SYNTHESIS AND ANTIMICROBIAL PROPERTIES OF 1-CHLORO(BROMO, THIOCYANATO)-BUTOXY-2-ARYLETHANES

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Previously, we used the reaction of anion arylation [1] for the synthesis of compounds possessing antibacterial and antimycotic properties [2-5].

In this work we have for the first time carried out the anion arylation process with the participation of vinylbutyl ester [2].

It was found that aryldiazonium tetrafluoroborates interact with butyl ester in a water – acetone (1:2) medium in the presence of chlorides (bromides) of alkali metals or ammonium, with the evolution of nitrogen and the formation of 1-chloro(bromo)-1-butoxy-2-arylethanes:

$$RC_{6}H_{4}N_{2}BF_{4} + CH_{2} = CHOBu + MSCN \xrightarrow{Cu^{2+}} RC_{6}H_{4} - CH_{2} - CH - OBu + MBF_{4} + N_{2}$$

Hal

1: R = H, Hal = Cl; 11: R = 4-Me, Hal = Br.

The chloro- and bromoarylation reactions proceed in the temperature intervals 12 - 20 and 7 - 20°C, respectively, in the presence of a catalyst, copper(II) chloride or bromide. The yields of 1-chloro-1-butoxy-2-phenyl- and 1-bromo-1-butoxy-2-p-tolylethanes are 35 and 51%, respectively. The chloro-or bromoarylation processes are accompanied by side reactions with the formation of chloro(bromo)benzenes and substituted phenols with the yields within 13 - 20 and 15 - 20%, respectively.

The interaction of aryldiazonium tetrafluoroborates with vinylbutyl ester in the presence of rhodanides of alkali metals or ammonium proceeds under similar conditions, leading to the formation of a mixture of 1-thiocyanato- and -isothiocyanato-1-butoxy-2-arylethanes (III, IV) and (IIIa, IVa):

$$RC_6H_4N_2BF_4 + CH_2 = CHOBu + MSCN \xrightarrow{Cu^{2+}} -MBF_4, -N_2$$

$$RC_{6}H_{4}-CH_{2}-CH-OBu$$

$$S-C\equiv N$$

$$R = H (III), 4-Me (IV), 3-NO_{2} (V)$$

$$RC_{6}H_{4}CH_{2}-CH-OBu$$

$$N=C=S$$

$$R = H (IIIa), 4-Me (IVa)$$

These reactions proceed at $-(15-10)^{\circ}$ C in the presence of a catalyst (copper rhodanide) and are accompanied by the formation of isothiocyanatobenzenes with a yield of $4 - 12^{\circ}$.

The optimum ratio of reagents for the chloro-, bromo, thiocyanato-, and isothiocyanatoarylation processes of vinylbutyl ester is as follows: diazonium salt – unsaturated compound – catalyst – anionoid element, 1:1.2:0.1:(1.2-1.5).

In contrast to the previously studied reactions of olefins with aromatic diazonium salts in the presence of thiocyanate anion, which led to the selective formation of either thiocyanates or isothiocyanates [1], the reaction with vinylbutyl ester yields a mixture of thio- and isothiocyanates.

The presence of a mixture of thiocyanates and isothiocyanates in the products of interaction between aryldiazonium tetrafluoroborates and vinylbutyl ester was confirmed by the IR spectroscopic data. The IR spectrum of a distillate, obtained upon the separation of isothiocyanatobenzenes, contains two absorption bands in the region of 2090 and 2170 cm⁻¹, which are characteristic of the isothiocyanate and thiocyanate groups, respectively. Since the mixture of thiocyanates and isothiocyanates boils within a very narrow temperature interval, we failed to separate the two fractions by the method of vacuum distillation.

It must be noted that only one product was obtained upon the reaction between 3-nitrophenyldiazonium tetrafluoroborate and vinylbutyl ester, where the thiocyanatoarylation

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process led to the formation of 1-thiocyanato-1-butoxy-2-(3-nitrophenyl)ethane (V).

Earlier [6] we have developed a quantitative method for obtaining thioureas by the reaction between isothiocyanates and aliphatic amines. This technique was used for the isolation of thiocyanates from a mixture of the reaction products.

Treatment of the product mixture obtained upon the distillation of side isothiocyanatobenzenes with an excess ammonia leads to crystalline N-(2-aryl-1-butoxyethyl)thioureas (IIIb, IVb):

IIIa,
$$IVa + NH_3 \longrightarrow RC_6H_4CH_2 - CH - OBu$$

 $HN - C - NH_2$
 S
IIIb, IVb
 $R = H$ (IIIb), 4-Me (IVb)

On separation of the thioureas, we obtained individual thiocyanates III and IV.

It was established that the ratio of thiocyanates and isothiocyanates in the reaction under study was on average (3 - 4):1. We suggested that thiocyanates III, IV could be subjected to isomerization in the course of vacuum distillation, with the formation of isothiocyanates IIIa and IVa. However, a 1-h exposure of a mixture of thiocyanates III, IV and isothiocyanates IIIa, IVa at 100°C did not change the ratio of components. Nor did the exposure of thiocyanates III, IV at this temperature lead to their isomerization and the appearance of isothiocyanates, which was confirmed by the data of IR spectroscopy and TLC. Therefore, we can affirm that both thiocyanates and isothiocyanates are formed simultaneously in the course of the reaction.

The yields, physicochemical constants, and the parameters of IR and ¹H NMR spectra of compounds I - V and thioureas IIIb, IVb are presented in Tables 1 and 2.

The proposed structures of the vinylbutyl anion arylation products I – V were confirmed by the data of IR and ¹H NMR spectroscopy. The IR spectra of compounds I, II contain absorption bands due to the C–Cl and C–Br bonds in the region of 600 – 800 and 500 – 600 cm⁻¹. The thiocyanate group of compounds III – V is represented by a narrow absorption band in the region of 2170 - 2175 cm⁻¹. The ¹H NMR spectra of compounds I – V contain signals due to the protons of

TABLE 1. Yields and Physicochemical Characteristics of Compounds I - V

Com- pound	Yield, %	B.p., °C (P, Torr)	α_{4}^{20}	n_D^{20}	Empirical formula
1	35	57 - 60 (0.5)	1.1362	1.5618	C12H17OCI
11	51	m.p., 18 – 19°C (ethanol)	—		C ₁₃ H ₁₉ OBr
111	69	48 - 50 (0.5)	1.1408	1.5754	C ₁₃ H ₁₇ NOS
١V	58	72 – 74 (1)	1.1166	1.5660	C14H19NOS
v	40	95 – 96 (1)	1.1382	1.4832	$C_{13}H_{16}N_2O_8S$

methine, methylene, and aromatic moieties in the regions of 3.88 - 3.99, 3.17 - 3.27, and 7.05 - 7.08 ppm, respectively.

The IR absorption spectra of thioureas IIIb, IVb display three bands at 3460, 3380, and 3440 cm⁻¹. The first two bands can be assigned to the v_{as} and v_s vibrations of the NH₂ group (in agreement with the published data [6]). The third band belongs to the stretching vibrations of the secondary NH group of the thiourea fragment.

EXPERIMENTAL CHEMICAL PART

The IR spectra were recorded on an IKS-29 spectrophotometer. The liquid samples were obtained as thin films, and the solid samples were measured as vaseline oil suspensions. The ¹H NMR spectra were measured on a Tesla BS-487 spectrometer operated at 80 MHz, using HMDS as the internal standard. The results of elemental analyses agree with the proposed empirical formulas (Tables 1 and 2).

1-Chloro-1-butoxy-2-phenylethane (I). To a mixture of 0.12 mole of vinylbutyl ester, 0.01 mole of copper(II) chloride, and 0.1 mole of phenyldiazonium tetrafluoroborate in 120 ml of a water – acetone mixture (1:2) was gradually added, over a period of 90 min, 0.12 mole of sodium chloride at a temperature of 10°C. Nitrogen evolved from the reaction mixture over a period of 3 h at a temperature of $12 - 20^{\circ}$ C. When the nitrogen evolution ceased, the reaction mixture was treated with 200 ml of diethyl ether, and the extracts washed with water and dried over magnesium sulfate. Then diethyl ether was evaporated and the residue distilled in vacuum to obtain 2.3 g of (20%) chlorobenzene, 1.8 g (20%) of phenol, and 7.4 g of compound I.

1-Bromo-1-butoxy-2-(4-tolyl)ethane (II). To a mixture of 0.12 mole of vinylbutyl ester, 0.01 mole of copper(II) bromide, and 0.1 mole of 4-tolyldiazonium tetrafluoroborate in 120 ml of a water – acetone mixture (1:2) was gradually added, over a period of 90 min, 0.12 mole of sodium chloride. Nitrogen evolved from the reaction mixture over a pe-

TABLE 2. Physicochemical and Spectral Characteristics of Compounds IIIb and IVb

Com- pound	M.p., °C (solvent)	Empirical formula	IR spectrum (v _{max} , cm ⁻¹)		¹ Η NMR spectrum (δ. ppm)	
			NH	NCS		
IIIb	151 – 152 (methanol)	C ₁₃ H ₂₀ N ₂ OS	3285	1470	7.18 (s, 5H, C_6H_5), 6.62 (bs. 2H, NH ₂), 4.13 (t, 2H, CH ₂ O), 3.96 – 3.90 (m, 1H, CH), 3.27 – 3.17 (m, 2H, CH ₂), 1.76 – 0.92 (7H, C ₃ H ₇)	

riod of 2.5 h at a temperature of $7 - 20^{\circ}$ C. When the nitrogen evolution ceased, the reaction mixture was treated with 200 ml of diethyl ether, and the extracts washed with water and dried over magnesium sulfate. Then the solvent was evaporated and the residue distilled in vacuum to obtain 2.2 g (13%) of 4-bromotoluene, 1.3 g (11%) of 4-cresol, and 13.7 g of compound II (b.p., 68 - 70°C/0.5 Torr); the latter product crystallizes within 30 min.

Interaction of vinylbutyl ester with phenyldiazonium tetrafluoroborate in the presence of potassium rhodanide. To a mixture of 0.1 mole of vinylbutyl ester, 0.01 mole of copper(II) tetrafluoroborate bromide, and 0.15 mole of potassium rhodanide in 120 ml of a water – acetone mixture (1:2) was gradually added, over a period of 60 min, 0.1 mole of solid phenyldiazonium tetrafluoroborate. Nitrogen evolved from the reaction mixture over a period of 60 min at a temperature of $-(10-5)^{\circ}$ C. When the nitrogen evolution ceased, the reaction mixture was treated with 200 ml of diethyl ether, and the extracts washed with water and dried over magnesium sulfate. Then the solvent was evaporated and the residue distilled in vacuum to obtain 0.5 g (4%) of phenylisothiocyanate [b.p., 69 – 71°C/1 Torr; IR spectrum (v_{max} , cm⁻¹): 2095 (NCS); ¹H NMR spectrum, (δ, ppm): 7.07 (s, arom. protons)] and 20.4 g (87%) of a mixture of 1-butoxy-1-thiocyanato-2-phenylethane (III) and 1-butoxy-1-isothiocyanato-2phenylethane (IIIa) [IR spectrum (v_{max} , cm⁻¹): 2095 (NCS), 2175 (SCN)].

Interaction between a mixture of vinylbutyl ester rhodanine arylation products with ammonia. To 0.008 mole of a mixture of 1-butoxy-1-thiocyanato-2-phenylethane (III) and 1-butoxy-1-isothiocyanato-2-phenylethane (IIIa) was added 0.04 mole of a 25% ammonia solution. The crystals precipitated within a 30 min time period were separated by filtration and repeatedly washed with ethanol and diethyl ether. Then the residue was recrystallized from methanol to give 0.37 g of N-(2-phenyl-1-butoxyethyl)thiourea (IIIb). The filtrate was treated with 50 ml of diethyl ether and washed with water. The extract was dried over magnesium sulfate, evaporated, and distilled in vacuum to obtain 1.5 g of 1-thiocyanato-1-butoxy-2-phenylethane (III).

A similar procedure was used to obtain N-[2-(4-tolyl)-1butoxyethyl]thiourea (IVb) and separate 1-thiocyanato-1-butoxy-2-(4-tolyl)ethane (IV). In the case of 4-methylphenyldiazonium tetrafluoroborate, the contents of thiocyanate and isothiocyanate in the reaction mixture were 78 and 22%, respectively.

EXPERIMENTAL BIOLOGICAL PART

The antimicrobial activity of the synthesized compounds was studied by the method of serial double dilutions in Sabouraud's liquid medium. The tests were performed on the yeast fungi species *C. albicans* and *S. cerevisiae* and on Gram-negative (*E. coli* K-12, *P. aeruginosa* 40), Gram-posi-

TABLE 3. Antimicrobial Activity of Compounds I - V

	Minimum inhibiting concentration (MIC), µg / ml:								
Compoun d	E. coli K-12	S. aureus F-49	P. aeru- ginosa 40	B. antracoides	C. albicans	S cerevisiae			
1	*	*	500	500	500	250			
II	*	*	500	500	500	250			
111	500	500	250	500	125	125			
IV	500	*	250	500	250	125			
<u>v</u>	425	125	250	250	125	62.5			

* - Inactive

tive (S. aureus F-49), and spore-forming (B. antracoides) bacteria.

The results of these experiments are presented in Table 3. which indicates that the maximum antibacterial and antimycotic activity and the broadest activity spectrum among the compounds studied was manifested by compound V. A somewhat lower effect, at the same breadth of the activity spectrum, was observed for compound III.

Compound IV, albeit close to the two former compounds with respect to the overall antimicrobial activity, was inactive toward the *S* aureus F-49 strain. Compounds I and II were inferior to V, III, and IV in both the breadth of the activity spectrum and the magnitude of the effect.

A comparative analysis of the chemical structure of compounds active and inactive with respect to *E. coli* K-12 and *S. aureus* F-49 leads to the conclusion that the presence of halogen atoms in the hydrocarbon chain promotes loss of activity, while the substitution of thiocyanate groups for halogens increased the activity of the compounds studied. The level of activity depends on the type of substituent in the aromatic nucleus. The maximum effect was produced by introducing a nitro group into the *meta* position of the benzene nucleus, which led to the maximum inhibiting effect and the broadest activity spectrum. Thus, with respect to the general level of antibacterial and antimycotic activity and the breadth of the activity spectrum, compound V is the most promising object for further investigation.

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