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SYNTHESIS OF CERTAIN HYDROXYAZOBENZENES AND INVESTIGATION OF THEIR ANTIMICROBIAL ACTIVITY

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Compounds were found among the hydroxyazobenzenes, having antimicrobial activity and low toxicity [3, 4].

In continuation of the search for new compounds with antimicrobial action, a synthesis was carried out in the present work of certain hydroxyazobenzenes and their antimicrobial activity was studied.

$C_6H_5N{=}NR$,
I—VII
where R=2-OH-4-BrC_6H_3 (I), 2-OH-3-BrC_6H_3 (II), 2-OH-3,4,5-Br_3C_6H (III), 2-OH-3,5-$NO_2C_6H_2$ (IV), 2-OH-3-COO (V), 2-OH-3-F (VI), 2,5-$(OH)_2$ (VII).

The hydroxyazobenzene derivatives obtained are crystalline substances, which are readily soluble in alcohol, benzene and other solvents and are insoluble in water. Their structure was established by elemental analysis and IR spectral data.

Absorption bands were observed in the IR spectra corresponding to the —N=N—, —OH, C=O groups and halogen atoms. In the 1450-1600 cm^{-1} region, the stretching vibrations of the —N=N— group and the aromatic rings are superimposed on one another, a broad band at 3450-3500 cm^{-1} corresponds to the OH group and the 1700 cm^{-1} band — to the C=O group vibrations. These data conform with the published data [2].

The physicochemical data of the synthesized compounds are given in Table 1.

EXPERIMENTAL (CHEMICAL)

The IR spectra were run on a UR-20 spectrophotometer in KBr tablets. The elemental analysis data correspond to the calculated values.

2-Hydroxy-4-bromobenzene (I). A 7.0 g portion of sodium nitride in 20 ml of water was added with stirring and cooling (0-5°C) to a solution of 9.3 g (0.12 mole) of aniline in a mixture of 100 ml of water and 25 ml of concentrated hydrochloric acid; then 17.29 g (0.1 mole) of m-bromophenol in 50 ml of a 5% sodium hydroxide were added to the solution, without interrupting the stirring and cooling. The brown precipitate that separated out was filtered off and washed several times with water, dried, and compound I was obtained.

Compounds II-VII were obtained in a similar way.

The purity of the obtained compounds was verified by TLC on a nonstationary layer of Al_2O_3, grade II of activity, in solvent systems (Table 1).

EXPERIMENTAL (BIOLOGICAL)

The antimicrobial activity of compounds I-VII was studied by the sample testing method and the method of serial dilutions in a liquid culture medium [1].

Examination of the antimicrobial properties of the preparations was carried out on test-microbes, inducers of suppurative and intestinal infections, conditionally pathogenic

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TABLE i. Physicochemical Data of Compounds I-VII

Compound	Mp, °C (solvent)	R_f	Empirical formula	IR spectra, cm^{-1}		
				N=N	halogen	OH
I	86	0,76 (benzene:ethanol: hexane 4:1:1)	$C_{12}H_9BrN_2O$	1610	760	3420
II	62—64	0,62 (benzene:ethanol: hexane 8:1:1)	$C_{12}H_9BrN_2O$	1600	750	3400
III	88—90 (ethanol)		$C_{12}H_7Br_3N_2O$	1610	760	3420
IV	67—68	0,25 (benzene:hexane, 10.1)	$C_{12}H_8N_4O_5$	1420	—	3390
V	62—64	0,61 (benzene:hexane, 10:1)	$C_{13}H_{10}N_2O_3$	1450	—	3400
VI	81—82	0,45 (benzene:hexane, 10:1)	$C_{12}H_9FN_2O$	1600	750	3400
VII	68—70	0,31 (benzene:ethanol: hexane 10:1:1)	$C_{12}H_{10}N_2O_2$	1460	—	3420

TABLE 2. Results of Testing the Antimicrobial Action of the Preparations by the Sample Testing Method (in mm)

Compound	Test-microbe						
	Micrococcus	Staphylococcus aureus 209	Salm. typhi murium	Sigella flexneri 2a	E. coli O55	Proteus	Bac. anthracoides
I	20	13	—	12	13	12	20
II	29	22	15	27	15	18	22
III	23	15	—	17	—	—	31
IV	24	23	15	26	18	25	16
V	13	10	—	12	11	—	11
VI	14	—	—	—	—	—	10
VII	18	12	14	14	—	—	11

TABLE 3. Method of Serial Dilutions

Compound	Concentration of the preparations, μg/ml	Test microbe						
		Micrococcus	Staphylococcus aureus 209	Salm. typhimurium	Shigella Flexneri 2a	E. coli O55	Proteus	Bac. anthracoides
II	1:100	—	—	—	—	—	—	—
	1:1000	—	—	+	+	+	+	—
	1:10000	—	—	+	+	+	+	+
	1:100000	—	—	+	+	+	+	+
	1:1000000	—	—	+	+	+	+	+
III	1:100	—	—	—	—	—	—	—
	1:1000	—	—	+	+	+	+	—
	1:10000	—	—	+	+	+	+	+
	1:100000	—	—	+	+	+	+	+
	1:1000000	—	—	+	+	+	+	+
IV	1:1000	—	—		—			—
	1:10000	—	—	n/t	+	n/t	n/t	+
	1:100000	—	—		+			+
	1:1000000	—	+		+			+
Penicillin	1:100	—	—	—	—	—	—	—
	1:1000	—	—	+	—	—	—	—
	1:10000	—	—	+	—	—	—	—
	1:100000	—	+	+	+	+	+	+
	1:1000000	—	+	+	+	+	+	+
Tetracycline	1:1000	—	—	—	—	—	—	—
	1:10000	—	—	—	+	—	+	—
	1:100000	—	—	+	+	—	+	—
	1:1000000	+	+	+	+	+	+	+
Control of solvent	—	+	+	+	+	+	+	+
Control of culture	—	+	+	+	+	+	+	+

Note. — absence of growth; + growth observed; n/t — not tested.

and spore-forming microorganisms. To determine the antimicrobial activity of the preparations, the following methods were used.

A. Method of Sample Testing. To determine the antimicrobial activity of the preparations samples of them (0.1 g/ml) were placed in recesses in meat peptone agar or sugar agar preliminarily inoculated by the corresponding microbial suspension. The dishes were incubated for 18 h at 37°C. The presence of the antimicrobial properties was determined from the diameter of the bactericidal action zone of the preparations (in mm) (Table 2).

B. Method of serial dilutions was carried out similarly as in the preceding case. Preparations having a pronounced antimicrobial action (compounds II-IV) in concentrations from 0.000001 to 0.1 g/ml were used. Control experiments with marketed antibiotics (penicillin, tetracycline) and solvent (dimethyl sulfoxide) were carried out in parallel.

It is seen from the results presented in Table 3 that compounds II-IV have pronounced antimicrobial properties with respect to the microbes tested. In the degree of activity with respect to suppurative infection inducers (Micrococcus, Staphylococcus aureus 209), compounds II-IV surpass the known antibiotics, penicillin by 10-100 times and tetracycline by 10 times.

It was found that the minimal inhibiting concentration of compounds II-IV against the suppurative infection inducers is 0.00001-0.0001 g/ml.

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SYNTHESIS OF 1,2-(2-DIMETHYLAMINOMETHYL-1-OXOPOLYMETHYLENE) BENZENES AND THEIR 4,5-DIETHOXY DERIVATIVES AND THEIR ANTI-INFLAMMATORY ACTIVITY

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Certain derivatives of 3-dimethylaminopropionylbenzene exhibit anti-inflammatory activity (AA) and are slightly toxic [2, 3]. Therefore, in order to study the relationship between the chemical structure and the AA, and also to search for new drugs, we synthesized and studied the cyclic analogs of these compounds (IIa-f), which were previously unknown or had not been examined for AA.

The hydrochlorides of β-aminoketones IIc-f were synthesized by the Mannich reaction of the corresponding ketones (Ic-f) with $Me_2NH{\cdot}HCl$ and paraform, while ketones Ie, f were obtained by heating the corresponding acids IIId, f) with polyphosphoric acid. Acid IIId was obtained by hydrogenation of unsaturated acid IIIc, synthesized by condensation of aldehyde (IIIb) with malonic acid in a pyridine solution in the presence of piperidine, while acid IIIf was obtained by reduction with amalagamated zinc and HCl of keto-acid (IIIe), synthesized by acylation of 1,2-diethoxybenzene (IIIa) with succinic anhydride in the presence of anhydrous $AlCl_3$.

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