SYNTHESIS AND ANTIMICROBIAL PROPERTIES OF N-ARYL-N-CHLOROBENZENESULFAMIDES

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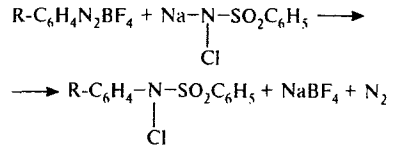
Chloramine derivatives, such as chloramine-B, chloramine-T, chloramine-X, and pantocid, are used in medicine for the treatment of infected wounds, the disinfection of hands and various accessories used for nursing contagious patients, and the neutralization of vesicant substances [1].

In continuation of the search for new antimicrobial agents, we have synthesized a series of new chloramine derivatives using the anionarylation reaction [2 – 4] and studied their antimicrobial activity.

It was found that aryldiazonium tetrafluoroborates interact with sodium N-chlorobenzenesulfamide trihydrate in acetone or a water – acetone (1 : 2) mixture. The reaction leads to the liberation of nitrogen from diazo groups and the formation of N-aryl-N-chlorobenzenesulfamides I – VI (chloramine-B derivatives) by the scheme



R = H (I), 4-Me (II), 4-MeO (III), 2-Br (IV), 4-COOH (V), 4-SO_2OH (VI).

The reaction proceeds in the temperature interval + 20 – 25°C, except for 2-bromoaniline where the process was conducted at + 10 – 15°C. The reactions were catalyzed by copper(II) acetate or tetrafluoroborate. It was found that the process may well proceed in the absence of catalyst, but at the expense of a 15 – 20% decrease in the yield of target products. The optimum ratio of diazonium salt to sodium N-chlorobenzenesulfamide trihydrate is 1 : 1.5. As the ratio of diazonium salt to catalyst increases from 1 : 0.1 to 1 : 1, the yields of the target N-aryl-N-chlorobenzenesulfamides reach 76 – 87%. The yields, parameters of the IR and ^{1}H NMR spectra, and the data of elemental analyses of N-aryl-N-chlorobenzenesulfamides I – VI are presented in Table 1.

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TABLE 1. Melting Points, Yields, IR Frequencies, and ^{1}H NMR Chemical Shifts of N-aryl-N-chlorobenzenesulfamides

Compound	R	Yield*, %		M.p., °C (solvent)	Empirical formula	IR spectrum: ν, cm^{-1}		^{1}H NMR spectrum: δ, ppm
		A	B			ν_{as}, SO_2	ν_s, SO_2	
I	H	76	61	153.5 (ethanol)	$C_{12}H_{10}O_2ClNS$	1325	1160	7.73 – 7.64 (m, 5H, C_6H_5N), 7.58 – 7.36 (m, 5H, C_6H_5S)
II	4-CH_3	79	59	154 (2-propanol)	$C_{13}H_{12}O_2ClNS$	1330	1160	7.87 – 7.81 (m, 4H, C_6H_4), 7.59 – 7.35 (m, 5H, C_6H_5); 2.38 (s, 3H, *p*-CH_3)
III	4-CH_3O	82	65	(2-propanol – octane, 1 : 1)	$C_{13}H_{12}O_3ClNS$	1335	1165	7.88 – 7.82 (m, 4H, C_6H_4), 7.59 – 7.37 (m, 5H, C_6H_5); 3.81 (s, 3H, *p*-CH_3O)
IV	2-Br	85	68	156 (2-propanol)	$C_{12}H_9O_2BrClNS$	1330	1165	7.82 – 7.71 (m, 4H, C_6H_4), 7.57 – 7.38 (m, 5H, C_6H_5)
V	4-COOH	81	67	138 – 139 (water)	$C_{13}H_{10}O_4ClNS$	1335	1160	12.3 (s, 1H, HO), 7.91 – 7.68 (m, 4H, C_6H_4), 7.58 – 7.36 (m, 5H, C_6H_5)
VI	4-SO_3H	87	71	154.5 (propanol)	$C_{12}H_{10}O_5ClNS_2$	1330	1165	11.7 (s, 1H, HOS), 7.87 – 7.80 (m, 4H, C_6H_4), 7.61 – 7.35 (m, 5H, C_6H_5)

* A, with catalyst; B, without catalyst.

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The proposed structures of N-aryl-N-chlorobenzenesulfamides were confirmed by the results of IR and ^{1}H NMR spectroscopic measurements. The IR spectra of compounds I – VI contain absorption bands due to the antisymmetric (ν_{as}) and symmetric (ν_s) stretching vibrations of SO_2 groups in the regions of 1325 – 1335 and 1160 – 1165 cm^{-1}, respectively [5, 6]. The ^{1}H NMR spectra of compounds I – VI display signals due to the aromatic protons.

The purity of the synthesized substances was checked by TLC on Silufol UV-254 plates eluted with an acetone – chloroform (1 : 2) mixture.

EXPERIMENTAL CHEMICAL PART

The IR spectra of compounds I – VII were recorded on an IKS-29 spectrophotometer using samples prepared as nujol mulls. The ^{1}H NMR spectra were recorded on a Varian-300 spectrometer (working frequency, 300 MHz) using $CDCl_3$ as the solvent and HMDS as the internal standard.

N-Phenyl-N-chlorobenzenesulfamide (I). To a mixture of 0.15 mole of sodium N-chlorobenzenesulfamide trihydrate and 0.1 mole of $Cu(BF_4)_2 \cdot 6H_2O$ in 150 ml of a water – acetone (1 : 2) mixture was gradually added (over 45 min) with stirring 0.1 mole of phenyldiazonium tetrafluoroborate. In the temperature interval + 20 – 25°C, the nitrogen evolution continued during about 150 min. After the gas evolution ceased, the reaction mixture was treated with 200 ml of diethyl ether. The ether extract was washed with water and dried over calcium chloride. Then diethyl ether was evaporated and the residue was recrystallized from ethanol to obtain 20.33 g (76%) of compound I; m.p., 153.5°C; IR spectrum (ν, cm^{-1}): 1325 (ν_{as}, SO_2), 1160 (ν_s, SO_2).

Compounds II – VI were obtained by similar procedures. The results of elemental analyses agree with the values calculated according to the empirical formulas.

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 micro-

TABLE 2. Antimicrobial Properties of N-aryl-N-chlorobenzenesulfamides

Compound	Minimum bacteriostatic concentration, μg / ml						
	S.typhimurium 1534	*P.mirabilis*	*S.aureus* F 49	*P.aeruginosa* 51	*B.subtilis* 39	*C.albicans*	*S.cerevisiae*
I	NA	NA	NA	NA	NA	500	125
II	NA	NA	NA	NA	NA	NA	500
III	NA	NA	NA	NA	NA	NA	500
IV	NA	NA	NA	NA	NA	NA	500

Note. NA = no activity.

modification of the liquid Sabouraud medium for fungi) using 96-well immunological plates and a Takachi microtitrator.

The tests were performed on Gram-positive (*St. aureus* F-49), Gram-negative (*P. aeruginosa* F-51, *S. typhimurium* 1534, *P. mirabilis*), and spore-forming (*B. subtilis*) bacteria and one yeast fungi (*C. albicans* TsShVI and *S. cerevisiae*) species.

The working solutions were prepared by dissolving 10 mg of each compound in 0.25 ml DMSO, followed by adding distilled water to the necessary solution concentration.

As is seen from the data presented in Table 2, compounds I – IV exhibited only weak antimicrobial activity with respect to the *S. cerevisiae* yeast fungus.

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