SYNTHESIS AND BIOLOGICAL INVESTIGATION OF SOME DIMETHYLAMINOALKYL ESTERS OF BENZHYDROL

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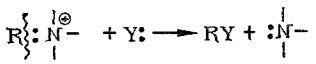
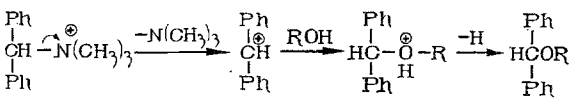
It is known that benzhydrylamino esters possess pharmacological activity particularly of the antihistamine or antispasmodic type [1].

We have studied the effect of lengthening the aminoalkanol chain on the activity mentioned. With this aim the hydrochlorides and methiodides of the obtained amino esters have been synthesized and investigated.

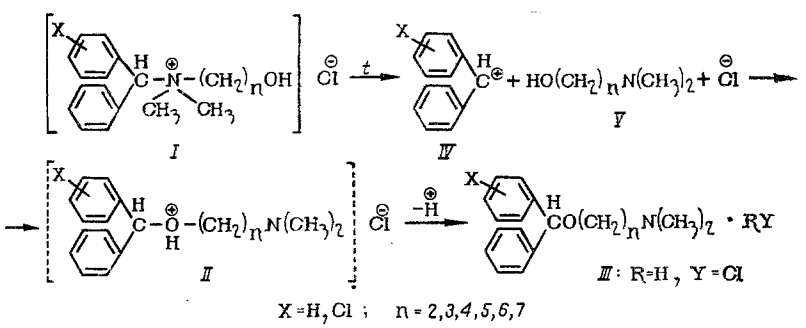
The intramolecular rearrangement of ammonium salts (I) into amino ether hydrochlorides (III) has been studied during the synthetic process by the methods of thin layer and gas–liquid chromatography (GLC) and NMR spectroscopy [2]. It is known that alkylation by compounds of ammonia [3] is a reaction of heterolytic substitution [4]



and that transfer of a radical from the ammonium nitrogen to the molecule of the substance being alkylated (alcohol) takes place asynchronously [5] through the formation of carbonium ions



On the basis of this and also of the experimental data obtained we came to the conclusion that the main route (A) of the reaction, after the thermal heterolytic fission of the ammonium salt, included the interaction of the benzhydryl carbonium ion with the nucleophile (oxygen) by the elimination of a proton and its transfer from oxygen to nitrogen with the formation of an amino ether hydrochloride (III):



X = H, Cl; n = 2,3,4,5,6,7

Results are given in Tables 1 and 2 on the rearrangement of ammonium salts (I). As is seen, in addition to the main product (III), the amino alcohol (V), benzhydryl chloride (VI), benzhydrol (VII), and dibenzhydryl ether (VIII) were isolated; bisdimethylaminoalkyl ethers (IX) and tetraphenylethane (X) were detected chromatographically, the reason for the formation of which required special study. Analysis with the aid of gas–liquid chromatography (GLC) of extracts of acid and alkaline treatment confirmed thin layer chromatographic data.

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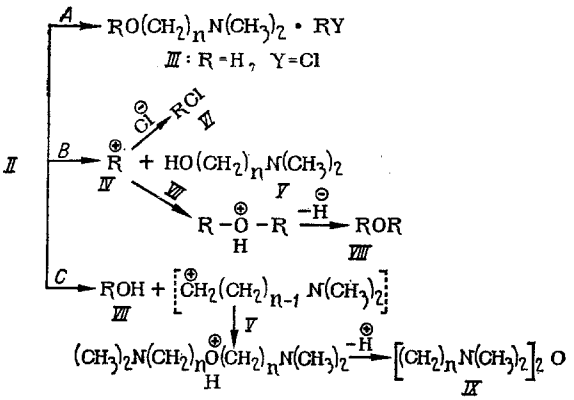
As an example the analysis of the products of rearrangement of (I) where X is H and n is 5 may be cited (Fig. 1). In addition to the main (A) direction of the reaction the secondary reaction routes (B) and (C) for the fission of (II) are possible and if $XC_6H_4CHC_6H_5$ is designated as R it is possible to draw the following scheme:



The course of the reaction was also observed by NMR spectroscopy in the case of (I) where X = H and n = 2. Spectra were taken after 2, 5, 10, 20, and 30 min from the start of heating (t = 175°).

The ratio of the concentrations of the initial quaternary salt (I) (Fig. 2A) and the resulting (III) (X = H, n = 2; Fig. 2B) was determined from the integrated intensities of the singlet signals of methine protons observed at 6.77 and 5.43 ppm, respectively. The spectrum taken 2 min from the start of heating (Fig. 3A) comprised a complex group of signals in the 2.33-4.00 ppm region which was assigned to a mixture of starting, final, and intermediate reaction products. At low field, in addition to the signal for the quaternary ammonium salt methine proton (6.77 ppm), the formation of two signals at 6.07 and 5.43 ppm was observed the first of which corresponded to the methine proton of benzhydryl chloride and the second to the methine proton of (III) (X = H, n = 2). After 5 min from the start of heating (Fig. 3B) disappearance of the singlet for the methine proton of the initial ammonium salt was observed which indicated its complete decomposition. Further heating led to a reduction of the integrated intensity of the methine group proton signal at 6.07 ppm. A spectrum taken 30 min from the start of heating (Fig. 2B) coincided with the spectrum of (III) (X = H, n = 2).

The presence of the methine proton of benzhydryl chloride in the spectrum (Fig. 3A) may seemingly be explained by generated (IV) reacting concurrently with chloride ion. The benzhydryl chloride obtained in this way reacts with amino alcohol (V) with the intermediate formation of (II) giving the amino ether hydrochloride (III).

It was established that the best yield of amino ether corresponded to a value of n = 4.

To confirm the proposed reaction scheme and to exclude the possibility of a bimolecular reaction in which the intermediate carbonium ion (IV) may form an intermediate product at the expense of an oxygen of another molecule of the ammonium salt we carried out rearrangement of a mixture of the two ammonium salts (I) X = H, n = 7 and X = Cl, n = 2. The results of GLC analysis of the extract after alkaline and acidic treatment (Fig. 4) verified the intramolecular course of the reaction. The chromatogram of the extract of alkaline treatment consisted of four peaks attributed to two amino alcohols and two amino ethers and in particular to dimethylaminoheptyl benzhydryl ether (XI) and dimethylaminoethyl p-chlorobenzhydryl ether (XII) which have been synthesized by another route (see Table 1) [6].

On the chromatogram of the extract after acid treatment (see Fig. 4, ac) 7 peaks were obtained (as was to be expected) which belonged to two benzhydryl chlorides, two benzhydrols, two dibenzhydryl ethers, and to tetraphenylethane. GLC analysis of the rearrangement product of (I) (X = Cl, n = 2) carried out separately did not reveal 1,2-di-(p-chlorophenyl)-1,2-diphenylethane in the extract after acid treatment. These data and also the gradual increase in yield of amino ether on going from n = 2 to n = 4 and then its fall indicated that the cyclic or semicyclic constitution of the molecule of the initial ammonium salt (I) evidently was preserved and aided the reaction.

TABLE 1. Dimethylaminoalkyl Ethers of Benzhydrol (I)

X	n	Yield (%)	Boiling point (°C at 1 mm)	d_4^{20}	n_D^{20}	Found, %			Empirical formula	Calculated, %			R_f in system (a)	Melting point of hydrochloride (deg)
						C	H	N		C	H	N		
H	3	61,1	172—3	1,0193	1,5437	80,21	8,54	5,40	$C_{18}H_{23}NO$*	80,25	8,96	5,19	0,56	91—2
H	4	73,3	180—7	0,9889	1,5360	80,35	8,87	5,16	$C_{19}H_{25}NO$*	80,52	8,89	4,93	0,53	101—3
H	5	53,6	198—9	0,9828	1,5311	80,50	8,74	5,02	$C_{20}H_{27}NO$†	80,76	9,14	4,70	0,57	85—7
H	6	53,0	203—4	0,9718	1,5272	81,18	9,56	5,01	$C_{21}H_{29}NO$†	80,95	9,38	4,49	0,59	119—21
H	7	52,2	211—2	0,9637	1,5260	81,49	10,02	4,18	$C_{22}H_{31}NO$	81,18	9,56	4,30	0,58	— ‡
Cl	2	50,0	173—4	1,0892	1,5523	70,94	7,20	4,80	$C_{17}H_{20}ClNO$**	70,46	6,97	4,83	0,55	139—42

Note. Here and in Table 2 for systems (a) and (b) see text.
*Synthesized according to [13].
†Synthesized according to [7].
‡Hygroscopic.
**Synthesized according to [6].

Of the benzhydryl dimethylaminoalkyl ethers with n = 5, 6, and 7 the latter has not been described. The first two have been mentioned in a patent [7]; however the constants of these compounds were not quoted.

Biological investigation of the described compounds was carried out on the hydrochlorides and methiodides. Antihistamine properties, peripheral and central cholinolytic, and also antispasmodic and antimicrobial actions were studied.

Antihistamine action was studied on lengths of guinea pig ileum, and peripheral cholinolytic action was tested on pieces of cat intestine. The concentrations of perparations reducing spasms caused by histamine and the acetylcholine contraction by 50% were calculated statistically by regression analysis [8] on a Nairi-2 computer. The activity of compounds was compared with the known preparation dimedrol. Central cholinolytic action was studied in experiments on mice in relation to arecoline tremor and nicotine convulsions, antispasmodic by antagonium with corazole and by the ability to prevent the tonic phase of maximal electroshock.

It was established that all the studied compounds possessed marked antihistamine and cholinolytic properties. Depending on the change in number of methylene groups the ability of the compounds to prevent spasm of smooth muscle caused by histamine changed. This proved to be the greatest at n = 2 or 3. Further increase in the size of n up to 7 led to a gradual fall in activity (Table 3). The hydrochlorides of all the compounds were more active than the methiodides. On analyzing the action of preparations in relation to acetylcholine spasm the most active compound proved to be the methiodide of benzhydryl γ-dimethylaminopropyl ether. A comparative quantitative assessment of the antihistamine activity did not reveal significant advantages of the studied compounds over dimedrol.

It was also established that the hydrochlorides of dimethylaminoalkyl benzhydryl ethers possessed antimicrobial action *in vitro* against *Staphylococcus aureus* strain 209 p. The most active compound proved to be the hydrochloride of dimethylaminoheptyl benzhydryl ether, the concentration for maximal inhibition of growth (MIC) of which was 40 μg/ml, the least active was the hydrochloride of dimethylaminoethyl benzhydryl ether with an MIC of 1250 μg/ml. All the quaternary ammonium salts (I) (from n = 2 to n = 7) [9] were more active than the corresponding (III). For example if n = 2 the quaternary salt (I) inhibited the growth of *Staphylococcus aureus* at a concentration of

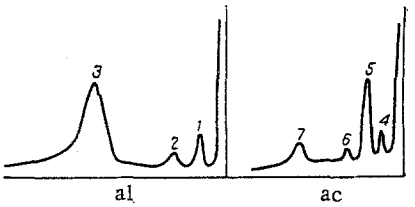


Fig. 1. Chromatogram of ether extracts after alkaline (al) and acidic (ac) treatment of products of rearrangement of (I) (X = H, n = 5). 1) 5-Dimethylaminopentanol; 2) bisdimethylaminoamyl ether; 3) dimethylaminoamyl ether of benzhydrol; 4) dibenzhydryl ether; 5) benzhydryl chloride; 6) tetraphenylethane; 7) benzhydrol.

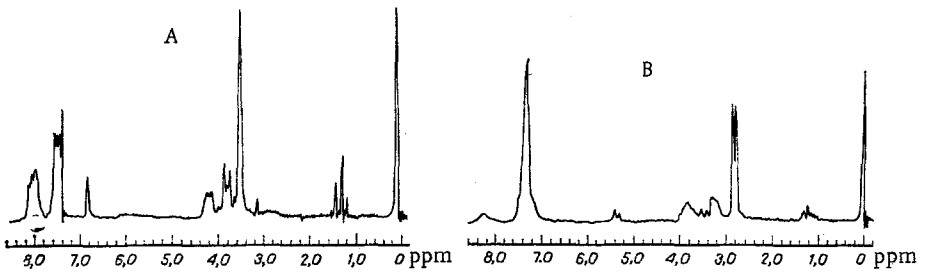
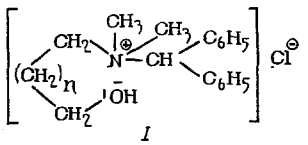


Fig. 2. PMR Spectrum of A) compound (I) and B) compound (III).

TABLE 2. Results of Rearrangement of Compounds (I)



I

X	n	Yield of by-products from rearrangement reaction (%)				R_f					
						system (a)			system (b)		
		V	VI	VII	VIII	VI	IX	V	VII	VIII	X
H	3	10,1	17,1	2,2	2,9	0,41	0,14	0,95	0,79	0,86	0,97
H	4	8,2	9,8	2,0	2,1	0,36	0,20	0,94	0,80	0,87	0,98
H	5	13,4	14,5	2,5	2,1	0,32	0,18	0,96	0,82	0,88	0,97
H	6	12,0	16,0	1,2	1,1	0,39	0,19	0,95	0,80	0,89	0,98
H	7	12,8	17,3	0,9	1,4	0,36	0,24	0,94	0,83	0,87	0,98
Cl	2	5,6	12,7	1,6	2,9	0,35	0,20	0,89	0,76	0,86	—

10.6 μg/ml and the corresponding (III) inhibited growth of the same microorganism at a concentration of 84.8 μg/ml.

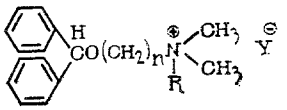
EXPERIMENTAL

NMR spectra were taken on a Varian-60 instrument in deuterochloroform; tetramethylsilane was used as internal standard.

IR spectra were taken on a UR-20 spectrophotometer with a prism for paraffin oil pastes.

GLC analysis was carried out in a Khrom-4 chromatograph with a flame ionization detector in mobile phase polyethylene glycol (PEG) 6%, suspended on chromaton (0.2-0.25 mm), treated with 1% potassium hydroxide, temperature was 140-180°C, column length was 1.2 m, and diameter 3 mm. The carrier gas was nitrogen, flow rate 22-42 ml/min, and sensitivity was 1:50.

TABLE 3. Antihistamine and Cholinolytic Activity of Compounds (III) in Experiments on an Isolated Length of Cat Intestine



n	R	I	Concentrations reducing histamine spasm by 50% (g/ml), P = 0.05	Concentrations reducing an acetylcholine contraction by 50% (g/ml), P = 0.05
2	H	Cl	$7{,}3 \cdot 10^{-9}$ ($3 \cdot 10^{-9} \div 14 \cdot 10^{-9}$)	$3 \cdot 10^{-8}$ ($2 \cdot 10^{-8} \div 6 \cdot 10^{-8}$)
2	CH_3	I	$5 \cdot 10^{-8}$ ($4 \cdot 10^{-8} \div 7 \cdot 10^{-8}$)	$5{,}3 \cdot 10^{-7}$ ($1{,}8 \cdot 10^{-7} \div 15 \cdot 10^{-7}$)
3	H	Cl	$8{,}1 \cdot 10^{-9}$ ($4{,}7 \cdot 10^{-9} \div 14{,}1 \cdot 10^{-9}$)	$3{,}1 \cdot 10^{-7}$ ($1{,}3 \cdot 10^{-7} \div 7{,}3 \cdot 10^{-7}$)
3	CH_3	I	$4 \cdot 10^{-7}$ ($2 \cdot 10^{-7} \div 1 \cdot 10^{-6}$)	$6 \cdot 10^{-9}$ ($2 \cdot 10^{-9} \div 17 \cdot 10^{-9}$)
4	H	Cl	$1{,}6 \cdot 10^{-7}$ ($1 \cdot 10^{-7} \div 2{,}3 \cdot 10^{-7}$)	$3{,}7 \cdot 10^{-6}$ ($2{,}2 \cdot 10^{-6} \div 6{,}3 \cdot 10^{-6}$)
4	CH_3	I	$3 \cdot 10^{-7}$ ($2{,}1 \cdot 10^{-7} \div 4{,}1 \cdot 10^{-7}$)	$1{,}4 \cdot 10^{-7}$ ($0{,}7 \cdot 10^{-7} \div 2{,}6 \cdot 10^{-7}$)
5	H	Cl	$3 \cdot 10^{-8}$ ($2 \cdot 10^{-8} \div 4 \cdot 10^{-8}$)	$3{,}1 \cdot 10^{-7}$ ($1{,}5 \cdot 10^{-7} \div 6{,}2 \cdot 10^{-7}$)
5	CH_3	I	$1{,}13 \cdot 10^{-6}$ ($0{,}5 \cdot 10^{-6} \div 2{,}57 \cdot 10^{-6}$)	$1{,}68 \cdot 10^{-6}$ ($1{,}17 \cdot 10^{-6} \div 2{,}4 \cdot 10^{-6}$)
6	H	Cl	$4{,}6 \cdot 10^{-7}$ ($2{,}3 \cdot 10^{-7} \div 9{,}1 \cdot 10^{-7}$)	$6 \cdot 10^{-8}$ ($3{,}1 \cdot 10^{-8} \div 12 \cdot 10^{-8}$)
6	CH_3	I	$0{,}77 \cdot 10^{-6}$ ($0{,}29 \cdot 10^{-6} \div 2 \cdot 10^{-6}$)	$1{,}2 \cdot 10^{-7}$ ($0{,}7 \cdot 10^{-7} \div 1{,}2 \cdot 10^{-7}$)
7	H	Cl	$1{,}23 \cdot 10^{-6}$ ($0{,}7 \cdot 10^{-6} \div 2{,}1 \cdot 10^{-6}$)	$7 \cdot 10^{-8}$ ($4 \cdot 10^{-8} \div 13 \cdot 10^{-8}$)
7	CH_3	I	$3{,}3 \cdot 10^{-6}$ ($2 \cdot 10^{-6} \div 5{,}6 \cdot 10^{-6}$)	$1{,}2 \cdot 10^{-8}$ ($0{,}7 \cdot 10^{-8} \div 2 \cdot 10^{-8}$)

Note. Limits of variation are in parentheses.

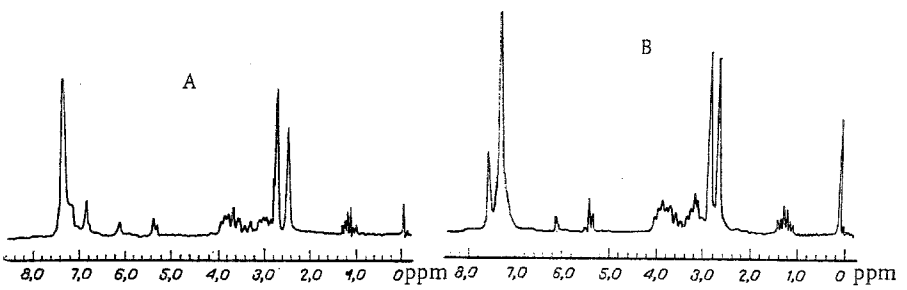


Fig. 3. PMR spectrum of compound (I) after A) 2 min and B) 5 min from the start of heating.

The initial dimethylaminoalkanols (n = 5, 6, and 7) were synthesized by a known method [10], and the ammonium salts were obtained by a method described previously [9]. The dibenzhydryl and bisdimethylaminoalkyl ethers were synthesized in the alternative way [11, 12].

Rearrangement of ammonium salts (I) was effected at a temperature of 175° for 30-45 min. After cooling, the reaction mixture was treated with 9% hydrochloric acid and extracted with ether, the extract from acid treatment was subjected to chromatography on a thin layer of silica gel bound with gypsum in a mobile phase (b) of petroleum ether:ether (16:24) with visualization with iodine vapor (see Table 1). To the aqueous acid layer alkali was added and the product was extracted with ether, the extract from alkaline treatment was subjected to chromatography on a silica gel thin layer bound with gypsum in solvent system (a) n-butanol:ethanol:acetic acid:water (8:2:1:3). Characteristic absorption bands were present in the 1080-1100 cm^{-1} (—O—) and 1500-1600 cm^{-1} (benzene ring) regions of the IR spectra of the amino ethers (n = 3-7).

Rearrangement of a Mixture of (I) (X = H, n = 7) and (I) (X = Cl, n = 2). A mixture of (I) (X = Cl, n = 2) (3.2 g: 0.1 mole) and (I) (X = H, n = 7) (3.6 g: 0.1 mole) was heated at 175° for 40 min. The reaction product was treated as indicated above. The ether extracts of acidic and alkaline treatment were analyzed by GLC (Fig. 4). Solvent was distilled from

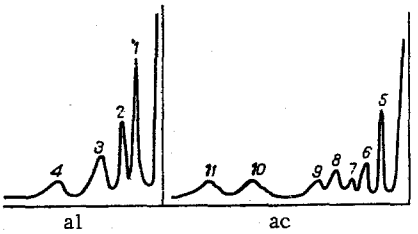


Fig. 4. Chromatograms of ether extracts after alkaline (al) and acidic (ac) treatment of the rearrangement products of the mixture of ammonium salts (I) (X = Cl, n = 2) and (I) (X = H, n = 7). 1) Dimethylaminoethanol; 2) 7-dimethylaminopentanol; 3) dimethylaminoethyl p-chlorobenzhydryl ether: 4) dimethylaminoheptyl benzhydryl ether; 5) p-chlorobenzhydryl chloride; 6) benzhydryl chloride; 7) tetraphenylethane; 8) p-chlorobenzhydryl ether; 9) dibenzhydryl ether; 10) p-chlorobenzhydrol; 11) benzhydrol.

the extract from alkaline treatment and the residue was redistilled in vacuum. Four fractions were taken: First fraction 40-60°/1 mm; second fraction 100-110°/1 mm; third fraction 173-174°/1 mm (XI); fourth fraction 190-194°/1 mm (XII). The yields of amino ethers amounted to 52% (XI) and 44.9% (XII).

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