INVESTIGATION OF 2,6-DICHLOROJULOLIDINES AND 1-ARYL-2,5-DI(CHLOROMETHYL)PYRROLIDINES

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9-Substituted 2,6-dichlorojulolidines and 1-aryl-2,5-di(chloromethyl)pyrrolidines – alkylating compounds with alkylating centers in fixed positions – were synthesized, and their basicities and rates of hydrolysis were determined. The relationship between the structure, basicity, and rate of hydrolysis of these compounds is discussed.

Among the numerous alkylation reactions that determine the biological activity of arylbis(2-chloroethyl)amines, the reaction with nucleic acids, including the formation of transverse bonds between the individual DNA filaments, is of great significance. In this case, the three-dimensional orientation of the alkylating centers of bis(2-chloroethyl)amine may vary within definite limits due to free rotation about the C–C and C–N bonds, such that the distance between them becomes close to the distance between the nucleophilic centers of the DNA helixes. To obtain information regarding the reaction conditions and the character of the bond formed during the reaction of the alkylating compounds with the nucleic acids, it seems of interest to investigate compounds with fixed spatial orientations of the alkylating centers. One of the first studies in this area was an investigation in which it was possible, although with great difficulty, to synthesize 1-polybromoaryl-3,4-dibromopyrrolidine [1]. A number of chloromethyl derivatives of 1-arylpyrrolidine and 1-arylpiperidine have also been synthesized [2, 3].

In the present paper, we describe the synthesis and properties of compounds that are related to arylbis(2-chloroethyl)amines in which the alkylating centers are included in the heterocyclic systems to restrict their spatial shifting – 2,6-dichlorojulolidines (I) and 1-aryl-2,5-di(chloromethyl)pyrrolidines (II). Compounds I were obtained by cyclization of bis(3-chloro-2-hydroxypropyl)arylamines (III) and subsequent chlorination without isolation of the intermediate hydroxyjulolidines, since considerable difficulties are involved in the isolation [4]. The synthesis of Ic was also accomplished by another route: initial chlorination of dihydroxy compound IIIc with phosphorus oxychloride and subsequent thermal cyclization of dichloro derivative Vc.

1-Phenyl-2,5-di(chloromethyl)pyrrolidine (IIa) was synthesized from 1-phenyl-2,5-di(carbomethoxy)-pyrrolidine (VIa) via the method described in [2, 5, 6]. In this case, it turned out that one chlorinated product (IIa) is obtained from both stereoisomers of VIa [5]. 1-(p-Tolyl)-2,5-di(chloromethyl)pyrrolidine (IIb) was also similarly obtained.

A study of the nitrosation and azo coupling of IIa demonstrated that the paraposition of the benzene ring has reduced reactivity as compared with related noncyclic compounds, for example, N,N-bis(2-chloroethyl) aniline, which can be explained by the decrease in the conjugation of the nitrogen atom with the aromatic ring. The reason for this is disruption of the coplanarity of the system under the influence of a pyrrolidine ring with chloromethyl groups. (See scheme on following page.) The reaction of IIa with potassium thiocyanate gave 2,5-di(thiocyanatomethyl)-1-phenylpyrrolidine which, however, does not form an additional ring with the S – S bonds on treatment with alkaline reagents, as described for bis(2-thiocyanatoethyl)arylamines [8], apparently because of the unfavorable steric conditions.

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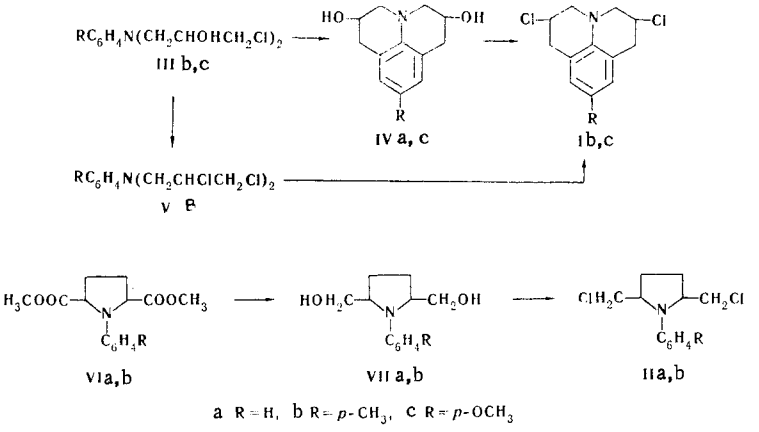
TABLE 1. Basicity Constants and Hydrolysis Rates of Chlorine-Containing Compounds

Compound	pK_a in acetonitrile	Hydrolysis in 50% acetone at 66°C for 30 min: compound concentration, M*	ions formed, %: H^+	ions formed, %: Cl^-
1-Phenyl-2,5-di(chloromethyl)pyrrolidine (IIa)	6,43	0,005	52,1	50,8
1-Tolyl-2,5-di(chloromethyl)pyrrolidine (IIb)†	—	0,005	55,0	54,0
9-Methyl-2,6-dichlorojulolidine (Ib)	6,16	0,0025	10,6	10,1
9-Methoxy-2,6-dichlorojulolidine (Ic)	6,70	0,005	14,1	14,0
N,N-Bis(2-chloroethyl)aniline	7,21	0,01	20,0	20,0
		0,005	20,0	20,0
		0,0025	22,0	22,3

*In view of the low solubility of the investigated compounds in 50% aqueous acetone, the hydrolysis was studied at lower concentrations than those indicated in [9].
†Under nitrogen.

TABLE 2. Basicity Constants of the Starting Amines and Some 2-Hydroxyalkylamino Compounds in Acetonitrile at 25°C

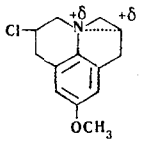
Compound	pK_a	Compound	pK_a
Julolidine	10,85	N,N-Bis(2-hydroxyethyl)aniline	11,11
2,5-Dimethylol-1-phenylpyrrolidine	10,75	N,N-Bis(2-hydroxypropyl)aniline	12,10
		Aniline	10,56[10]



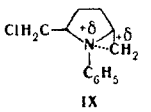
To compare the alkylating ability of the synthesized compounds with that of the previously known 2-chloroalkylamines, we studied the rates of hydrolysis of julolidines I and pyrrolidines II under standard conditions [9, 12] (Table 1). In connection with the fact that the basicity of the nitrogen atom has a substantial effect on the rate of hydrolysis of aryl(2-haloalkyl)amines, we determined the basicity constants of I and II and several starting and intermediate hydroxy compounds (Tables 1 and 2). The determination was carried out with acetonitrile solutions via the method in [10, 11].

The data presented demonstrate that the presence of two chlorine atoms in the 2 position relative to the nitrogen of the aliphatic chain or the heterocyclic ring markedly lowers the basicity of the compound, while the effect of hydroxyl groups is comparatively small. On the basis of the literature data, according to which chlorine atoms attached to the secondary carbon atoms of 2-haloalkylamines are hydrolyzed considerably more readily than primary amines, the presence of methyl and methoxy groups in the paraposition relative to nitrogen also accelerates hydrolysis [9, 12], and one should have expected a high reactivity for 9-alkyl-2,6-dichlorojulolidines (I). However, the rate of hydrolysis of I is in fact lower than that of the noncyclic analog – N,N-bis(2-chloropropyl)aniline. This reduction in reactivity cannot be explained by

the difference in the basicities of the compounds, since 2,5-di(chloromethyl)pyrrolidine (IIa) has a lower basicity and, at the same time, a higher rate of hydrolysis than Ic. The decrease in the stabilization of the intermediate cation (VIII) by virtue of an increased distance between $C_{(2)}$ and nitrogen, which enter into the composition of the rigid heterocyclic system, should be assumed to be the reason for the reduced reactivity of 2,6-dichlorojulolidines.



VIII



IX

The heteroring of the pyrrolidine cation (IX), like acyclic 2-chloroalkylarylamines, does not interfere with the establishment of the optimum distance between the nitrogen and the β-carbon and thereby the achievement of the best stabilization; the presence of a pyrrolidine ring instead of two individual chloroethyl chains may promote an increase in the nucleophilicity of the nitrogen. The fact that the presence of a methyl group in the paraposition of the benzene ring of IIb only slightly increases the rate of hydrolysis is also evidence for weakening of the transmission of the effect of the p-methyl group to the nitrogen atom of the pyrrolidine ring.

EXPERIMENTAL

Thin-layer chromatography on activity II aluminum oxide was used to monitor the reactions and to determine the purities of the products. The solvent systems were as follows: A) benzene – n-hexane (1:1), and B) benzene – methanol (9:1). Iodine was used as the developer. The IR spectra of KBr pellets were recorded with a UR-10 spectrophotometer.

9-Methyl-2,5-dichlorojulolidine (Ib). A mixture of 1.07 g (0.01 mole) of p-toluidine and 1.86 g (0.02 mole) of epichlorohydrin was heated at 140-150° for 9 h under nitrogen. Phosphorus oxychloride [7.5 g (0.05 mole)] was added to the resulting mass; the mixture was heated at 120-123° for 4 h. The mixture was cooled, and the excess $POCl_3$ was decomposed with a 2% sodium carbonate solution. The mixture was extracted with chloroform, and the extract was dried with magnesium sulfate. The chloroform was removed by vacuum distillation, and the residue was chromatographed with a column filled with aluminum oxide with elution by system A. The fraction with R_f 0.9* was collected to give 0.54 g (21%) of a product with mp 119-120° (from ethanol). Found: Cl 27.7; N 5.7%. $C_{13}H_{15}Cl_2N$. Calculated: Cl 27.7; N 5.5%. IR spectrum, cm^{-1}: 622 medium (m), 695 weak (w) (C – Cl).

9-Methoxy-2,5-dichlorojulolidine (Ic). A) This compound was similarly obtained in 23% yield from p-anisidine and had mp 135-136° (from ethanol) and R_f^A 0.9. Found: Cl 27.7; N 5.6%. $C_{13}H_{15}Cl_2NO$. Calculated: Cl 26.1; N 5.2%. IR spectrum, cm^{-1}: 638 m, 695 strong (s) (C – Cl).

B) A solution of 3.08 g (0.01 mole) of N,N-bis(γ-chloro-β-hydroxypropyl)-p-anisidine and 4.5 g (0.03 mole) of phosphorus oxychloride in 15 ml of chloroform was refluxed for 5 h. The excess phosphorus oxychloride was decomposed with 2% sodium carbonate solution. The aqueous solution was extracted with chloroform, and the extract was dried with magnesium sulfate. The chloroform was removed by distillation, the residue was dissolved in 6 ml of tetrachloroethane, and 3 ml of $TiCl_4$ was added to the solution. The mixture was heated at 100-105° for 30 min and cooled. The $TiCl_4$ was decomposed with water, and the aqueous solution was extracted with chloroform. The chloroform extract was worked up in the usual manner to give an oil. The oil was chromatographed with a column filled with aluminum oxide with elution by system A to give Ic, which was identical to the sample described above.

1-Phenyl-2,5-di(chloromethyl)pyrrolidine (IIa). A) A solution of 2.63 g (0.01 mole) of cis-1-phenyl-2,5-di(carbomethoxy)pyrrolidine (VIa) in 50 ml of absolute ether was added dropwise to a solution of 0.95 g (0.025 mole) of lithium aluminum hydride in 30 ml of absolute ether, and the reaction mixture was refluxed for 12 h. It was then cooled, and the excess lithium aluminum hydride was decomposed with 2 ml of 25% potassium hydroxide. The ether layer was dried with magnesium sulfate, and the ether was removed by vacuum distillation to give 1.6 g (77%) of 1-phenyl-2,5-dimethylpyrrolidine (VIIa) as a light-yellow oil

*The upper index indicates the system for which the R_f value is presented.

with R_f^B 0.5. Found: N 6.5%. $C_{12}H_{17}NO_2$. Calculated: N 6.4%, ν_{OH} 3510 cm^{-1}. A 2.07-g (0.01 mole) sample of VIIa was dissolved in 15 ml of chloroform, 7.5 g (0.05 mole) of phosphorus oxychloride was added, and the mixture was refluxed for 2 h and worked up as indicated for I to give 1.76 g (72%) of IIa with mp 80.5-80.7° (from ethanol) (mp 81.5-82° [4]). Found: Cl 29.3; N 5.9%. $C_{12}H_{15}Cl_2N$. Calculated: Cl 29.1; N 5.7%. IR spectrum, cm^{-1}: 650 w, 693 s (C – Cl).

B) A 2.3 g (0.01 mole) sample of trans-VIa was treated as above to give 1.2 g (58%) of IIa with mp 80-80.5° (from ethanol). This product did not depress the melting point of the sample obtained in experiment A.

1-Tolyl-2,5-dimethylolpyrrolidine (VIIb). The reaction of 2.77 g (0.01 mole) of 1-tolyl-2,5-di(carbomethoxy)pyrrolidine (VId) and 0.95 g (0.025 mole) of lithium aluminum hydride was carried out as above to give 1.8 g (81%) of VIIb as a light-yellow oil with R_f^B 0.49. Found: N 6.4%. $C_{13}H_{19}NO_2$. Calculated: N 6.3%.

1-Tolyl-2,5-di(chloromethyl)pyrrolidine (IIb). A 2.19-g (0.01 mole) sample of VIIb was dissolved in 20 ml of chloroform, 7.5 g (0.05 mole) of phosphorus oxychloride was added, and the mixture was refluxed for 2 h. It was then cooled and worked up as indicated for Ib to give 2.06 g (80%) of IIb with mp 99.5-100° (from ethanol). Found: Cl 27.9; N 5.5%. $C_{13}H_{17}Cl_2N$. Calculated: Cl 27.4; N 5.4%.

1-Phenyl-2,5-di(thiocyanatomethyl)pyrrolidine. A solution of 2.44 g (0.01 mole) of IIa and 9.7 g (0.1 mole) of potassium thiocyanate in 75 ml of ethanol was refluxed for 8 h. The ethanol was removed by vacuum distillation, and the residue was washed with water and extracted with chloroform. The extract was worked up in the usual manner to give 2 g (69%) of a product with mp 84.5-85° (from ethanol). Found: N 14.4%. $C_{14}H_{15}N_3S_2$. Calculated: N 14.6%.

4-Nitro-4'-[2,5-di(chloromethyl)-1-pyrrolidinyl]azobenzene. A 2.44-g (0.01 mole) sample of IIa was dissolved in 50 ml of methanol, and a solution of p-nitrobenzenediazonium hydrochloride, obtained from 1.38 g (0.01 mole) of p-nitroaniline, was added. The resulting precipitate was removed by filtration and dried to give 3.25 g (82%) of a product with mp 137-138° (from n-hexane). Found: Cl 18.1; N 14.1%. $C_{18}H_{18}Cl_2N_4O_2$. Calculated: Cl 18.0; N 14.3%.

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