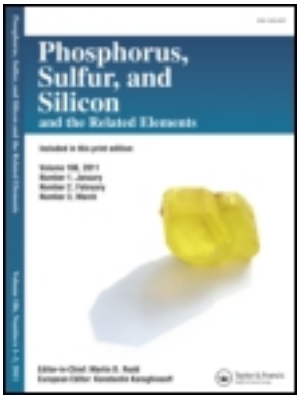

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Synthesis and Antimicrobial Activities of Phosphonium Salts on Basis of Triphenylphosphine and 3,5-Di-Tert-Butyl-4-Hydroxybenzyl Bromide

Irina Galkina [a], Yuliya Bakhtiyarova [a], Vitaliy Andriyashin [a], Vladimir Galkin [a] & Rafael Cherkasov [a]
[a] A. M. Butlerov Chemical Institute, Kazan Federal University, Kazan, Tatarstan, Russian Federation
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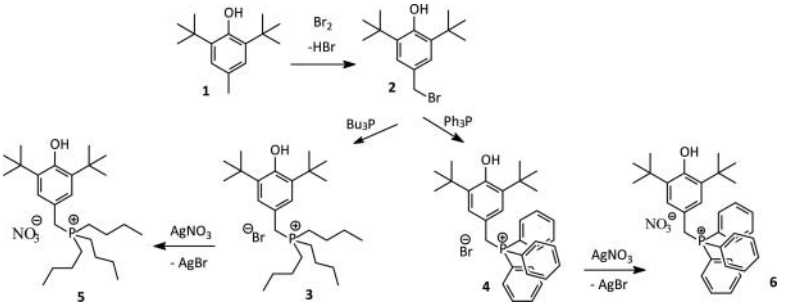
SYNTHESIS AND ANTIMICROBIAL ACTIVITIES OF PHOSPHONIUM SALTS ON BASIS OF TRIPHENYLPHOSPHINE AND 3,5-DI-TERT-BUTYL-4-HYDROXYBENZYL BROMIDE

Irina Galkina, Yuliya Bakhtiyarova, Vitaliy Andriyashin, Vladimir Galkin, and Rafael Cherkasov

A. M. Butlerov Chemical Institute, Kazan Federal University, Kazan, Tatarstan, Russian Federation

GRAPHICAL ABSTRACT



Abstract *We report the structures of two new phosphonium salts prepared via the reaction of (substituted)benzyl bromides with triphenylphosphine. The antibacterial and antifungal activities are reported.*

Keywords Phosphonium; antibacterial; antifungal; synthesis; X-ray structure

RESULTS AND DISCUSSION

A new series of quaternary phosphonium salts **3–6** have been prepared by the reaction of triphenylphosphine with 3,5-di-*tert*-butyl-4-hydroxybenzyl bromide **2** in order to obtain novel compounds **5** and **6**, soluble in water, for potential medical purposes. All the synthesized compounds were screened for their antibacterial, antifungal activity (Table 1), and the target compounds **5** and **6** for their antioxidant activity (Table 2). The structure of new compounds was established from the IR, ^{1}H, ^{31}P-NMR spectra and from TG/DSC, XRD, and elemental analysis.

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We are most grateful to Dr. Ziyatdinova G. K. for TAC determination.
Address correspondence to Irina Galkina, A. M. Butlerov Chemical Institute, Kazan Federal University, Kremlevskaya 29/1, Kazan, Tatarstan 420008, Russian Federation. E-mail: gal.irina.2012@yandex.ru

Table 1 The in vitro antimicrobial activity of the synthesized salts and the control drugs (100 μg/0.1 mL)

Compounds	Microorganisms, zone of inhibition, (diameter, in mm)				
	Staphylococcus aureus	*Escherichia coli*	*Pseudomonas aeruginosa*	*Salmonella p .B*	*Candida albicans*
3	45	19	15	7	35
4	43	18	16	16	46
5	39	22	13.5	8	48
6	35	17	12	13	47
Chlorhexidine	16	15	13	14	16.5
Penicillin	23	16	8	10	—
Griseofulvin	—	—	—	—	19

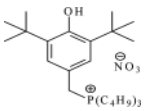
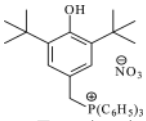
Scheme 1 depicts the synthesis of different quaternary phosphonium salts (**3–6**) from 2,6-di-*tert*-butyl-4-methylphenol (ionol) **1**. Compound **2** was prepared from **1** according to reported method,[1] which was then refluxed in diethyl ether with the solutions of corresponding phosphines to afford products **3**, **4**, **5**, and **6**. The obtained products were filtered, dried, and recrystallized. Both of phosphonium nitrates **5** and **6** were synthesized from corresponding phosphonium bromides **3** and **4** by reaction with $AgNO_3$ in 2:1 EtOH:H_2O solution. The precipitate of AgBr was isolated; filtrate was concentrated in vacuum and gave the corresponding colorless products **5** and **6**.

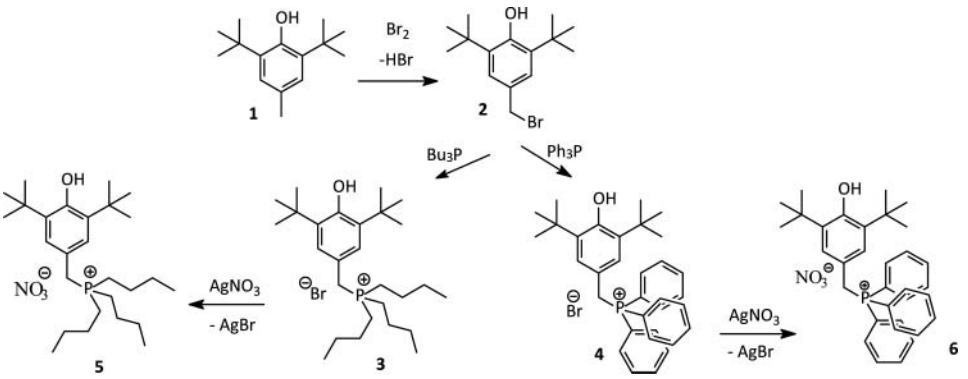
The molecular structure of products **5** and **6** has been confirmed by X-ray analysis (Figures 1 and 2).

The need of new antimicrobial and antioxidant drugs is justified because more microorganisms are being resistance to the present drugs available on the market. Resistance of pathogenic bacteria to antibiotics is rapidly becoming a major problem in the medical community and hospital-based healthcare settings. The search for novel agents to combat resistant bacteria has become one of the most important areas of antibacterial research today.[2]

The synthesized compounds **3**, **4**, **5**, and **6** were screened for antibacterial and antifungal activity at 100 μg/0.1 mL concentrations by using the cup–plate agar diffusion method,

Table 2 Total antioxidant capacity of quaternary phosphonium salts **5** and **6**

N	Compounds	TAC (kC mol$^{-1)}$	RSD (%)
5		275 ± 5	1.6
6		237 ± 10	3.5
Control 1	α-Tocopherol	195 ± 3	1.4
Control 2	Ascorbic acid	185 ± 4	2.2



Scheme 1

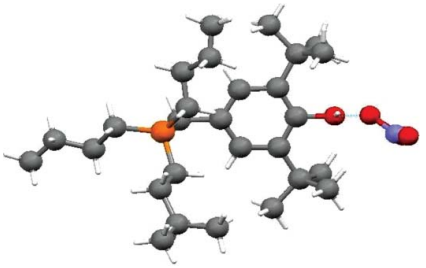


Figure 1 Structure of 5. (Color figure available online).

and standard drugs used were chlorhexidine, penicillin, and griseofulvin. The novel synthesized phosphonium salts **3–6** show maximal activity against pathogenic microorganisms. Starting compounds **1** and **2** were not active at all. These results are reported in Table 1.

Such a high biological activity of phosphonium bromides **3–6**, we explain by their ability to be integrated into the lipid layers of biomembranes of pathogenic microflora eventually leading to the destruction of this last. To confirm this idea, we studied the interaction mechanism of phosphonium salts – synthetic phosphorus analogs of biomembranes – with natural biological membranes (lecithin) using the model of Langmuir monolayers. It was discovered that phosphonium salts interact with lecithin, by forming a pores, and thus deteriorating the membrane functions.[3]

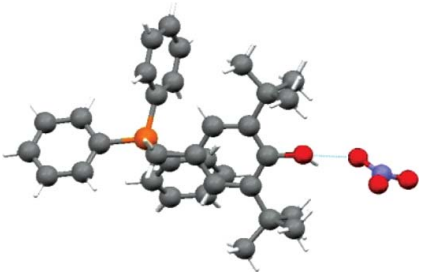


Figure 2 Structure of 6. (Color figure available online).

Determination of TAS (Total Antioxidant Activity) is based on the coulometric titration of analyte by electrogenerated bromine. Bromine has been electrochemically generated at a current density 5 mA cm^{-2} providing 100% current yield. The end-points in amperometric titration have been measured with two polarized platinum electrodes ($\Delta E = 300$ mV). TAC experiments have been carried out at ambient temperature $23 \pm 2^{\circ}$C. These results are reported in Table 2.

So, it may be concluded from our results that the synthesized compounds are potent antimicrobial agents against pathogenic bacteria and fungi.

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