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Synthesis and antimicrobial activity of mono- and bisphosphonium salts based on tertiary phosphines and ethyl bromoacetate

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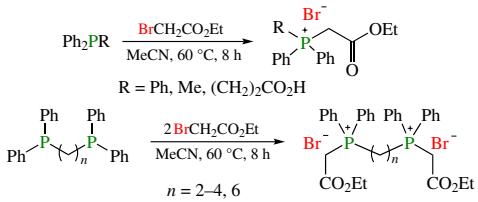
The nucleophilic substitution reaction between tertiary phosphines and ethyl bromoacetate affords the quaternary EtOC(O)CH$_2$-substituted phosphonium salts. In the cases of bisphosphines, the corresponding bisphosphonium salts are formed. The synthesized phosphonium compounds were evaluated for *in vitro* antimicrobial activity.



Keywords: quaternary phosphonium salts, tertiary phosphines, bromoacetates, antibacterial activity, antifungal activity.

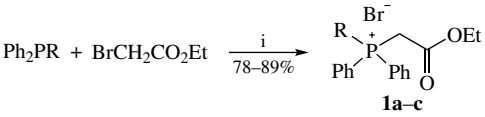
Quaternary phosphonium salts represent an important class of organophosphorus compounds because they are environmentally friendly and have many beneficial properties. They can be employed as catalysts in oxetane ring-opening reactions,[1] in CO_2 cycloaddition[2] or as bifunctional catalysts in organic synthesis.[3] Quaternary phosphonium salts display an inhibitory effect on cancer cells,[4,5] and triarylphosphonium compounds can be used as effective vectors for mitochondria-targeted delivery systems.[6] In recent years, the interest in usage of quaternary phosphonium salts as bactericides and sanitizers has increased.[7–10]

Previously, our research group investigated reactions of tertiary phosphines with electrophilic substrates. The nucleophilic addition reactions between tertiary phosphines and unsaturated carboxylic acids afford the corresponding carboxylate phosphabetaines.[11] The nucleophilic substitution reactions between tertiary phosphines and ω-halocarboxylic acids give carboxy-containing quaternary phosphonium salts.[12]

In this paper, we report on the reaction of tertiary phosphines and bisphosphines with halo carboxylic acid esters, namely, ethyl bromoacetate. The structure–activity relationship is important for the development of biocides and disinfectants. The main goal of this work was to clarify the effect of the number of cationic centers on antimicrobial activity. The antimicrobial activity of these compounds was also compared with previously synthesized phosphonium salts based on halogenated carboxylic acids.[12]

Initially we carried out the synthesis of phosphonium salts based on triphenylphosphine, methyldiphenylphosphine and 3-(diphenylphosphino)propionic acid (Scheme 1). The quaternization reactions were carried out at 60 °C in acetonitrile. After removing most of the solvent, the salts were precipitated with diethyl ether. The resulting phosphonium salts **1a–c** appear as colorless crystalline products. Their ^{31}P NMR spectra show one signal in the range of 19–25 ppm.

Although compounds **1a** and **1b** have already been described in the literature,[13,14] their antimicrobial activity has not been studied yet. Phosphonium salt **1c** based on 3-(diphenylphosphino)propionic acid is new. Along with the tertiary phosphorus atom, this phosphine contains the carboxy group which can play the role of an additional donor of the protons promoting quaternization of the phosphorus atom. The structure of salt **1c** was confirmed by X-ray diffraction (Figure 1).†



Scheme 1 *Reagents and conditions*: i, MeCN, 60 °C, 8 h.

† *Crystal data for* **1c**. Crystals of **1c**, mp 156–160 °C, $C_{19}H_{22}BrO_4P$, M = 425.24, were obtained by slow evaporation of an acetonitrile solution; monoclinic. At 100(2) K, a = 9.7007(5), b = 15.8909(8) and c = 24.7977(13) Å, β = 91.905(2)°, V = 3820.5(3) A^3, Z = 8 (dication on the special position), d_{calc} = 1.479 g cm^{-3}, space group $C2/c$, μ(Mo) = 2.256 mm^{-1}. The data were obtained on a Bruker SMART Apex II diffractometer (graphite monochromator, MoKα radiation, λ = 0.71073 Å). The intensities of 32291 reflections were measured, 5859 of which were independent (R_{int} = 0.059) and 5250 were observed with $I \geqslant 2\sigma(I)$. The recording ranges were: θ = 2.431–28.765°, reflection dataset: h –13: 13; k –21: 21; l –33: 33.

Crystal data for **2c**. Crystals of **2c**, mp 166–167 °C, $C_{36}H_{42}Br_2O_4P_2$, M = 760.45, were obtained by slow evaporation of an acetonitrile solution; monoclinic. At 100(2) K, a = 9.3562(9), b = 21.3652(19) and c = 9.3906(9) Å, β = 108.969(3)°, V = 1775.2(3) A^3, Z = 2 (dication on the special position), d_{calc} = 1.423 g cm^{-3}, space group $P2_1/n$, μ(Mo) = 2.410 mm^{-1}. The data were obtained on a Bruker D8 Quest diffractometer (MoKα radiation, λ = 0.71073 Å). 37926 reflections collected ($-12 \leqslant h \leqslant 12$; $-28 \leqslant k \leqslant 28$; $-12 \leqslant l \leqslant 12$), θ range = 1.906 to 28.782°, 2741 independent (R_{int} = 0.059) and 4617 observed reflections

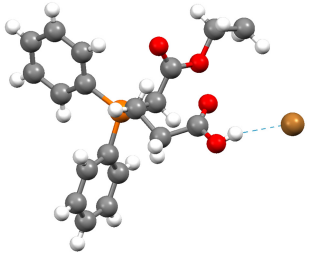


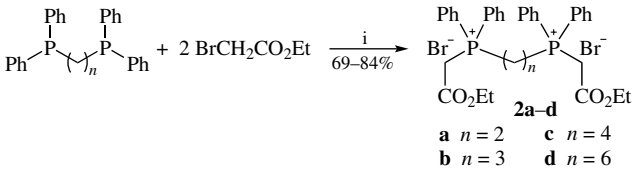
Figure 1 The structure of phosphonium salt **1c** in the crystal. OH···Br hydrogen bond is shown by dashed lines.

The next stage of this work was the synthesis of bisphosphonium salts from tertiary bisphosphines. For this purpose, 1,ω-bis(diphenylphosphino)alkanes were reacted with ethyl bromoacetate to afford compounds **2a–d** (Scheme 2) as crystalline substances in yields from 69 to 89%. The structure of phosphonium salt **2c** was confirmed by X-ray diffraction data (Figure 2).† The supramolecular organization of the crystal **2c** is determined by numerous weak interactions O···H and Br···H; there are no hydrogen bonds in this compound.

The lower yield (69%) was indicated for bisphosphonium salt **2a** synthesized from 1,2-bis(diphenylphosphino)ethane (see Online Supplementary Materials, Table S1) which contains two methylene groups between the phosphorus atoms. Apparently, the first quaternized phosphorus atom being a strong acceptor group should really reduce the nucleophilicity of the second proximal phosphorus atom. Moreover, a lower yield of **2a** can be also affected by the steric factor.

The *in vitro* antibacterial and antifungal activities of the salts **1a–c** and **2a–d** against the Gram-positive bacterial strains *Staphylococcus aureus* and *Bacillus cereus*; Gram-negative bacterial strains *Escherichia coli*, *Pseudomonas aeruginosa* and fungi strains *Candida albicans* were evaluated (Table 1). Chlorhexidine and Clotrimazole were used as the control substances.

According to data obtained, monophosphonium salt exhibited the highest activity against bacteria and *C. albicans* while compounds **2a–d** showed slightly lower activity. The reason for this may be worse penetration into the membrane of a pathogenic



Scheme 2 *Reagents and conditions*: i, MeCN, 60 °C, 8 h.

[$I \geqslant 2\sigma(I)$], 200 refined parameters, $R = 0.0556$, $wR^2 = 0.0986$, GOF = 1.028, max (min) residual electron density 1.626 (–1.952) e Å^{-3}. Semi-empirical corrections for absorption were performed in the SADABS program.[16] The structure was solved by the direct method using the SHELXT program.[17] Non-hydrogen atoms were refined in isotropic and then in anisotropic approximation using the SHELXL program.[18] Hydrogen atom of hydroxy group was solved from difference Fourier map, all the other hydrogen atoms were placed in the calculated positions and refined using the riding model. All calculations were performed using the WinGX[19] and APEX2[20] programs. Analysis of intermolecular contacts in the crystal and the drawings were performed using the PLATON[21] and MERCURY[22] programs. The final divergence factors were $R = 0.0454$, $Rw = 0.1273$ for the observed reflections with $I \geqslant 2\sigma(I)$. The goodness-on-fit was 1.100; the residual electron density extremums were –0.469 and 0.79 e A^{-3}.

CCDC 2362910 and 2293863 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.

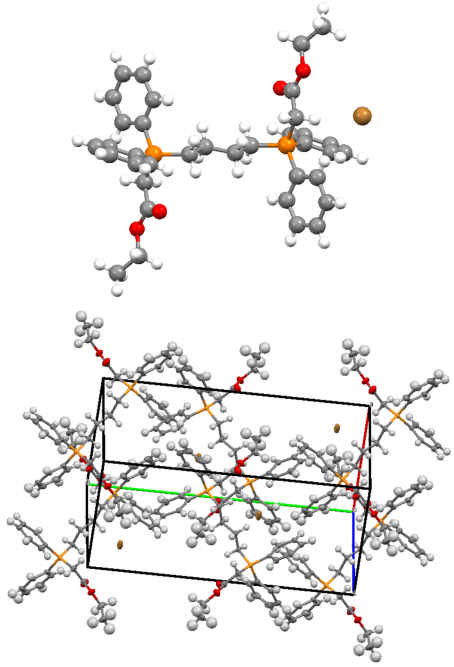


Figure 2 The structure of phosphonium salt **2c** in the crystal.

Table 1 Antibacterial and antifungal activity of salts **1a–c** and **2a–d** and reference compounds (c = 10 mg ml^{-1}, H_2O).[a]

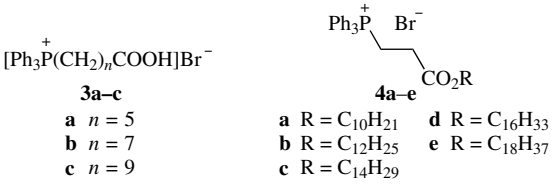
Compound	Zone of inhibition, *d*/mm				
	Escherichia coli	*Bacillus cereus*	*Pseudo-monas aeruginosa*	*Staphylo-coccus aureus*	*Candida albicans*
1a	24	28	11	30	18
1b	12	15	10	17	8
1c	7	10	7	12	–
2a	–	–	–	28/12	–
2b	8	13	13	35/15	20
2c	–	–	–	10	–
2d	–	13	–	15	8
Chlorhexidine	15	14	13	17	16
Clotrimazole	–	–	–	–	17

[a] Dashes indicate no activity.

microorganism due to an additional cationic center. However, bisphosphonium salts **2a**,**b** demonstrated structure-dependent selective bacteriostatic activity against gram-positive bacterium *Staphylococcus aureus*. Anyway, almost all compounds showed higher activity than the control substances, Chlorhexidine and Clotrimazole.

A comparison of biological activities of compounds **1a–c** and **2a–d** synthesized herein with those of earlier prepared phosphonium salts **3a–c**[12] revealed that phosphonium salts **1**, **2** containing an ester group exhibit higher activity. For example, salt **1a** exhibited significantly higher antimicrobial activity than more lipophilic salt **3c**. Also compounds synthesized in this work showed activity comparable with that of the previously described phosphonium salts **4a–e**.[15]

In conclusion, we have synthesized new mono- and bisphosphonium salts bearing $EtOC(O)CH_2$ moiety. All the



obtained phosphonium salts exhibit antibacterial and antifungal activities against pathogenic microflora of humans and animals, so they can be recommended as sanitizers for further research.

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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.7560.

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