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Synthesis, structure and antimicrobial activity of sterically hindered bis-phosphonium derivatives of 2,6-di-*tert*-butyl-4-methylphenol

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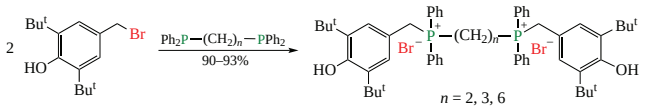
New biologically active quaternary bis-phosphonium salts were obtained by quaternization of 4-bromomethyl-2,6-di-*tert*-butylphenol with several α,ω-bis(diphenylphosphino)-alkanes. All synthesized compounds demonstrated high antibacterial and antifungal activities against pathogenic microflora of humans and animals.



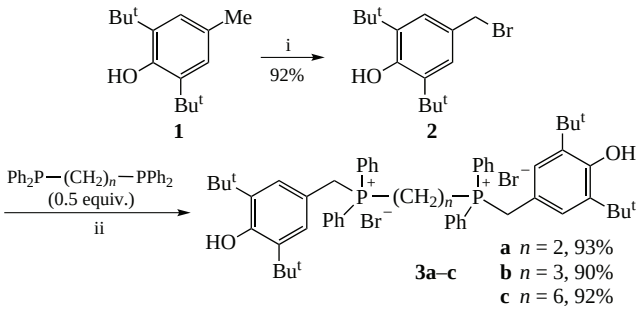
Keywords: quaternary phosphonium salts, 2,6-di-*tert*-butyl-4-methylphenol, sterically hindered phenols, antibacterial activity, antifungal activity.

Pathogenic microorganisms surround us everywhere. During the Covid-19 and Omicron pandemic, due to a decrease in immunity, the danger of pathogenic microflora increased greatly. Although many antiseptics as halogen-containing compounds, oxidants, acids and alkalis, aldehydes and alcohols, and many others[1,2] are known today, much attention is paid to quaternary ammonium salts, *e.g.*, Miramistin, Cetrimonium bromide, Cetylpyridinyl- and Benzalkonium chloride, and others.[2–4] Unfortunately, pathogenic microorganisms develop resistance to them over some time.[5] Therefore, today the search for new antiseptics is a strategic task of pharmaceutical chemistry.

For modification, we have chosen hindered phenols, which are low-toxic readily available compounds with pronounced biological activity. Dibunol ('dibutylhydroxytoluene', 2,6-di-*tert*-butyl-4-methylphenol) **1** combining low acute toxicity and high antioxidant and antimicrobial activity[6] is successfully used to treat certain types of cancer,[7] radiation and trophic lesions of the skin and mucous membranes.[8] On the other hand, phosphonium salts are promising compounds with different and wide biological activity.[9–11] Since our research group is focused on the study of quaternary phosphonium salts and their derivatives,[12,13] the goal of this work was to synthesize new quaternary phosphonium salts on the basis of hindered phenols. It is noteworthy that similar compounds can be used as micellar nanocontainers[14] or antimicrobial agents.[15]

In this study, new stable quaternary diphosphonium salts were obtained (Scheme 1). The first step of the synthesis was the chemoselective bromination of benzylic methyl group in 2,6-di-*tert*-butyl-4-methylphenol **1** affording 4-bromomethyl-2,6-di-*tert*-butylphenol **2** obtained as a crystalline product with a melting point of 56 °C.

The second step of the synthesis of salts **3a–c** was the quaternization of tertiary bisphosphines, such as 1,2-bis-(diphenylphosphino)ethane, 1,3-bis(diphenylphosphino)propane and 1,6-bis(diphenylphosphino)hexane, with the above mentioned sterically hindered 4-bromomethyl-2,6-di-*tert*-butylphenol **2**. Bis(diphenylphosphino)alkanes were chosen because they should afford phosphonium salts with two cationic centers in one molecule. We were interested in comparing their properties with those of previously synthesized monophosphonium salts.[15] The quaternization was carried out at room temperature in acetonitrile. After removing most of the solvent, the salts were precipitated with diethyl ether. All bis-phosphonium salts **3a–c** are colorless crystalline substances with high melting points (215 °C for **3a**, 195 °C for **3b** and 162 °C for **3c)**. Their ^{31}P NMR spectra contained single signal in the range of 24–29 ppm. The structure of phosphonium salt **3a** has been ultimately proven by X-ray diffraction analysis (Figure 1).†



Scheme 1 *Reagents and conditions*: i, Br_2, CCl_4, room temperature; ii, MeCN, room temperature.

† *Crystal data for* **3a**. $C_{56}H_{70}O_2P_2^{2+} \cdot 2CH_3CN \cdot 2Br^-$, $M = 1078.97$. Crystals of **3a**, mp 215 °C, were obtained by slow evaporation of an acetonitrile solution; monoclinic. At 296(2) K: $a = 9.1123(11)$, $b = 18.346(2)$ and $c = 17.444(2)$ Å, $\beta = 103.175(1)°$, $V = 2839.4(6)$ Å^3, $Z = 2$ (dication on the special position), $d_{calc} = 1.262$ g cm^{-3}, space

Table 1 Antibacterial and antifungal activity of salts **3a–c** and reference compounds (c = 10 mg ml^{-1}).

Compound	Zone of inhibition, *d*/mm				
	Escherichia coli	*Bacillus cereus*	*Pseudomonas aeruginosa*	*Staphylococcus aureus*	*Candida albicans*
3a	17±3	23±5	7±2	32±5	25±4
3b	21±4	20±4	11±3	27±4	25±3
3c	17±2	19±3	9±2	25±3	25±5
Chlorhexidine	15±3	14±2	13±3	17±4	16±2
Clotrimazole	–	–	–	–	17±3

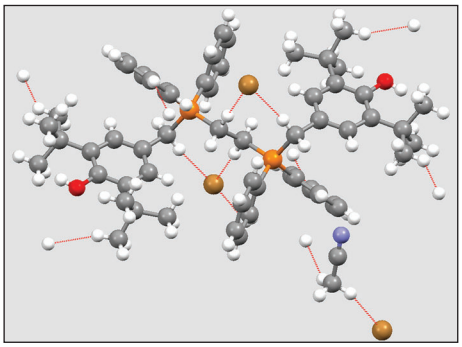


Figure 1 The structure of phosphonium salt **3a** (solvate with MeCN) in the crystal. The C–H···Br hydrogen bonds are shown by dashed lines.

X-ray diffraction study (see Figure 1) showed that compound **3a** would form a crystal solvate with acetonitrile in a ratio of 1:2. A feature of this structure is that the dication has a centrosymmetric conformation and is located in a special position in the crystal. It should also be noted that hydroxy groups do not form hydrogen bonds in the crystal, apparently due to steric shielding by bulky *tert*-butyl and diphenylphosphonium groupings. Therefore, bromide anions, cations and solvate molecules are linked by C–H···Br type hydrogen bonds into closed 0D associates, the geometry of which is shown in Figure 1 (hydrogen bonds are shown by dashed lines).

The *in vitro* antibacterial and antifungal activities of the salts **3a–c** 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 examined as the control substances. All new compounds **3a–c** were active against Gram-positive bacteria and *Candida albicans*, but they were less active against Gram-negative bacteria. Salt **3b** exhibited moderate activity in comparison with the standard in relation to *Escherichia coli*. Phosphonium salts **3a**,**b** may be considered as the lead compounds and are recommended for further study. One may conclude that compounds **3a–c** show slightly lower activity comparing with previously synthesized monophosphonium salts.[13] The reason for this may be poorer penetration into the membrane of a pathogenic microorganism due to an additional cationic center.

In conclusion, we have developed a new efficient synthesis of ethane-1,2-, propane-1,4- and hexane-1,6-diylbis[(3,5-di-*tert*-butyl-4-hydroxybenzyl)diphenylphosphonium]bromides **3a–c**. All the obtained bis-phosphonium salts exhibit antibacterial and antifungal activities against pathogenic microflora of humans and animals.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2023.09.014.

group $P2_1/c$, μMo 1.526 mm^{-1}. The data were obtained on a Bruker SMART Apex II diffractometer (graphite monochromator, MoKα radiation, λ = 0.71073 Å). The intensities of 22989 reflections were measured, 6170 of which were independent (R_{int} = 0.059) and 3624 were observed with $I \geqslant 2\sigma(I)$. The recording ranges were: θ = 2.2–27.0°, reflection dataset: h –11: 11; k –23: 23; l –22: 22.

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 atoms of the hydroxy groups were 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 = 0.0521, R_w = 0.1085 for the observed reflections with $I \geqslant 2\sigma(I)$, and R = 0.1201, R_w = 0.1292 for all the 6170 reflections. The goodness-on-fit was 1.003; the residual electron density extremums were –0.57 and 1.01 e A^{-3}.

CCDC 2162340 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* http://www.ccdc.cam.ac.uk.

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