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SYNTHESIS OF THIOCYANATO-, ISOTHIOCYANATO-, AND HALO DERIVATIVES OF 1-ARYLPROPANES AND THEIR ANTIMICROBIAL PROPERTIES

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It has previously been shown [1-3] that thiocyanates and isothiocyanates, obtained by the anion-arylation of divinyl, isoprene acrylic, and methacrylic acid esters, vinyl chloride and vinylidene chloride, exhibit antibacterial and antifungal properties. A correlation has been made between their structure and physiological activity.

Of special interest in this context are derivatives of halo- and isothiocyanatopropanes, which occur in plants in the free state or in glycoside form [4, 5]. These are physiologically active compounds, and therefore find medical application as therapeutical preparations [4-6].

For the synthesis of the functional derivatives of 1-arylpropanes anion-arylation has been used [7].

We found that aryldiazonium tetrafluoroborates react vigorously with 3-chloro(bromo, isothiocyanato)propene in acetone or an aqueous-acetone solution (1:3), in the presence of sodium thiocyanate (bromide), with the evolution of nitrogen from the diazo group and addition of the aryl group and the anion at the site of the double bond cleavage, with the formation of 1-aryl-2-thiocyanato(bromo-, isothiocyanato)-3-chloro(bromo, isothiocyanato)propanes, respectively.

$$R^1C_6H_4N_2BF_4 + CH_2{=}CHCH_2R^2 + NaAn \xrightarrow[-N_2]{} \longrightarrow R^1C_6H_4CH_2\underset{\text{I—VII}}{CH(An)}CH_2R^2 + NaBF_4$$

$R^1 = H$, $R^2 = Cl$ (I); $R^1 = n$-Me, $R^2 = Cl$ (II);

$R^1 = m$-Me, $R^2 = Cl$ (III); $R^1 = n$-MeO, $R^2 = Cl$ (IV);
$R^1 = H$, $R^2 = Cl$, An = Br (V); $R^1 = H$, $R^2 = Br$ (VI);
$R^1 = H$, $R^2 = NCS$ (VII); An = SCN (I—IV, VI), NCS (VII).

The thiocyanato-, and isothiocyanatoarylation of halo- and isothiocyanatopropenes proceeds at a temperature of −40 to −20°C. For the reaction to occur it is necessary that a catalyst, namely copper or iron salts [7], be present. The bromination was carried at the temperature of ~10-15°C. The yields of 1-aryl-2-thiocyanato(bromo-, isothiocyanato)-3-chloro(bromo-, isothiocyanato)propanes are in the range of 25-54%.

The thiocyanato-, isothiocyanato, and bromoarylation of halo- and isothiocyanatopropenes is accompanied by a side process of azo-coupling, which is most strongly manifested in the case of m-tolyldiazonium.

In the case of 3-bromopropene the side reaction — the formation of isothiocyanatobenzenes — competes markedly with the formation of 1-phenyl-2-thiocyanato-3-bromopropane, as indicated by the yields — 30 and 25%, respectively.

It was found that the ratio of reagents: the diazonium salt — the unsaturated compound — sodium thiocyanate (bromide) 1:1.25:1, is the optimal ratio.

The products of anion-arylation of halo- and isothiocyanatopropenes are light-yellow oils. Heating of the thiocyanates obtained does not lead to their isomerization into isothiocyanates.

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TABLE 1. Characteristics of 1-Aryl-2-thiocyanato(bromo-, isothiocyanato)-3-chloro(bromo, isothiocyanato)propanes

Compound	Yield, %	Bp, °C*	d_4^{20}	n_D^{20}	Empirical formula	IR spectrum, An, ν_{max}, cm^{-1}	PMR spectra, δ, ppm
I	54	105—6	1,2376	1,5738	$C_{10}H_{10}ClNS$	2160	2.85 dd(2H, CH_2Cl, 8 Hz), 3.16 dd (2H, CH_2Ph, 6 Hz), 3,62—3,86 m (1H, CH), 7.09 s (5H, C_6H_5)
II	46	115—6	1,2172	1,5672	$C_{11}H_{12}ClNS$	2165	2.25 s (3H, p-CH_3), 2.86 dd(2H, CH_2Cl, 8 Hz), 3.15 dd(2H, CH_2Ar, 6 Hz), 3,60—3,88 m(1H,CH), 7,10 s (4H, C_6H_4)
III	25	113—4	1,2165	1,5712	$C_{11}H_{12}ClNS$	2160	2.25 s (3H, m-CH_3), 2,87 dd(2H, CH_2Cl, 8 Hz), 3,18 dd(2H, CH_2Ar, 6 Hz), 3.71 — 3.92 m (1H, CH), 7.02—7.42 br.s (4H, C_6H_4)
IV	48	127—9	1,2740	1,5742	$C_{11}H_{12}ClNOS$	2165	2.86 dd(2H, CH_2Cl, 8 Hz), 3,15 dd (2H, CH_2Ar, 6 Hz), 3,70 s (3H, CH_3O), 3,69—3,96 m (1H, CH), 6,84 d,7,13 d (4H, C_6H_4)
V	38	110—2	1,4773	1,5678	$C_9H_{10}BrCl$	800—860	2.86 dd(2H,CH_2Cl, 8 Hz), 3,16 dd (2H, CH_2Ph, 6 Hz), 3,61—3,90 m (1H,CH), 7,08 s (5H, C_6H_5)
VI	34	145—6	1,4747	1,6048	$C_{10}H_{10}BrNS$	2160	2.87 dd (2H,CH_2Br, 8 Hz), 3,16 dd (2H, CH_2Ph, 6 Hz), 3,62—3,92 m(1H, CH), 7.07 s (5H, C_6H_5)
VII	39	152—4	1,1312	1,5920	$C_{11}H_{10}N_2S_2$	2084	2.84 dd(2H,CH_2, 8 Hz), 3,16 dd (2H,CH_2Ph, 6 Hz), 3,62—3,90 m (1H,CH), 7.08 s (5H,C_6H_5)

*At a residual pressure of 1 mm Hg.

The structure of 1-aryl-2-thiocyanato(bromo-, isothiocyanato)-3-chloro(bromo, isothiocyanato)propanes obtained was confirmed by their IR and PMR spectra. In the IR spectra of compounds I-IV, VI, the thiocyanate group is represented by a narrow band in the region of 2160-2165 cm^{-1}. The two isocyanate groups in compound VII are indicated by a broad band with a maximum at 2084 cm^{-1}.

The reaction of compound VII with an aqueous solution of ammonia according to [8] gave a thiourea, in the IR spectrum of which the broad absorption band with a maximum at 2084 cm^{-1}, characteristic for the isothiocyanate groups, is absent, while absorption bands characteristic for the thioureide fragment NHC(=S)NH_2 fragment appear. This confirms that in the case of 3-isothiocyanatopropene the addition of the thiocyanate group occurs in the isothiocyanate form.

The PMR spectra of 1-aryl-2-thiocyanato(bromo-, isothiocyanato)-3-chloro(bromo-, isothiocyanato)propanes contain signals of protons of aromatic nuclei in the region of 7.02-7.42 ppm. The signals of protons of methylene groups bound to aromatic nuclei and halogens, through the isothiocyanate group, appear in the form of two doublets in the regions of 3.16 and 2.85 ppm and with spin–spin coupling constants of 6 and 8 Hz, respectively. The signals of the methane group protons give a multiplet in the 3.60-3.98 ppm region.

EXPERIMENTAL (CHEMICAL)

The IR spectra in thin layers of compounds I-VII were run on an IKS-29 spectrophotometer (Russia). The PMR spectra were recorded on a Varian VXR-300 spectrometer (USA) with a working frequency of 300 MHz, using $(CD_3)_2CO$ as a solvent and HMDS as an internal standard. The purity of the synthesized compounds was established by the TLC method on Silufol UV-254 plates, using a hexane–ether–chloroform (1:1:2) mixture of solvents as eluent. The results of the elemental analyses corresponded to the calculated values.

1-Phenyl-2-thiocyanato-3-chloropropane (I). A 0.1 mole portion of phenyldiazonium tetrafluoroborate was added in the course of 30 min to 0.125 mole of 3-chloropropene, 0.01 mole of cupric thiocyanate and 0.125 mole of sodium thiocyanate in 160 ml of an aqueous–acetone mixture (1:3). Nitrogen evolved at −40 to −20°C over a period of 90 min. After nitrogen ceased to evolve, the reaction mixture was treated with 200 ml of diethyl ether, the extracts were washed with water and dried over $CaCl_2$. After evaporation of ether and distillation of the residue under vacuum, 1.35 g (10%) of phenyl isothiocyanate, bp 69-71°C (1 mm Hg), d_4^{20} 1.1305, n_D^{20} 1.6494 and 11.42 g (54%) of compound I were obtained.

TABLE 2. Antimicrobial Properties of Compounds I-VII

Compound	Minimal inhibiting concentrations, μg/ml					
	E. coli K-12	S. aureus 209	P. aeruginosa	B. subtilis 39	Candida alb. 23	S. cerevisia
I	i/a	7.8	500	125	125	62.5
II	i/a	125	500	500	500	62.5
III	i/a	15.6	500	125	500	62.5
IV	500	62.5	250	250	250	62.5
V	i/a	125	250	500	500	250
VI	i/a	125	125	i/a	250	125
VII	500	250	31.2	125	7.8	0.24

Note. i/a) inactive.

The reactions in the presence of iron salts are carried out in the same way. Compounds II-IV, VI, VII are obtained in a similar way. In the case of the preparation of compound V, 0.125 mole of sodium bromide was used and cupric bromide or ferric bromide was used as the catalyst. The characteristics of the synthesized compounds I-VII are given in Table 1.

EXPERIMENTAL (BIOLOGICAL)

The antimicrobial activity of the synthesized compounds was studied by the method of double serial dilutions in a liquid Saburo medium with respect to yeast fungi S. cerevisia, S. albicans 23, and also by the method of double dilutions in a MPB medium with respect to Gram-positive (S. aureus 209), Gram-negative (E. coli K-12, P. aeruginosa 40) and spore-forming (S. subtilis 39) bacteria.

It is seen from Table 2 that all the compounds studied have antimicrobial properties with respect to the targets used. The activity of the thiocyanatoarylation products of 3-chloropropene (I, III, IV) with respect to the Gram-positive bacteria on the example of S. aureus 209 is noteworthy. Compounds I-IV have stronger antimycotic properties in comparison with the thiocyanatoarylation product of 3-bromopropene — 1-phenyl-2-thiocyanato-3-bromopropane V. Using compound VI as an example, it was shown that an exchange of the thiocyanate group by bromine leads to a decrease in the antimicrobial activity. The structure of the aryl in the carbon chain of compounds I-V practically does not influence their antifungal and antibacterial activity. The isothiocyanatoarylation product of isothiocyanatopropene — 1-phenyl-2,3-diisothiocyanatopropane VII shows a high antimycotic activity with respect to the yeast microorganisms, which indicates good prospects for its derivatives as starting materials for producing effective antimicrobial preparations with a broad spectrum of activity.

Analysis of the relationship between the structure of compounds I and VII and the physiological activity exhibited by them, while taking into account the results obtained in [3], confirms that introduction of a chlorine atom or a thiocyanate group in an isothiacyanate form into the carbon chain of the molecule in addition to thiocyanate or isothiocyanate group already present in them intensifies the antimicrobial activity.

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