SYNTHESIS AND ANTIMICROBIAL PROPERTIES OF 4-(2-THIOCYANATO-3-ARYLPROPIONYLOXY)BUTYL ACRYLATES

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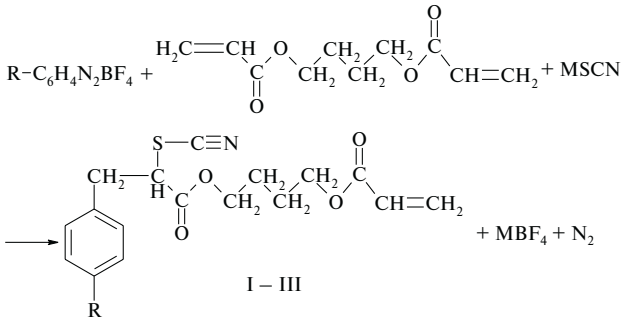
Previously [1] we developed the synthesis of 1-thiocyanato-1-alkoxycarbonyl-2-arylethanes and showed that some of these compounds possess antibacterial properties [2, 3].

Of certain interest in the search for new antibacterial agents are 4-(2-thiocyanato-3-arylpropionyloxy)butyl acrylates which can be obtained using reactions of aryldiazonium tetrafluoroborates with 4-acryloyloxybutyl acrylate in the presence of rhodanides. The process of thiocyanatoarylation, involving a single multiple bond, leads to the formation of 4-(2-thiocyanato-3-arylpropionyloxy)butyl acrylates (I – III).



R = H (I), CH_3 (II), NO_2 (III); M = Na, K, NH_4

The interaction of aryldiazonium tetrafluoroborates with 4-acryloyloxybutyl acrylate proceeds in a water – acetone (1 : 2) mixture in the temperature interval from –10 to –5°C in the presence of a catalytic amount of copper tetrafluoroborate and alkali metal or ammonium rhodanide additives. The catalyst is necessary for this reaction to proceed. The optimum ratio of reagents is as follows: aromatic diazonium salt – 4-acryloyloxybutyl acrylate – sodium (potassium, ammonium) rhodanide – copper tetrafluoroborate, 1 : 1.2 : 1.3 : 0.1. The side products in this reaction are arylisothiocyanates, the yield of which amounts to 10 – 12 %.

A twofold increase in the amount of diazonium salt, sodium (potassium, ammonium) rhodanide, or copper tetrafluoroborate against the optimum level neither alters the direction of the 4-acryloyloxybutyl acrylate thiocyanatoarylation reaction nor changes the target product yield. Thus, 4-acryloyloxybutyl acrylate offers an example of the unsaturated compound with molecules containing two like multiple bonds in which the anionarylation process can proceed only at one of these bonds.

The yields, physicochemical constants, data of elemental analyses, and the parameters of the IR and ^{1}H NMR spectra of the synthesized 4-(2-thiocyanato-3-arylpropionyloxy)butyl acrylates are presented in Table 1.

The IR spectra display the characteristic absorption bands due to carbonyl and thiocyanate groups in the region of 1716 and 2152 – 2156 cm^{-1}, respectively. The multiple bond of the terminal vinyl group is manifested by the absorption band 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 – III show the signals from protons of the aromatic nuclei in the form of a multiplet at 7.44 – 7.26 ppm. The signals from methylene protons of the terminal vinyl group are manifested as a doublet of doublets in the region of 6.36 – 6.33 ppm (*cis*-H) and 5.98 – 5.93 ppm (*trans*-H) with spin – spin coupling constants J = 11 and 14 Hz, respectively. The signals from methine protons of the terminal vinyl group are manifested as a doublet of doublet with a chemical shift of 6.18 – 6.16 ppm and a spin – spin coupling constant of J = 10 Hz.

EXPERIMENTAL CHEMICAL PART

The IR spectra of compounds I – III were recorded on a Specord M80 spectrophotometer (Germany) using thin optical cells. The ^{1}H NMR spectra were measured with a Varian Gemini spectrometer (working frequency 300 MHz, internal standard HMDS). The purity of the synthesized compounds was checked by TLC on Silufol UV-254 plates and by column chromatography using a Milikhrom-4 liquid chromatograph equipped with an UV detector and a Separon

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TABLE 1. Yields and Physicochemical Characteristics of 4-(2-Thiocyanato-3-arylpropionyloxy)butyl Acrylates (I – III)

Compound	R	Yield, %	n_D^{20}	d_4^{20}	Empirical formula	^{1}H NMR spectrum: δ, ppm (J, Hz)
I	H	61	1.4928	1.1067	$C_{17}H_{19}NO_4S$	7.34 – 7.26 (m, 5H, Ph), 6.33 (dd, J_{HH} 11 Hz, H-*cis*, =CH_2), 6.16 (dd, J_{HH} 10 Hz, 1H, =CH–), 5.93 (dd, J_{HH} 14 Hz, H-*trans*, =CH_2), 4.50 (dd, J_{HH} 7 Hz, 1H, CH), 4.11 (t, 4H, 2(–OCH_2)), 3.35 (dd, J_{HH} 8 Hz), 3.13 (dd, J_{HH} 8 Hz, 2H, CH_2Ph), 1.48 – 1.70 (m, 4H, –CH_2–CH_2–)
II	CH_3	56	1.4980	1.0854	$C_{18}H_{21}NO_4S$	7.36 – 7.26 (m, 4H, C_6H_4), 6.35 (dd, J_{HH} 11 Hz, H-*cis*, =CH_2), 6.18 (dd, J_{HH} 10 Hz, 1H, =CH–), 5.97 (dd, J_{HH} 14 Hz, H-*trans*, =CH_2), 4.51 (dd, J_{HH} 7 Hz, 1H, CH), 4.12 (t, 4H, 2(–OCH_2)), 3.35 (dd, J_{HH} 8 Hz), 3.12 (dd, J_{HH} 8 Hz, 2H, CH_2–C_6H_4), 2.45 (s, 3H, *p*-CH_3–C_6H_4), 1.46 – 1.72 (m, 4H, –CH_2–CH_2–)
III	NO_2	41	1.5112	1.1688	$C_{17}H_{18}N_2O_6S$	7.44 – 7.36 (m, 4H, C_6H_4), 6.36 (dd, J_{HH} 11 Hz, H-*cis*, =CH_2), 6.18 (dd, J_{HH} 10 Hz, 1H, =CH–), 5.98 (dd, J_{HH} 14 Hz, H-*trans*, =CH_2), 4.53 (dd, J_{HH} 7 Hz, 1H, CH), 4.14 (t, 4H, 2(–OCH_2)), 3.37 (dd, J_{HH} 8 Hz), 3.14 (dd, J_{HH} 8 Hz, 2H, –CH_2–C_6H_4), 1.47 – 1.69 (m, 4H, –CH_2–CH_2–)

SC × PR – Super C_{18} (5 μm) column eluted with an isopropanol – water – acetonitrile (6 : 11 : 33) mixture. The data of elemental analyses coincided with the results of analytical calculations using the empirical formulas. The yields, physicochemical constants, and parameters of the ^{1}H NMR spectra are presented in Table 1.

4-(2-Thiocyanato-3-phenylpropionyloxy)butyl acrylate (I). To a mixture of 0.12 mole 4-acryloyloxybutyl acrylate, 0.01 mole copper(II) tetrafluoroborate, and 0.13 mole of ammonium rodanide in 200 ml of a water – acetone mixture (1 : 2) was gradually (over one hour) added 0.15 mole of phenyldiazonium tetrafluoroborate. The reaction mixture was kept at –5 to –10°C until the evolution of nitrogen ceases (~2 h) and diluted with 250 ml of diethyl ether. The ether layer 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 – methanol – diethyl ether (5 : 3 : 3 : 1) mixture. Finally, the eluent was distilled off and traces of solvents were removed by purging with gaseous argon to obtain 24.2g (61%) of the target compound I and 3.8 g (9.6%) of isothiocyanatobenzene.

Compounds II and III were obtained using analogous procedures with the corresponding aryldiazonium tetrafluoroborates.

EXPERIMENTAL BIOLOGICAL PART

The antimicrobial activity of the synthesized compounds 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 the 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 2022), Gram-negative (*Escherichia coli* ATCC 25922), and spore-forming (*Bacillus cereus* ATCC 10702) bacteria.

Double serial dilutions of the stock solutions in 2 ml of the nutrient medium were prepared immediately before test, 0.2 ml of a bacterial suspension (with a load of 10^5 bacterial cells per ml) of the test microbe species were introduced into tubes, and the samples were incubated at 37°C for 18 – 24 h, after which the microbial growth was visually assessed. The activity was characterized by the minimum inhibiting concentration (MIC, μg/ml) corresponding to a dilution completely suppressing the test microbe growth. Each experiment was triply repeated.

It was established that the synthesized compounds I – III are most active with respect to *St. aureus* (MIC = 62.5 – 250 μg/ml). Somewhat less sensitive were the species of *B. cereus* (MIC = 312.3 μg/ml), and a minimum effect was observed for *E. coli* (MIC = 625 – 1250 μg/ml). A comparison of the antimicrobial properties of 1-thiocyanato-1-alkoxycarbonyl-2-arylethanes with those of 4-(2-thiocyanato-3-arylpropionyloxy)butyl acrylates shows that the introduction of acrylic acid fragments leads to a decrease in this activity.

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