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Nucleophilic Substitution of Chlorine in Haloid Ethers and Study of their Bactericide Properties

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ABSTRACT: There action of nucleophilic substitution of halogen inβ-haloid ethers was studied. It was established that halogen ethers easily interact with diethylamine, morpholine and other nucleophiles. The reaction nucleophiles with dihalogenethers at the ratio of dihalogenether and amine 1:2,5leads to diamine ethers. Nucleophilic activity of reagentshaveadecisive role in reactivity of haloid ethers in the reactions with nucleophiles. Mobility of halogen increases a sitisre moved from oxygen atom. Synthesized compounds have high antimicrobial activity.

KEYWORDS: haloid ethers, alkylamines, spiroundecane, chloride diamylmorpholinium, dialkyldiamine ethers, bactericide

I. INTRODUCTION

Recently haloid ethers have been widely involved in the reactions which lead to multifunctional compounds. This is explained by specific reactivity of this class in the reactions of nucleophilic substitution of haloides with amines, as well as essential increase of practical value of their synthesis. They are frameworks in the construction of many classes of natural compounds and bioactive substances. Ether which contains isothiazolepolyurethane is antimicrobial agent against mcrobacteria [1]. According to authors[2], derivatives of 1-N-vinylpirimidinedion are analogs of nucleotides.

It was established that N-sulphonylcycloamino-2-carbohydroxyamide derivatives are inhibitors of metalloprotease [3]. The interaction of some 2,2-dihalogenethers with dialkylamines which contain 8-12-carbon atoms, was studied [4]. Reactivity of haloid ethers, particularly, depends on the nature of halogen: bromium atom is substituted more easily than chlorine.

Earlier the interaction of dihalogenethers with hydrazine-[5] and dimethylamine was studied [6]. It was established that [7], the reactions of 1,5-dichlorine-2-ethyl-3 oxapentane and 1,5-dibromium-2-methyl-3-oxapentane with morpholine proceed very easily. Thus, relevant azospiroundecanehalogenides (quaternary ammonium salts) are formed. It turned out that during the reactions of 1,5-dibronium-3-oxapentane, 1,5-dibromium-2-methyl- (or ethyl-, ordiethyl-) 3-oxapentanes with pyrrolidone analogues quaternary ammonium salts – 3-oca-azophenylspirodecanebromides are formed [8].

Morpholine derivatives were obtained by the reaction of 1,5-dibromium substituted alkylethers with substituted dialkylamines [9].

Considering high antiarrhythmic [10]and receptor [11] properties different methods of their obtaining have been developed [12-14].

II. EXPERIMENTAL PART

IR-spectra of obtained aminoalkylethers were registered on spectrophotometer «Nicolet İS 10»,PMR-spectra were registered on spectrophotometer «Bruker-250».

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3-Benzyl-2-(2-haloidcyclohexyloxy)-alkylamines (Ia, b, IIa, b).General technique. 0.05 mol of 1-haloid-2-haloidcyclohexyloxy-3-phenylpropane and 0.065 mol of diethylamine or morpholine and 50 ml of propyl alcohol were heated 6 hours during mixing. Then 0.011 mol of potassium hydroxide in 30 ml of propyl alcohol was added into cooled mixture.The precipitate was filtered. After removing isopropyl alcohol and residues of amine during obtaining of crystalline product it was crystallized from acetone, but in obtaining of liquid product it was distilled under vacuum. Physical and chemical properties of compounds IaandIb are given in the table 1.

The compounds IIaandIib were obtained using a similar method. However, for increasing the output the reaction mixture was heated for 18 hours. Their chracteristics are given in the table 1.

2-Chlorine-2-benzyl-3-oxa-7-diethylaminoheptane (III). 26.1 g of (0.1 mol) 1,7-dichlorine-2-benzyl-3-oxaheptane, 10.25g of (0.14 mol) diethylamine and 70-80g ofpropyl alcohol were heated while mixing for 18 hours at 95-100^{o}C. Then the mixture was cooled, the solution of 5.6 g of (0.1 mol) calium hydroxide was added into 30 ml of propyl alcohol, crystals (KCl) were filtered. After distillation the filtrate of propylate and diethylamine were distilled under vacuum. Physical and chemical features are given in the table 1.

4,9-3-Alkyl-4,9-dioxa-6-aza-spiroundecanehaloides (IVa-g).General technique. The mixture of 0.1 mol of relevant dihaloidether, 0.2 mol of morpholinium and 50 ml of propyl ether was boiled while mixing for 18-20 hours. After distillation of propanol solid precipitate is a product of chloride salt of morpholinium. The mixture was dissolved in 30 ml of methyl alcohol and the solution of 0.1 mol of KOH was added in methyl alcohol for separation of morpholinium salt.Crystals were filtered.After distillation of methanol the crystals were crystallized from the mixture of hexane and methanol (1:1). Melting temperature, outputs and results of analysis are given in the table 1.

4,4^{1}-Diamylmorpholinium chloride(V).1.7g of 1-chlorine-5-iodine-3-oxapentane, 15.7 g ofdiamylamine and 35 g of butyl alcohol were boiled while mixing for 15-18 hours, cooled till 35-40^{o}C,the solution of 2.8g of KOHin 10 ml of butanol was added. The crystals KJ were filtered, the filtrate was boiled over calcium oxide. After removing butyl alcohol and residue of diamylamine, crystalline precipitate was crystallized from acetone. Physical and chemical properties of the compound V are given in the table 1.

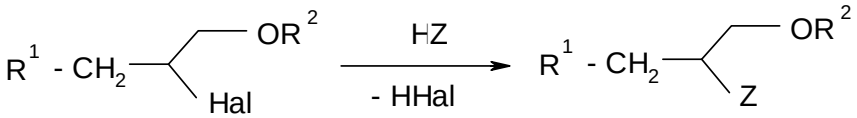
Synthesis of dialkyldiaminoethers(VIa-e). In the ratio ofhaloidethers and secondary amines 1:3÷4, they were dissolved in toluene or xylene and the reaction was conducted at120-150^{o}Cfor 10-12 hours.

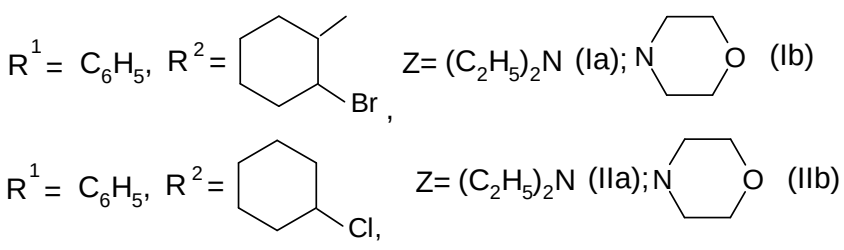
The solution was filtered, the solvent was distilled, the residue was distilled under vacuum. Physicalandchemicalpropertiesaregiveninthetable1.

In PMR-spectra of 1,7-diphenyl-3-oxaheptyldiamine (VIf) protons of two methylene groups (CH_2N) appear in the form of singlet in the field of 1.4 ppm. Protons of methylene groups connected to oxygen and nitrogen atoms are observed in nonseparated form in the range of 2.5-3.7 ppm, but protons of two aromatic fragments are in the range of 6.2-7.1 ppm. Integral intensity conforms to the amount of protons in the compound(VIf).

III. RESULTS AND DISCUSSION

We performed the reaction of nucleophilic substitution of halogen atoms in haloidethers which contain aromatic dialkyl and cyclohexane radicals:





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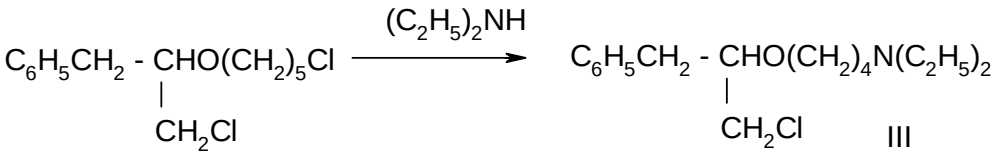
Inertness to nucleophilic substitution of halogen atoms in the compoundsIa, band cof cyclohexane fragment is explained by the fact that according to SN_2-mechanism nucleophile for substitution attacks from backside, however this side is screened with methylene group and that's why is hardly substituted.

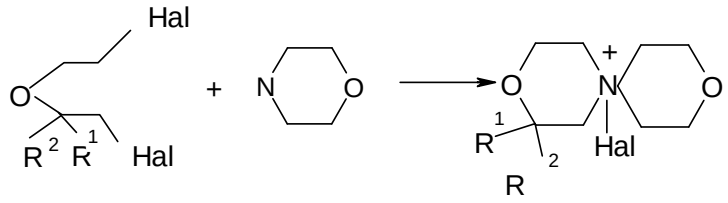
The substitution of a chlorine atom is observed during the interaction of 1,7-dichlorine-2-3-oxaheptane with diethylamine:



III

According to literature data[11],as oxygen atom is removed, halogen mobility increases, but space isolation of reactionary centers prevents cyclization and formation of cyclic ammonium salt.

The reaction of nucleophilic substitution of haloids in dihaloidethers with amines was studied. 3,9-dioxa-6-azospiroundecanehaloids are formed during interaction of 1,5-dihaloid-3-oxa-2,2-dialkylpentane with morpholine:



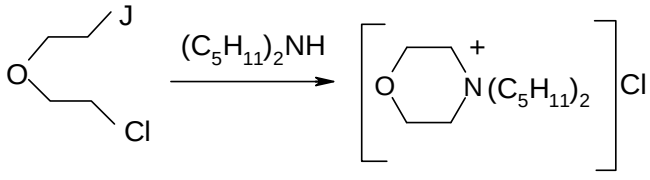
$R^1 = R^2 = H$, Hal = Cl (IVa), $R^1 = R^2 = H$, Hal = Br (IVb),

$R^1 = H$, $R^2 = CH_3$, Hal = Br (IVc); $R^1 = H$, $R^2 = C_2H_5$, Hal = Br (IVd);

$R^1 = R^2 = CH_3$ Hal = Br (IVe), $R = H$, $R^2 = CH_3$, Hal = Cl (IVf);

$R = H$, $R^2 = C_2H_5$, Hal = Cl (IVg)

The reaction of 1,5-dihaloid-3-oxapentane with diamylamine also leads to formation of quaternary ammonium salts of morpholinium:



V

In a case when aminogroup is removed from ether group, only diamine derivatives are formed in the reaction of amines with ethers:

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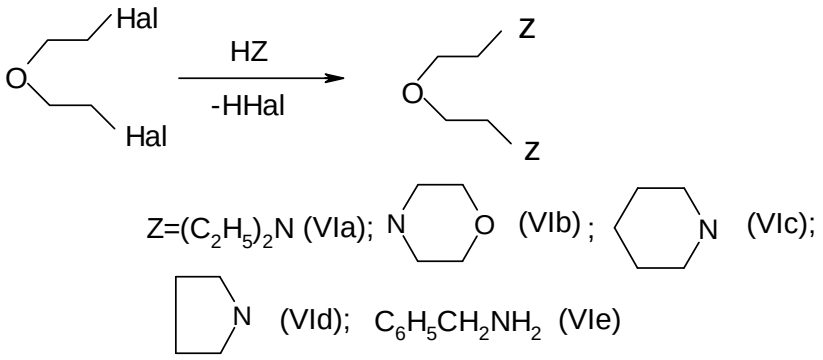

Antimicrobial activity of compoundsI-VI was studied. It was determined using a method of serial dilutions in sterile distilled water relative to gram-positive (Staphylococcus aureus)and gram-negative (P. Aeroginosa,E.coli) bacteria,as well as to fungi (Candida, C.aevicans). Dilution was begun from 500 mkg\ml. Culture was performed after 10, 20, 40 and 60 minutes. Duration of incubation in thermostat for bacteria at 37°Cwas 24 hours, for fungi - 48 hours at 28°C. The results are given in table 2.

As table 2 shows dialkyldiamineethers have high bacteriostatic properties. Minimum inhibitory concentration (MIC) is 15,6 - 31,2 mkg\ml for S.aureus, for fungi C.aevicans - 62,5 - 125 mkg\ml. By bactericide activity morpholinium derivatives are more effective than substances which contain diethylamine and piperidinic fragments.

Table 2.Antimicrobial activity of compounds I-VIby serial dilution method (MICinmkg/ml)

№№	S.aureus	P. Aeroginosa	E.coli	C.aevicans
Ia	31,2	62,5	250	15,6
IIв	62,5	250	500	62,5
III	48,5	200	150	19,5
IVв	35,8	150	200	32,4
IVe	41,8	200	250	69,5
V	71,6	150	300	72,3
VIв	96,9	250	200	46,6
VIc	69,4	200	350	39,5
VId	82,5	350	400	100

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