ANTIMICROBIAL ACTIVITY OF PHOSPHONIUM ANALOGS OF AZOMETHINES AND STILBENES

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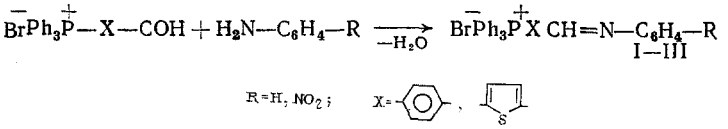
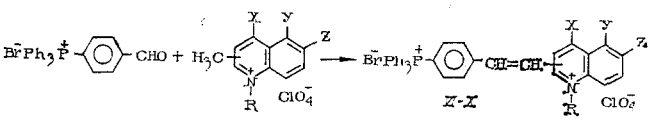
Despite the significant successes achieved in the treatment of infectious diseases by antibiotics, the problem of the study of new antimicrobial agents is still urgent. This is due to the appearance of microorganisms possessing multiple drug resistance, which prevents successful antibiotic therapy [1, 2]. Many now comparatively easily synthesized quaternary phosphonium salts possesss pronounced antimicrobial properties with respect to pathogenic and conditionally pathogenic microorganisms [3]. Therefore, a study of the antimicrobial properties of compounds of this kind is justified for the search for new and effective antimicrobial preparations.

For the detection of new highly active phosphorus-containing antimicrobial preparations, we synthesized and studied the antimicrobial properties of a number of derivatives of tetraarylphosphonium salts: phosphonioazomethines, bis-phosphonioazomethines, and phosphonioostilbenes. The investigated compounds (I-IV) are yellow or light brown crystalline substances, stable under normal conditions, readily soluble in polar organic solvents (ethanol, DMFA, etc.), and sparingly soluble in water with heating.

The phosphonioazomethines I-III were produced according to the method that we developed by condensation of p-formylphenyltriphenylphosphonium bromide and 2-formyl-5-triphenylphosphoniobromide thienylene with aniline and p-nitroaniline according to the reaction:



Bis-(phosphonioazomethines $[\overset{+}{P}h_3P-X-CH=N-C_6H_4-N=CH-X-\overset{+}{P}Ph_3]2Br^-$ (IV, V) were produced analogously, i.e., by condensation of p-phenylenediamine with a twofold excess of p-formylphenyltriphenylphosphonium bromide and 2-formylthiophene-5-triphenylphosphonium bromide, respectively. By condensation of benzo-f-(N-phenylquinaldinium perchlorate), 2-(N-methyllepidinium perchlorate), and 4-N-(p-bromophenylacetyl) quinolinium perchlorate with p-formylphenyltriphenylphosphoniobromide and 5-triphenylphosphoniobromide furan, we obtained phosphonioquinostyryls VI-IX with good yields:



VI: R = C_6H_5, X = H, Y = Z = C_4H_4; VII: R = X = CH_3, Y = Z = H;
VIII: R = p-$BrC_{16}H_4COCH_2$, X = Y = Z = H; IX: R = C_6H_5, X = H, Y = Z = C_4H_4.

A phosphonium-indolenyl analog of the chalcone X was synthesized by the reaction of 1,3,3-triphenyl-2-formylmethyleneindoline with p-triphenylphosphoniobromide acetophenone.

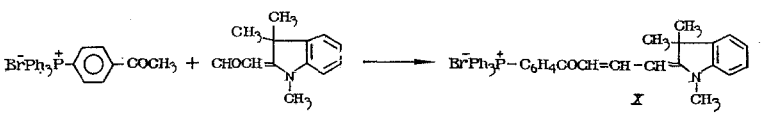


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TABLE 1. Antimicrobial Properties of Phosphonium Analogs of Azomethines and Stilbenes

Compound	Staph. aureus 209		B. anthracoides 297		Esch. coli		Proteus vulgaris		Sal. typhimurium		Kl. Shinoserlero-		Strept. viridens		Cand. albicans	
	MBSC	MBCC	MBSC	MBCC	MBSC	MBCC	MBSC	MBCC	MBSC	MBCC	MBSC	MBCC	MBSC	MBCC	MBSC	MBCC
I	0,24	62,5	3,9	125	15,6	62,5	31,2	125	31,2	32,5	62,5	250	7,8	31,2	15,6	125
II	1,95	15,6	0,48	1,95	15,6	125	62,5	250	31,2	250	125	500	15,6	62,5	31,2	125
III	3,9	31,2	7,8	125	31,2	125	125	500	125	500	250	500	31,2	62,5	62,5	250
IV	1,95	125	62,5	260	250	250	250	500	125	250	250	500	31,2	125	62,5	250
V	1,95	250	3,9	125	62,5	500	250	500	125	500	250	500	62,5	250	62,5	500
VI	0,97	15,6	1,95	500	7,8	62,5	62,5	250	31,2	125	125	500	7,8	31,2	15,6	62,5
VII	0,97	31,2	125	125	31,2	31,2	15,2	31,2	7,8	31,2	15,6	62,5	3,9	31,2	31,2	125
VIII	3,9	500	125	500	62,5	500	125	500	31,2	125	125	500	15,6	125	125	500
IX	7,8	250	7,8	250	15,6	125	62,5	500	31,2	250	125	500	15,6	61,5	31,2	250
X	1,95	15,6	500	500	31,2	62,5	62,5	250	15,6	31,2	62,5	250	15,6	62,5	31,2	125

Note. MBSC is the minimum bacteriostatic concentration (in μg/ml); MBCC is the minimum bactericidal concentration (in μg/ml).

The antimicrobial activity of the synthesized preparations I-X was studied by the method of two serial dilutions in liquid nutrient medium [4] with respect to pathogenic and conditionally pathogenic species of bacteria and fungi.

As was shown by the investigations, the antimocrobial activity of the tested compounds I-X was exhibited with respect to all the test microbes studied and depended on the chemical structure of the compound (see Table 1). Thus, Gram-positive bacteria (*Staph. aureus, Str. viridens, Bac. anthracoides*) proved rather sensitive to the investigated compounds: A bacteriostatic effect on the above-mentioned bacteria was exhibited in concentrations from 0.24 to 123 μg/ml, bactericidal from 1.95 to 500 μg/ml. Gram-negative bacteria (*Escherichia coli, Proteus vulgaris,* salmonellae, klebsiellae) and yeast-like fungi of the genus *Candida* proved less sensitive to the compounds studied. In this case the bacteriostatic concentrations ranged from 7.8 to 250 μg/ml, the bactericidal concentrations from 31.2 to 500 μg/ml. However, the pathogenic Gram-negative bacteria proved more sensitive to the investigated compounds. As a result of our experiments it was found that of the series of investigated compounds, substances I, II, III, VI, etc. possess the greatest antimicrobial activity. The phosphoniobisazomethine IV, the phosphoniostyryl VIII, and the furyl-phosphoniostilbene IX, containing a phosphonium group at the thiophene and furan rings, respectively, exhibited the weakest antimicrobial effect.

EXPERIMENTAL CHEMICAL PART

2-(N-methyllepidiniumperchlorate)-p-triphenylphosphoniobromide Styryl (VIII). A mixture of 0.43 g p-formylphenyltriphenylphosphoniobromide and 0.45 g N-methylleepidinium perchlorate in 10 ml pyridine was heated on an oil bath for 6 h. Then 50 ml of ether was added to the reaction mixture, cooled to room temperature. After 2 h the resinous mass that formed on the bottom of the flask was removed, dissolved in 20 ml of chloroform, and the product VII precipitated from the solution obtained by the addition of 100 ml of ether. The precipitated green crystals were filtered off, washed with hexane, and dried in air. Compound VII was purified by recrystallization from butanol. Yield 0.6 g (85%), mp 183-185°C. Found, %: N 1.77. $C_{37}H_{32}BrClNO_4P$. Calculated, %: N 1.99.

4-[N-(p-Bromophenacyl)]quinolinioperchlorate-p-triphenylphosphoniobromide Styryl (VIII). This was produced analogously to compound VII from 0.5 g p-formylphenyltriphenylphosphoniobromide and 0.45 g N-(p-bromophenacyl)lepidinium perchlorate. Yield 0.6 g (68%), mp 167°C Found, %: N 2.03: P 3.12. $C_{41}H_{33}Br_2ClNO_5P$. Calculated, %: N 1.65; P 3.66.

p-Triphenylphosphoniobromide Benzoylvinyl(1,3,3-trimethyl-2-methylenindolenyl (X). A mixture of 0.46 g p-triphenylphosphoniobromide acetophenone [5] and 0.21 g 1,3,3-trimethyl-2-formylindole was heated in 10 ml of acetic anhydride for 4 h. The isolation and purification of compound X were performed analogously to the production of compound VII. Yield 0.29 g (70%), mp 196-198°C. Found, %: N 2.62. $C_{39}H_{35}BrNOP$. Calculated, %: N 2.25.

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