SYNTHESIS AND ANTIMICROBIAL PROPERTIES OF 2-[2-(2-THIOCYANATO-3-ARYLPROPIONYLOXY)-ETHOXY]ETHYL ACRYLATES

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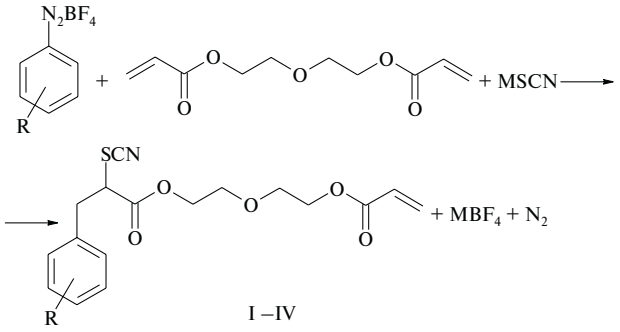
Previously [1], we have synthesized a series of 1-thiocyanato-1-alkoxycarbonyl-2-arylethanes and revealed compounds possessing pronounced antistaphylococcal and antibacterial properties [2, 3]. Another group of substances effective in this respect is offered by 2-thiocyanato-1-aryl-3-allyloxypropanes [4] containing ester oxygen atoms and free allyl moieties.

In continuation of the research in this direction, we have recently employed an anionarylation process to synthesize for the first time a series of 2-[2-(2-thiocyanato-3-arylpropionyloxy)ethoxy]ethyl acrylates (I – IV) [5]. Under the selected conditions (see the experimental part below), the catalytic thiocyanatoarylation reaction involves a single vinyl fragment:



I –IV

R = H (I), *o*-CH_3 (II), *m*-CH_3 (III), *p*-CH_3 (IV); M = Na, K, NH_4.

The interaction of aryldiazonium tetrafluoroborates with 2-(2-acryloyloxyethoxy)ethyl acrylate proceeds in a water – acetone (1 : 2) mixture in the temperature interval from 0 to –5°C in the presence of a catalytic amount of copper tetrafluoroborate and alkali metal or ammonium rhodanide additives. The optimum ratio of reagents is as follows: diazonium salt – 2-(2-acryloyloxyethoxy)ethyl acrylate – sodium (potassium, ammonium) rhodanide – copper tetrafluoroborate, 1.2 : 1.0 : 1.4 : 0.1. The side products in this thiocyanatoarylation reaction are arylisothiocyanates and arylthiocyanates, the yield of which amounts to 9 – 15% and 5 – 7%, respectively.

A change in the order of reagents introduction into the reaction medium did not affect the target product yields, but adding rhodanides in the last stage requires the process temperature to be reduced down to – 30 to – 25°C.

A twofold increase in the amount of diazonium salt, sodium (potassium, ammonium) rhodanide, or copper tetrafluoroborate against the optimum level did not lead to the appearance of bisthiocyanatoarylation reaction products. Thus, the synthesis of 2-(2-acryloyloxyethoxy)ethyl acrylate shows that, when two like isolated multiple bonds are present in the molecule of an unsaturated compound, the anionarylation process can proceed under certain conditions only at one of these multiple bonds.

The yields, physicochemical constants, data of elemental analyses, and the parameters of IR and ^{1}H NMR spectra of the synthesized 2-[2-(2-thiocyanato-3-arylpropionyloxy)ethoxy]ethyl acrylates I – IV are presented in Table 1.

The IR spectra display the characteristic absorption bands due to carbonyl and thiocyanate groups in the regions of 1720 – 1724 and 2156 – 2160 cm^{-1}, respectively. Multiple bonds of the terminal vinyl groups are manifested by the absorption bands at 1636 – 1640 cm^{-1}. The out-of-plane CH vibrations in this group can be assigned to narrow absorption bands in the region of 812 and 984 cm^{-1}.

The ^{1}H NMR spectra of compounds I – IV show signals from protons of the aromatic nuclei in the form of a multiplet at 7.44 – 7.26 ppm. The signals from protons of the terminal vinyl group are manifested by double doublets in the region of 6.34 – 6.30 ppm (*cis*-H) and 5.94 – 5.92 ppm (*trans*-H) and 6.16 – 6.14 ppm (C(O) – CH).

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TABLE 1. Yields and Physicochemical Characteristics of 2-[2-(2-Thiocyanato-3-arylpropionyloxy)ethoxy]ethyl Acrylates (I – IV)

Compound	R	Yield, %	n_D^{20}	d_4^{20}	Empirical formula	^{1}H NMR spectrum: δ, ppm (J, Hz)
I	H	59	1.5052	1.1580	$C_{17}H_{19}NO_5S$	7.30 – 7.20 (m, 5H, Ph), 6.30 (dd, J_{HH} 10 Hz, H-*cis*, =CH_2), 6.14 (dd, J_{HH} 10 Hz, 1H, =CH–), 5.93 (dd, J_{HH} 15 Hz, H-*trans*, =CH_2), 4.50 – 4.44 (m, 1H, CH), 4.20 (t, 4H, 2(–OCH_2)), 3.48 (dd, J_{HH} 2 Hz, 4H, –CH_2–O–CH_2), 3.33 (dd, J_{HH} 7 Hz), 3.10 (dd, J_{HH} 7 Hz, 2H, CH_2Ph).
II	*o*-CH_3	35	1.5136	1.1598	$C_{18}H_{21}NO_5S$	7.22 – 7.10 (m, 4H, C_6H_4), 6.32 (dd, J_{HH} 10 Hz, H-*cis*, =CH_2), 6.15 (dd, J_{HH} 10 Hz, 1H, =CH–), 5.94 (dd, J_{HH} 15 Hz, H-*trans*, =CH_2), 4.51 – 4.45 (m, 1H, CH), 4.22 (t, 4H, 2(–OCH_2)), 3.46 (dd, J_{HH} 2 Hz, 4H, –CH_2–O–CH_2), 3.32 (dd, J_{HH} 7 Hz), 3.09 (dd, J_{HH} 7 Hz, 2H, CH_2–C_6H_4), 2.25 (s, 3H, *o*-CH_3–C_6H_4).
III	*m*-CH_3	42	1.5124	1.1608	$C_{18}H_{21}NO_5S$	7.34 – 7.16 (m, 4H, C_6H_4), 6.34 (dd, J_{HH} 10 Hz, H-*cis*, =CH_2), 6.15 (dd, J_{HH} 10 Hz, 1H, =CH–), 5.94 (dd, J_{HH} 15 Hz, H-*trans*, =CH_2), 4.50 – 4.44 (m, 1H, CH), 4.24 (t, 4H, 2(–OCH_2)), 3.45 (dd, J_{HH} 2 Hz, 4H, –CH_2–O–CH_2), 3.31 (dd, J_{HH} 7 Hz), 3.10 (dd, J_{HH} 7 Hz, 2H, CH_2–C_6H_4), 2.31 (s, 3H, *m*-CH_3–C_6H_4).
IV	*p*-CH_3	47	1.5128	1.1588	$C_{18}H_{21}NO_5S$	7.24 – 7.08 (m, 4H, C_6H_4), 6.32 (dd, J_{HH} 10 Hz, H-*cis*, =CH_2), 6.16 (dd, J_{HH} 10 Hz, 1H, =CH–), 5.92 (dd, J_{HH} 15 Hz, H-*trans*, =CH_2), 4.50 – 4.44 (m, 1H, CH), 4.23 (t, 4H, 2(–OCH_2)), 3.46 (dd, J_{HH} 2 Hz, 4H, –CH_2–O–CH_2), 3.33 (dd, J_{HH} 7 Hz), 3.12 (dd, J_{HH} 7 Hz, 2H, CH_2–C_6H_4), 2.37 (s, 3H, *p*–CH_3–C_6H_4).

EXPERIMENTAL CHEMICAL PART

The IR spectra of compounds I – II were recorded on the IKS-29 (Russia) and Specord M80 (Germany) spectrophotometers using samples prepared as thin films. The ^{1}H NMR spectra were measured with a Varian Gemini spectrometer (working frequency, 300 MHz) using DMSO-d_6 as the solvent and HMDS as the internal standard. Purity of the synthesized compounds was checked by TLC on Silufol UV-254 plates eluted with a hexane – chloroform – diethyl ether (7 : 5 : 2) mixture. The data of elemental analyses (N, S) coincided with the results of analytical calculations using the empirical formulas.

2-[2-(2-Thiocyanato-3-phenylpropionyloxy)ethoxy]-ethyl acrylate (I). To a mixture of 0.10 mole 2-(2-acryloyloxyethoxy)ethyl acrylate, 0.01 mole copper(II) tetrafluoroborate, and 0.14 mole of ammonium rhodanide in 200 ml of a water – acetone mixture (1 : 2) cooled to – 5 to 0°C was gradually (over 75 min) added 0.12 mole of phenyldiazonium tetrafluoroborate. At this temperature, the evolution of nitrogen continued for ~2 h. When the gas evolution ceased, the mixture was treated with 250 ml of diethyl ether. The extract was washed with water and dried over anhydrous magnesium sulfate. Then the solvent was evaporated and the residue was chromatographed on an Al_2O_3 column eluted with a hexane – chloroform – diethyl ether (7 : 5 : 2) mixture to obtain 20.7 g of the target compound I; IR spectrum (ν_{max}, cm^{-1}): 2156 (SCN), 1636 (CH=CH_2), 1724 (C=O); $C_{17}H_{19}NO_5S$.

Compounds II – IV were obtained using analogous procedures with the corresponding aryldiazonium tetrafluoroborates (Table 1).

EXPERIMENTAL BIOLOGICAL PART

The antimicrobial activity of the synthesized compounds I – IV was determined by the conventional method of double serial dilutions in a meat-infusion broth (pH 7.2 – 7.4). The initial dilution was prepared by dissolving 10 mg of a test substance in 1 ml of ethanol, followed by adding 9 ml of distilled water. The test objects were represented by standard strains of Gram-positive (*Staphylococcus aureus* ATCC 209), spore-forming (*Bacillus cereus* ATCC 10702), and Gram-negative (*Escherichia coli* ATCC O55K-59, *Pseudomonas aeruginosa* 103) bacteria.

Double serial dilutions of the stock solutions in 2 ml of the nutrient medium were prepared immediately before the test. Then 0.2 ml of a bacterial suspension (with a load of 10^5 bacterial cells per ml) of the test microbe species was introduced into test tubes and the samples were incubated at 37°C for 18 – 24 h, after which the microbial growth was visually

TABLE 2. Antimicrobial Activity (Minimum Bacteriostatic and Bactericidal Concentrations, μg/ml) of 2-[2-(2-Thiocyanato-3-arylpropionyloxy)ethoxy]ethyl Acrylates (I – IV)

Compound	Test culture							
	S. aureus		*B. cereus*		*E. coli*		*P. aeruginosa*	
	MBsC	MBcC	MBsC	MBcC	MBsC	MBcC	MBsC	MBcC
I	500	NA	NA	NA	NA	NA	500	500
II	62.5	62.5	500	NA	31.5	62.5	500	NA
III	250	500	250	NA	62.5	125	NA	NA
IV	500	500	62.5	125	500	NA	NA	NA

Note: NA = not assessed.

assessed. The experimental results were processed by method of variation statistics.

It was established that the synthesized compounds I – IV are most active with respect to *E. coli* (bacterial growth inhibited at 31.2 – 125 μg/ml, Table 2) and least active toward aerobic bacilli, staphylococci, and pseudomonads. Minimum bactericidal concentrations (MBcC) were either comparable with or greater (on the average, two times) than the minimum bacteriostatic concentrations (MBsC).

A comparison of the antimicrobial properties of 2-[2-(2-thiocyanato-3-arylpropionyloxy)ethoxy]ethyl acrylates to those of 1-thiocyanato-1-alkoxycarbonyl-2-arylethanes shows that the introduction of acrylic acid fragments leads to a significant decrease in activity. An increase in the antimicrobial activity can be achieved by modifying the aromatic core with substituents at the *ortho* and *para* positions.

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