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SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF γ-BROMOPROPARGYL ESTERS OF CARBAMIC ACIDS

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In order to study the reactivity of the terminal hydrogen atom in propargyl carbamates that we have previously synthesized [1], and also to prove their structure, we have carried out their bromination. The substitution of the acetylenic hydrogen in propargyl carbamates by bromine proceeds with the participation of equimolar amounts of propargyl carbamates and $CuBr_2$ in an organic solvent medium.

It should be noted that this method of bromination differs from the hypohalite method [2]. It is simpler, since the reaction proceeds in one step at room temperature.

The bromination was carried out at room temperature in a methanol medium according to the following scheme:

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TABLE 1. Physicochemical Properties of Bromopropargyl Esters of Mono- and Dicarbamic Acids I-VII

Compound	Yield, %	Mp °C	Empirical formula	IR spectrum, cm^{-1}	
				—NHCO—	—C≡CBr
I	78	91—92	$C_{10}H_8BrNO_2$	1710	2210
II	79	128—9	$C_{10}H_7ClBrNO_2$	1715	2220
III	80	47—48	$C_{10}H_6ClBrN_2O_2$	1710	2215
IV	79	112—3	$C_{14}H_{10}BrNO_2$	1700	2210
V	81	72—74	$C_{22}H_{40}BrNO_2$	1705	2220
VI	82	63—65	$C_{14}H_{18}Br_2N_2O_4$	1700	2230
VII	80	75—76	$C_{15}H_{12}Br_2N_2O_4$	1705	2222

TABLE 2. Antimicrobial Activity of Compounds I-VII

Compound	St. aureus 209	Micrococcus	S. typhimurium	S. typhi	Sh. flexneri 2a	Serratia
I	7	25	20	16	6	28
II	24	—	30	30	33	—
III	37	20	28	34	23	20
IV	13	9	14	13	7	7
V	7	10	13	11	5	11
VI	10	12	10	15	10	15
VII	14	18	15	22	25	10
Control penicillin	17	—	—	—	—	
levomycetin	—	11	—	—	12	—
polymixin	—	—	—	17	—	—

The compounds obtained are crystalline substances, which are readily soluble in organic solvents. The purity of the compounds was verified by TLC on Al_2O_3 in a MeOH—$CHCl_3$—petroleum ether (1:1:1) system of solvents.

The structure of the compounds obtained was established from elemental analysis data and IR spectroscopy.

There are absorption bands in the spectra of the compounds obtained in the 3340-3310 cm^{-1} region, which correspond to the NH group vibrations and absorption bands in the 2230-2210 cm^{-1} region corresponding to the substituted methine bond vibrations. In contrast to the spectrum of the initial propargyl carbamates, the absorption band corresponding to the stretching vibrations of the —C≡C—H bond is absent in the spectrum of the bromo derivative, which shows that the bromination proceeds in particular at the expense of the labile hydrogen atom.

The physicochemical characteristics are given in Table 1. The elemental analysis data correspond to the calculated values.

EXPERIMENTAL (CHEMICAL)

The IR spectra were obtained on a "Specord 75" spectrometer. The samples were prepared by pressing KBr tablets.

γ-Bromopropargyl Ester of Phenylcarbamate (I). A 2.23 g portion (0.01 mole) of $CuBr_2$ was added to 1.75 g (0.01 mole) of propargyl phenylcarbamate at room temperature, with stirring, and the mixture was allowed to stand for 24 h. The contents of the flask were then transferred to a beaker containing a saturated solution of ammonium chloride, and were extracted with ether. After evaparation of the solvent, the product was purified by TLC on Al_2O_3 in a CH_3OH—$CHCl_3$—petroleum ether (1:1:1) system; R_f 0.87. Yield, 1.87 g (78.5% of theoretical). The remaining propargyl carbamate derivatives were obtained under similar conditions.

EXPERIMENTAL (BIOLOGICAL)

The presence of halogens and a triple bond in the molecules of the synthesized compounds should favor the occurrence of biological activity.

Therefore, the synthesized compounds were tested for antimicrobial activity at the Microbiology Department of the Tashkent Medicinal Institute. The presence of the antimicrobial properties was determined by the "alveole" method or by the weighed samples method. On the surface of a meat-peptone agar (MPA), treated wtih the microbial suspension of the test culture (1 billion/ml), alveoles were extruded, into which the compounds studied were introduced in an amount of 0.2 to 1 mg, which diffused into agar. Following the incubation at 37°C, the result was recorded after 18-24 h according to the diameter of the bactericical action zone (in mm).

The results of the investigations are given in Table 2.

The data show that all the compounds studied have antimicrobial activity. The highest activity is found in compounds II and III. Among the chlorine-substituted compounds, the activity changes in the following order: dichlorophenyl > monochlorophenyl > phenyl, i.e., the chlorine-containing compounds II and III have the highest activity. Thus, it should be noted that the presence of chlorine in the p-position leads to a selective appearance of the activity, as indicated by the activity of compound II with respect to microorganisms such as St. aureus 209, S. typhimurium, S. typhi, Sh. flexneri 2^a, and the absence of activity with respect to Micrococcus Serratia. Compound III displays activity with respect to all the test microbes.

The activity of the synthesized preparations was compared with that of known antimicrobial preparations: penicillin, levomycetin, polymixin.

The data in Table 2 show that some of the compounds surpass known antimicrobial preparations in their activity.

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SYNTHESIS AND BIOLOGICAL INVESTIGATION OF A COPOLYMER OF ACRYLIC ACID WITH N-VINYLPYRROLIDONE

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The ability of some polyelectrolytes to show strong activity on different stages of immunogenesis, as well as their use as carriers of physiologially active compounds, has served to stimulate the intensive study of this class of compounds [8, 9]. Interest in this scheme has produced a copolymer of acrylic acid with N-vinylpyrrolidone (N-A), which can be used as an effective immunologic adjuvant for vaccination, and for producing high-titer antisera. The immunotropic activity of this copolymer and its conjugates with various antigens has been sufficiently widely studied [5, 6]; however, there are no data on its general biological activity in living organisms.

The purpose of this work was to study the local and general toxicity of N-A in animals.

EXPERIMENTAL (CHEMISTRY)

Synthesis of a Copolymer of Acrylic Acid and N-vinylpyrrolidone (N-A). Copolymerization of acrylic acid in N-A was carried out under vacuum in methanol solution at 60°C. As catalyst we used isobutyric acid azodinitrile. The composition of the monomer mixture was adjusted to give a known constant degree of copolymerization of acrylic acid and N-A [10]. To an ampule with a solution of catalyst at a concentration of $5 \cdot 10^{-3}$ M were added the freshly distilled

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