]	–	–	–	–	12

[a]None inhibition zone. [b]In DMSO/EtOH. [c]Ethanol solution, 1% (Mycoderil).

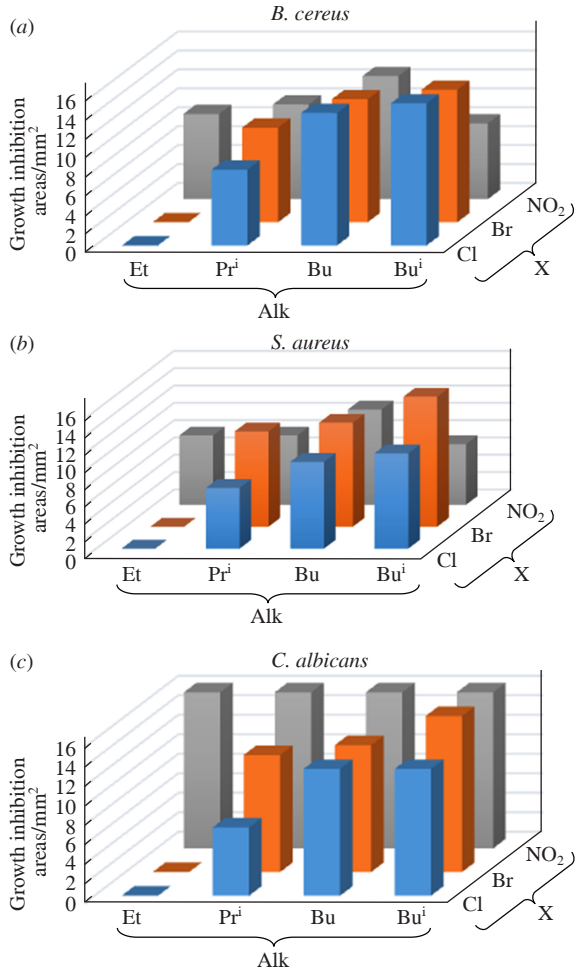


Figure 2 Dependence of growth inhibition areas of (*a*) *B. cereus*, (*b*) *S. aureus* and (*c*) *C. albicans* on the structure of compounds **1**–**4** and their halogeno analogs 4-$XC_6H_4CH(OH)P(O)(OAlk)_2$ in DMSO.

In conclusion, employing the Abramov reaction with potassium phosphate as the catalyst, a series of dialkyl [(hydroxy)(4-nitrophenyl)methyl]phosphonates with various alkyl substituents was obtained. All compounds demonstrate antibacterial activity against *B. cereus* and *S. aureus* bacterial strains and antifungal activity against fungi *Candida albicans*.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.71267/mencom.7587.

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