EXPERIMENTAL

The absorption spectra of $5 \cdot 10^{-5}$ M solutions of formazans I were recorded with an SF-4A spectrophotometer, and the absorption spectra of $1 \cdot 10^{-4}$ M solutions of I in alcoholic KOH and concentrated H₂SO₄ were recorded with an SF-10 spectrophotometer.

The Rf values of the formazans were determined on Silufol plates in an ethanol-chloroform-hexane system (3:5:10).

1-(1'-Phthalaziny1)-3,5-diphenylformazan (Ia). Sodium hydroxide solution (2 N) was added dropwise to a cooled mixture of solutions of 1.24 g (5 mmole) of benzaldehyde 1-phthalazinylhydrazone [8] in 40 ml of DMF and (5 mmole) of benzenediazonium chloride in 20 ml of 18% HCl in such a way that the temperature of the solution did not exceed 0°C. The mixture was allowed to stand for 2 h, after which it was diluted with a threefold amount of water and neutralized to pH 7. The resulting red precipitate was removed by filtration, washed with water, and dried to give 1.4 g of product. The formazan was purified by chromatography with a column filled with Al₂O₃ by elution twice with benzene. The excess solvent was removed by vacuum distillation, and the residue was crystallized. Compounds Ib,c,f were eluted with benzene, Id was eluted with propanol, and Ie was eluted with dioxane. Data on I are presented in Table 1.

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SYNTHESIS OF 1,4-DIAZABICYCL0[2.2.2]OCTANE

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Double intramolecular cyclization of N,N'-bis(2-chloroethyl)-N-N'-bis(2-cyanoethyl)ethylenediamine leads to 1,4-bis(2-cyanoethyl)-1,4-diazoniabicyclo[2.2.2]octane dichloride, which undergoes decyanoethylation to 1,4-diazabicyclo[2.2.2]octane when it is heated. The structures of the compounds were confirmed by their IR and PMR spectra.

The literature contains a great deal of data on the synthesis of 1,4-diazabicyclo[2.2.2]octane (I) and its practical applications (see reviews [1, 2]). However, up until now there has been no information on compounds with functional groups attached to the carbon atom of this heterocycle. Communications [3, 4] on the synthesis of quaternary salts of 1,4-diazabicyclo[2.2.2]octane containing C-hydroxymethyl and carboxyl groups appeared only recently. This situation is explained to a great degree by the absence of sufficiently reliable and convenient methods for the construction of heterocyclic system I under relatively mild conditions.

Novosibirsk Institute of Organic Chemistry, Siberian Branch of the Academy of Sciences of the USSR, Novosibirsk 630090. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 4, pp. 548-550, April, 1978. Original article submitted March 29, 1977; revision submitted October 21, 1977. It is known that aliphatic 2-haloethylamines under mild conditions undergo reactions involving cyclization to piperazine derivatives [5]. There is also an indication [6], although it is presented without experimental details, that the N,N'-bis(bromoethyl) derivatives of N,N'-diethylethylenediamine can undergo intramolecular alkylation to give 1,4diazabicyclo[2.2.2]octane bis(ethyl bromide). In this connection, we investigated the possibility of using bis(chloroethyl) derivatives of ethylenediamine with easily removable groups attached to the nitrogen atoms for the synthesis of this heterocyclic system. We selected N,N'-bis(2-chloroethyl)-N,N'-bis(2-cyanoethyl)ethylenediamine dihydrochloride (IV) as the starting compound. The cyanoethyl groups were introduced with allowance for their thermal lability [7]. Compound IV was obtained from N,N'-bis(2-cyanoethyl)ethylenediamine (II) by hydroxyethylation and subsequent exchange of the hydroxy groups by chlorine.

The hydroxyethylation conditions and the method for the isolation of N,N'-bis(2-hydroxyethyl)-N,N'-bis(2-cyanoethyl)ethylenediamine (III) were selected by determination of the tertiary amines in the reaction mixture [8] and by paper chromatography. In view of the complexity of the purification of amino alcohol III because of its low thermal stability and the difficulty involved in the separation of the mixture of secondary and tertiary amines, the reaction was carried out at room temperature by the action of excess ethylene oxides until quaternary ammonium salts, which were easily separated with a weak cation-exchange resin, appeared in the reaction mixture.

Because of the low solubility of III in the solvents ordinarily used for such purposes, the hydroxyl group in III was replaced by chlorine in sulfolane by the action of thionyl chloride by the method in [9]. N,N'-bis(2-Chloroethyl)-N,N'-bis(2-cyanoethyl)ethylenediamine dihydrochloride (IV) was a congealed hygroscopic mass without a definite melting point. The chromatographic homogeneity of the isolated product, the IR spectrum, and the ratio of the ionic and covalent chlorine make it possible to assign structure IV to the product.



When IV is refluxed in dimethylformamide (DMF) for 5 min, it undergoes double cyclization, and the resulting dichloride, which is formed in 85% yield, precipitates. The role of DMF in this reaction is not restricted to its high polarity, for in this case it also acts as a source of dimethylamine, which ties up the hydrogen chloride. This phenomenon has also been noted in the literature [10]. An increase in the heating time leads to gradual dissolving of precipitated V because of decyanoethylation; however, the isolation of I from the resulting mixture is a complex process, and decyanoethylation was therefore carried out by heating in vacuo, during which the dihydrochloride of I is sublimed almost quantitatively.

The double intramolecular cyclization of IV probably proceeds through the intermediate formation of 1-(2-chloroethy1)-1,4-bis(2-cyanothy1)piperazinium chloride. It is known [1] that compounds of this type can undergo cyclization to 1,4-diazabicyclo[2.2.2]octane derivatives. The observed ease of the reaction attests to the sufficient nucleophilicity of the nitrogen atoms and the considerable reactivities of the chloroethy1 groups in IV.

EXPERIMENTAL

The IR spectra of KBr pellets of the compounds (0.25%) were recorded with a UR-20 spectrometer. The PMR spectra in D₂O were recorded with a Varian A 56/60A spectrometer with tetramethylsilane as the external standard. Chromatography was carried out in the following systems: A) on B No. 1 paper in n-butanol saturated with 2 N ammonium hydroxide; B) on a thin layer of aluminum oxide in n-butanol-85% formic acid (6:1). Detection was accomplished with Dragendorff's reagent.

N,N'-Bis(2-hydroxyethyl)-N,N'-bis(2-cyanoethyl)ethylenediamine (III) Dihydrochloride. A solution of 10 g (60 mmole) of N,N'-bis(2-cyanoethyl)ethylenediamine (II) [11] in 20 ml of methanol and 7.9 g (180 mmole) of ethylene oxide was allowed to stand in a sealed flask at room temperature for 72 h, after which the reaction mixture (R_f 0.64 and 0.09, system A) was passed through a column filled with KB 4P-2 resin (in the H⁺ form); the column was washed with 500 ml of methanol. The eluate was evaporated, and the oily residue was dissolved in 50 ml of methanol. The methanol solution was cooled, acidified with a methanol solution of HCl, and treated with ether, and the resulting white oil was washed with ether and dissolved by heating in aqueous methanol. The solution was cooled, and the white crystalline precipitate was removed by filtration to give 11 g (51%) of a product with mp 143-147°C (from aqueous methanol) and Rf 0.64 (system A) and 0.48 (system B). IR spectrum: 2260 (CEN), 2300-2700 (NH), and 1080 and 3360 cm⁻¹ (O-H). PMR spectrum, δ : 3.45 (4H, t, J = 7 Hz, CH₂) and 3.64-4.43 ppm (16H, m). Found: C 23.0; N 17.1%. C₁₂H₂₂N₄O₂•2HCl. Calculated: C 22.3; N 17.1%.

N,N'-Bis(2-chloroethyl)-N,N'-bis(2-cyanoethyl)ethylenediamine Dihydrochloride (IV). A solution of 3.96 g (12 mmole) of III in 24 ml of thionyl chloride and 24 ml of sulfolane was heated to 80°C for 30 min, after which it was cooled and treated with 40 ml of dioxane. Ether was then added, and the liberated brown oil was washed with ether and dried *in vacuo*. The foamy product was reprecipitated from methanol by the addition of ether and vacuum dried to give 3.0 g (68%) of a product with R_f 0.88 (system A) and 0.65 (system B). IR spectrum: 2260 (C=N) and 2300-2700 cm⁻¹ (NH+). Found: Cl_{ion} 19.2; Cl_{tot} 38.5%.* Calculated: Cl_{ion} 19.5; Cl_{tot} 39.0%.

<u>1,4-Bis(2-cyanoethyl)-1,4-diazobicyclo[2.2.2]octane Dichloride (V) Monohydrate</u>. A solution of 0.5 g (1.4 mmole) of IV in 20 ml of DMF was refluxed for 5 min, after which it was cooled, and the precipitate was removed by filtration, washed with ether, and dried *in vacuo* to give 0.32 g (85%) of a product with mp 288-290°C (from aqueous methanol). IR spectrum: 2260 (C=N), 1620, and 3480 cm⁻¹. PMR spectrum, δ : 3.68 (4H, t, J = 7Hz, CH₂CN), 4.40 (4H, t, J = 7 Hz, NCH₂), and 4.46 ppm (12H, s, CH₂). Found: C1 23.2; N 1.81%. C₁₂H₂₂Cl₂N₂•H₂O. Calculated: C 23.0; N 18.1%.

<u>1,4-Diazabicyclo[2.2.2]octane Dihydrochloride (VI)</u>. A 0.75-g (2.6 mmole) sample of V was vacuum sublimed at 170-200°C and 11 mm (mercury column) to give 0.45 g (94%) of a white crystalline substance with mp 310-311°C (310-311°C [2]). The PMR spectrum contains a singlet at 4.1 ppm. The IR spectrum of the base coincides with the IR spectrum of hydrated I presented in [12, 14]. The p-nitrobenzoate of I had mp 182-183°C (182-183°C [14]).

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^{*}The Cl_{tot} value was determined by argentometric titration after refluxing for 0.5 h with 1.2 N KOH solution and subsequent acidification with HNO₃.