SYNTHESIS AND STUDY OF ANTIBACTERIAL AND ANTIFUNGAL PROPERTIES OF (2-THIOCYANATO-3-ARYLPROPOXYMETHYL)OXIRANES

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Previously, we have used a reaction between aryldiazonium tetrafluoroborates with chloro(bromo, isothiocyanato)propenes in the presence of sodium rhodanide (bromide) for the synthesis of a series of 2-thiocyanato(bromo, isothiocyanato)-1-aryl-3-chloro(bromo, isothiocyanato)propanes [1], among which are compounds possessing antimicrobial activity [2, 3].

In continuation of the search for new antibacterial and antifungal agents among the functionalized allyl derivatives formed as a result of the anionarylation reactions [4, 5], we have studied compounds synthesized from allylglycidyl ester.

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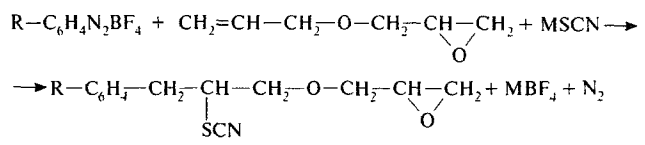
It was found that aryldiazonium tetrafluoroborates intensively interact with allylglycidyl ester in a water – acetone (1 : 2) medium in the presence of potassium or ammonium rhodanide. The reaction leads to the formation of (2-thiocyanato-3-arylpropoxymethyl)oxiranes (I – III):



R = H (I), *p*-CH_3 (II), *p*-CH_3O (III); M = K, NH_4.

The thiocyanatoarylation of allylglycidyl ester proceeds in the temperature interval from – 30 to – 25°C. In our work, the process was catalyzed by copper(I) rhodanide, but the

TABLE 1. Yields, Physicochemical Characteristics, and ^1H NMR Chemical Shifts of (2-Thiocyanato-3-arylpropoxymethyl)oxiranes I – III

Compound	Yield, %	B.p., °C (1 Torr)	n_D^{20}	d_4^{20}	^1H NMR spectrum: δ, ppm	Empirical formula
I	66	83 – 84	1.5689	1.2116	7.81 – 7.51 (m, 5H, C_6H_5), 5.93 (dd, 1H, J_{H-H} 5 Hz, –CH–), 5.87 (dd, 1H, J_{H-H} 5 Hz, –CH–), 5.29 (dd, 2H, J_{H-H} 2 Hz, $-CH_2-O-$), 5.14 (dd, 2H, J_{H-H} 2 Hz, $-CH_2-O-$), 4.19 – 3.92 (m, 3H, –CH(O)–CH_2–), 3.59 (dd, 2H, J_{H-H} 5 Hz, $-CH_2-Ph$), 3.52 (dd, 2H, J_{H-H} 5 Hz, $-CH_2-Ph$), 3.33 (dd, 2H, J_{H-H} 4 Hz, $-O-CH_2-$), 3.13 (dd, 2H, J_{H-H} 7 Hz, $-O-CH_2-$)	$C_{13}H_{15}NO_2S$
II	59	84 – 85	1.5658	1.1922	7.52 – 7.28 (m, 4H, C_6H_4), 5.94 (dd, 1H, J_{H-H} 5 Hz, –CH–), 5.88 (dd, 1H, J_{H-H} 5 Hz, –CH–), 5.27 (dd, 2H, J_{H-H} 2 Hz, $-CH_2-O-$), 5.13 (dd, 2H, J_{H-H} 2 Hz, $-CH_2-O-$), 4.29 – 3.95 (m, 3H, –CH(O)–CH_2–), 3.58 (dd, 2H, J_{H-H} 5 Hz, $-CH_2-Ph$), 3.52 (dd, 2H, J_{H-H} 5 Hz, $-CH_2-Ph$), 3.34 (dd, 2H, J_{H-H} 4 Hz, $-O-CH_2-$), 3.14 (dd, 2H, J_{H-H} 7 Hz, $-O-CH_2-$), 2.34 (s, 3H, *p*-CH_3),	$C_{14}H_{17}NO_2S$
III	60	99 – 100	1.5722	1.2473	7.71 – 7.05 (m, 4H, C_6H_4), 5.94 (dd, 1H, J_{H-H} 5 Hz, –CH–), 5.86 (dd, 1H, J_{H-H} 5 Hz, –CH–), 5.28 (dd, 2H, J_{H-H} 2 Hz, $-CH_2-O-$), 5.14 (dd, 2H, J_{H-H} 2 Hz, $-CH_2-O-$), 4.18 – 3.92 (m, 3H, –CH(O)–CH_2–), 3.84 (s, 3H, *p*-CH_3O), 3.57 (dd, 2H, J_{H-H} 5 Hz, $-CH_2-Ph$), 3.51 (dd, 2H, J_{H-H} 5 Hz, $-CH_2-Ph$), 3.35 (dd, 2H, J_{H-H} 4 Hz, $-O-CH_2-$), 3.15 (dd, 2H, J_{H-H} 7 Hz, $-O-CH_2-$),	$C_{14}H_{17}NO_3S$

yields of (2-thiocyanato-3-arylpropoxymethyl)oxiranes amount to 59 – 66 under both catalytic and noncatalytic conditions. The optimum reagent ratio diazonium salt – allylglycidyl ester – potassium rhodanide is 1.0 : 1.25 : 1.5. Note that the allylglycidyl ester thiocyanatoarylation is accompanied by a side reaction leading to the formation of isothiocyanatobenzenes with a yield of 14 – 18 %.

The proposed structures of (2-thiocyanato-3-arylpropoxymethyl)oxiranes were confirmed by the results of IR and ^{1}H NMR spectroscopic measurements. The IR spectra of compounds I – III contain absorption bands due to thiocyanate and epoxy groups (in the regions of 2140 – 2165 and 3060 – 3065 cm^{-1}, respectively). Their ^{1}H NMR spectra display signals due to aromatic protons in the region of 7.05 – 7.81 ppm (multiplets). The signals from protons of the methylene groups bound to aromatic nuclei are manifested as two doublets with δ = 3.51 – 3.52 and 3.58 – 3.59 ppm, while the signals from methine protons, as two doublets with δ = 5.86 – 5.88 and 5.93 – 5.94 ppm.

The yields and physicochemical constants of the synthesized compounds I – III and the parameters of their ^{1}H NMR spectra are given in Table 1.

The purity of the synthesized substances was checked by TLC on Silufol UV-254 plates eluted with a benzene – chloroform – diethyl ether (3 : 2 : 1) mixture.

EXPERIMENTAL CHEMICAL PART

The IR spectra of compounds I – III were recorded on an IKS-29 spectrophotometer using thin-layer samples. The ^{1}H NMR spectra were recorded on a Varian Gemini spectrometer using $CDCl_3$ as the solvent and HMDS as the internal standard.

The results of elemental analyses agree with the values calculated according to the empirical formulas.

(2-Thiocyanato-3-phenylpropoxymethyl)oxirane (I). To a mixture of 0.125 mole of allylglycidyl ester and 0.15 mole of potassium rhodanide in 150 ml of a water – acetone (1 : 2) mixture was gradually added (over 1 h) with stirring 0.1 mole of phenyldiazonium getrafluoroborate at a temperature of –30 to –25°C. When the nitrogen evolution ceased (~ 150 min), the reaction mixture was treated with 200 ml of diethyl ether. The ether extracts were washed with water and dried over magnesium sulfate. Then diethyl ether was evaporated and the residue was distilled in vacuum to obtain 2 g (14.8%) of isothiocyanatobenzene and 16.4 (66%) of compound I; b.p., 83 – 84 (1 Torr); n_D^{20}, 1.5689; d_4^{20}, 1.2116; MR_D, 67.32 (calc., 67.63).

Compounds II and III were obtained by similar procedures. Reactions under catalyzed conditions were conducted by adding 0.01 mole of copper(I) rhodanide per 0.1 mole of diazonium salt.

TABLE 2. Minimum Bacteriostatic Concentrations (MIC, μg/ml) of Compounds I – III

Compound	*S. typhimurium* 1534 his D 3052	*P. mirabilis* 410	*St. aureus* ATCC 25923 F-49	*P. aeruginosa* ATSS 27853 F-51	*B. subtilis* 8236 F-800	*C. albicans* TsShVI	*S. cerevisiae* 61
I	NA*	NA	NA	250	250	125	125
II	250	500	NA	125	62.5	62.5	62.5
III	500	NA	NA	250	250	250	125

* NA = nonactive.

EXPERIMENTAL BIOLOGICAL PART

The antimicrobial activity of the synthesized compounds was studied by the method of double serial dilutions in liquid nutrient media (a beef-infusion broth for bacteria, a modified Sabouraud liquid medium for fungi) using 96-cavity immunological plates and a Takachi microtitrator.

The working solutions were prepared by dissolving 10 mg of each compound in 0.25 ml DMF, followed by adding 9.75 ml of distilled water (no precipitate was formed). The solutions were thoroughly stirred before experiment.

The tests were performed on Gram-positive (*St. aureus* ATCC 25923 F-49), Gram-negative (*P. mirabilis* 410, *S. typhimurium* 1534 his D 3052, *P. aeruginosa* ATSS 27853 F-51), and spore-forming (*B. subtilis* 8236 F-800) bacteria and yeast fungi (*C. albicans* TsShVI and *S. cerevisiae* 61) species.

As is seen from the data presented in Table 2, compounds I – III exhibited weak antibacterial and antifungal activities.

A comparison of the results obtained in this work with the previous data [2, 3] indicates that the substitution of glycidyl radicals for chlorine (bromine) atoms in molecules of functionalized allyl derivatives obtained by thiocyanatoarylation of allylglycidyl ester leads to the complete loss of antibacterial properties with respect to *St. aureus* ATCC 25923 F-49, a slight decrease in the effect upon *S. cerevisiae* 61, and an increase in activity with respect to *P. aeruginosa* ATSS 27853 F-51 and *B. subtilis* 8236 F-800 bacteria and *C. albicans* TsShVI fungus. Replacement of the isothiocyanate group by a glycidyl fragment leads to a considerable decrease in activity with respect to all the microbial strains studied.

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