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PREPARATION OF 1-AMINO-4-METHYLPIPERAZINE

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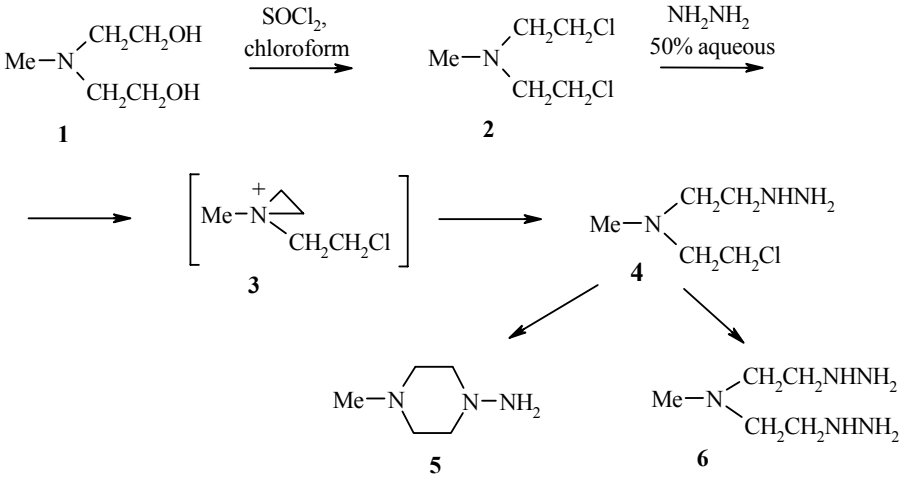
The selectivity of the formation of N-di(2-chloroethyl)methylamine in reactions with various chlorinating agents has been investigated and the optimum chlorinating agent has been found. 1-Amino-4-methylpiperazine has been obtained for the first time by the cyclization of N-di(2-chloroethyl)methylamine with aqueous hydrazine. A possible mechanism has been proposed for the cyclization reaction.

Keywords: 1-amino-4-methylpiperazine, haloalkylamines, N,N-di(2-chloroethyl)methylamine, N-(2-chloroethyl)-N-methylaziridinium chloride, N-(2-chloroethyl)-N-(2-hydrazinoethyl)methylamine.

1-Amino-4-methylpiperazine (**5**) is used widely as an intermediate in the synthesis of medicinal preparations [1]. Several methods of obtaining it are known.

The industrial application is a two-stage method of synthesis, starting from piperazine with subsequent nitrosation and reduction [2,3]. However this method has several drawbacks, mainly its low selectivity, the high toxicity of the intermediate products, and the difficulty of isolating the desired product [3].



The method of synthesis developed by us also contains two stages, the chlorination of methyldiethanolamine (**1**) and subsequent cyclization of N,N-di(2-chloroethyl)methylamine (**2**) in aqueous hydrazine. When carrying it out we investigated the selectivity of forming compound **2** in reactions with various

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chlorinating agents and the dependence of the completeness of the cyclization reaction on the ratio of compound **2** and 50% aqueous hydrazine.

The chlorination of diethanolamine **1** has been studied in a fairly detailed manner [4-6]. On interacting compound **1** with gaseous hydrogen chloride at 120°C, with phosgene, and with phosphorus trichloride, the target product **2** is formed in only trace amounts [4]. The use of thionyl chloride as chlorinating agent leads to the formation of chloro derivatives in almost quantitative yield (95%) [5, 6]. Regretably there is no systematic investigation in the literature of the effect of various factors on the yield of the target product, which does not enable a conclusion to be drawn on the optimal conditions for carrying out the synthesis.

We have investigated experimentally the effect of the solvent on the selectivity of the chlorination reaction, and have also studied by mathematical planning the dependence of the yield of compound **2** on the reaction temperature, the concentration of compound **1** in solution, and the molar ratio of $SOCl_2$ and compound **1**. In the course of the investigation we established that chloroform (yield of product **2** 95%) is the best of the solvents used (chloroform, chlorobenzene, trichloroethylene, benzene, toluene). As a result investigation of the effect of the remaining factors on the yield of chloro derivative **2** was carried out in chloroform. Analysis of the results of the mathematical treatment of the experiment showed that the yield of compound **2** essentially depends only on the molar ratio of $SOCl_2$ and compound **1**. The maximum yield of product (95.6%) was observed at $SOCl_2$:**1** equal to 3:1.

It has therefore been established that the chlorination of compound **1** with thionyl chloride proceeds in the best yield in chloroform at a molar ratio of reactants of 3:1.

Numerous investigations of the conversion of haloalkylamines on interaction with N-nucleophiles in aqueous alkaline medium or in the nucleophile showed that it proceeds according to a general scheme through the formation of an aziridinium ion [7]. However, on going over to di(2-haloalkyl)amines competition at ring closure is possible with the formation of three- and six-membered rings [3].

Although the reaction to obtain nitrogen-containing heterocycles by the interaction of haloalkylamines of general formula $RR^1NCH_2CH_2Cl$ with N-nucleophiles is not new [8], we obtained 1-amino-4-methylpiperazine **5** by the reaction of dihaloamine **2** with aqueous hydrazine solution for the first time.

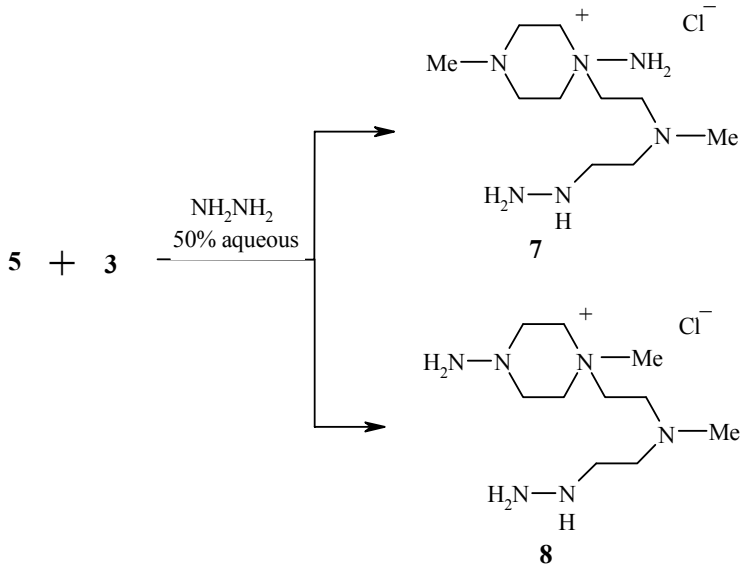
We carried out a series of investigations on the interaction of dichloro derivative **2** with aqueous hydrazine solution at a substrate **2** ratio to 50% N_2H_4 of 1:50, 1:10, and 1:5 at 20-30°C. It should be noted that the system of dihaloamine **2**:aqueous hydrazine was two-phase when using molar ratios of reactants less than 40:1. Visually the reaction mixture becomes homogeneous only after 90% conversion of compound **2**. In the case of two media the interaction of dihaloamine **2** with hydrazine is possible both in aqueous and in organic media. We have investigated the dynamics of the change of chloride ion concentration in the organic layer after mixing the reactants. The data obtained enable us to assert with a definite degree of probability that the reaction proceeds only in the aqueous hydrazine medium. Our investigations established that the maximum yield of cyclization product **5** (87%) was achieved at a ratio of substrate **2** to 50% N_2H_4 of 1:10.

Analysis of the reaction mixture using data of GLC, chromato-mass spectrometry, and ^{13}C NMR spectra showed that, in addition to the target product **5**, a series of contaminants is formed, which we have identified.

In particular, di(2-hydrazinoethyl)methylamine (**6**) (up to 2%) was detected by chromato-mass spectrometry, and at a degree of conversion of substrate **2** <80% N-(2-chloroethyl)-N-(2-hydrazinoethyl)methylamine (**4**) was established to be present in the reaction mixture (Scheme 1).

Our investigations permit a possible mechanism to be proposed for the cyclization of compound **2** in aqueous hydrazine through the formation of the reactive intermediate **3**. In addition to the identified compounds **4-6**, after distilling off the desired product **5**, substances remained in the still which we attribute to quaternary ammonium bases **7** and **8**. The latter are most probably formed by secondary reactions between the target compound **5** and the reactive compound **3**.

Scheme 1



EXPERIMENTAL

The ^{13}C NMR spectra were recorded on a Bruker DPX-200 (50 MHz) spectrometer, internal standard was D_2O.

The elemental composition of compounds was determined by high resolution mass spectrometry on a Varian MAT 311A instrument, the gas was xenon, accelerating voltage 2-6 kV, current 0.1-0.5 mA, resolution 30,000. A check on the progress of reaction was effected by TLC on Silufol UV 254 plates, eluent chloroform–hexane, 2:1 or chloroform–methanol, 9:1.

N,N-Di(2-chloroethyl)methylamine Hydrochloride (2). Solution of thionyl chloride (40.5 g, 30 mmol) in chloroform (120 ml) was added dropwise with vigorous stirring to solution of methyldiethanolamine **1** (11.9 g, 10 mmol) in chloroform (120 ml). The reaction mixture was kept at room temperature for 2 h, and chloroform then removed at atmospheric pressure. The residue was recrystallized from 2-propanol. Yield 14.9 g (96%); mp 108-110°C (110°C [6]). Mass spectrum (EI, 70eV), *m/z* (I_{rel}, %): 192 (12.5) $[M]^+$, 157 (10.2) $[M\text{-}Cl]^+$, 122 (35.3) $[M\text{-}2Cl]^+$. Found, %: C 31.23; H 6.17; N 7.32 $C_5H_{12}Cl_3N$. Calculated, %: C 31.19; H 6.28; N 7.28.

1-Amino-4-methylpiperazine (5) was obtained by the method of [9]. Yield 26.5 g (87%); bp 128-131°C (13 mm Hg). ^{13}C NMR spectrum, δ, ppm: 57.51 (NCH_2); 54.15 (CH_2N); 45.01 (CH_3). Mass spectrum (EI, 70 eV), *m/z* (I_{rel}, %): 116 (5.5) $[M+1]^+$, 115 (79.5) $[M]^+$, 99 (73.9) $[M\text{-}NH_2]^+$, 98 (21.3) $[M\text{-}NH_3]^+$, 58 (20.6) $[M\text{-}CH_3N(CH_2)_2]^+$, 57 (24.5) $[M\text{-}NH_2N(CH_2)_2]^+$. Found, %: C 52.58; N 11.21; N 36.39. $C_5H_{13}N_3$. Calculated, %: C 52.14; H 11.38; N 36.48.

REFERENCES

1. B. T. Golding and M. J. Kebbell, *J. Chem. Soc., Perkin Trans. 2*, 1859 (1988).
2. P. D. Barleff, S. D. Ross, and C. C. Swain, *J. Am. Chem. Soc.*, **69**, 2971 (1947).
3. V. S. Borisenko, V. A. Bobylev, and G. F. Tereshchenko, *Zh. Obshch. Khim.*, **55**, 1141 (1985).

4. H. W. Vallender and F. M. Woodward, *J. Am. Chem. Ind.*, **68**, 280 (1949).
5. K. A. Jensen and F. Lundquist, *Dansk Tid. Farm.*, **15**, 201 (1941).
6. K. Ward, *J. Am. Chem. Soc.*, **57**, 914 (1935).
7. V. A. Surkin, I. G. Zenkevich, P. S. Lobanov, and A. A. Potekhin, *Zh. Org. Khim.*, **19**, 2288 (1983).
8. S. M. Rida, A. S. Issa, and Y. A. Beltagy, *Pharmazie*, **33**, 711 (1978).
9. P. M. Kushakova, V. A. Kuznetsov, A. N. Chernobroviy, and A. V. Garabadgiu, *Khim. Geterotsikl. Soedin.*, 1111 (2004).