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DIAZABICYCLOALKANES WITH NITROGEN ATOMS IN THE NODAL POSITIONS. 4.* INTRAMOLECULAR CYCLIZATION OF N-(β-X-ETHYL)-1,2,3,4-TETRAHYDROQUINOXALINES AND BEHAVIOR OF BENZO[b]-1,4-DIAZABICYCLO[2.2.2]OCTENES IN ACIDIC MEDIA

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The intramolecular cyclization of N-(β-hydroxyethyl)-N'-acetyl-1,2,3,4-tetrahydroquinoxaline in refluxing HBr was investigated by liquid microcolumn chromatography. Under these conditions the amide group undergoes rapid hydrolysis, the hydroxy groups undergo relatively slow exchange by bromine, and the resulting N-(β-bromoethyl)-1,2,3,4-tetrahydroquinoxaline undergoes cyclization to give benzo[b]-1,4-diazabicyclo[2.2.2]octene. These transformations terminate with the establishment of equilibrium between VII and I. 7-Methyl-N-(β-chloroethyl)-1,2,3,4-tetrahydroquinoxaline similarly forms an equilibrium reaction mixture in HBr. The effect of various factors (the acid and bromide ion concentrations, the character of the acid, and the temperature) on the position of the equilibrium of the compounds obtained and on the occurrence of side reactions (hydrolysis and dealkylation) was studied.

We have previously described the synthesis of benzo[b]-1,4-diazabicyclo[2.2.2]octene (I) and 4'-methylbenzo[1',2'-b]-1,4-diazabicyclo[2.2.2]octene (II) and have shown that the earlier literature information on II is erroneous [1]. Continuing our study of the benzo[b]-1,4-diazabicyclo[2.2.2]octene system we made a detailed investigation of the intramolecular cyclization of N-(β-X-ethyl)-1,2,3,4-tetrahydroquinoxalines to give I and II, as well as the behavior of these compounds in various acids, by means of liquid microcolumn chromatography.

It is known that refluxing ethanolamines in hydrobromic acid leads to the formation of bromoethylamines [2], while mono(β-hydroxyethyl)-o-phenylenediamines undergo cyclization to

*See [1] for communication 3.

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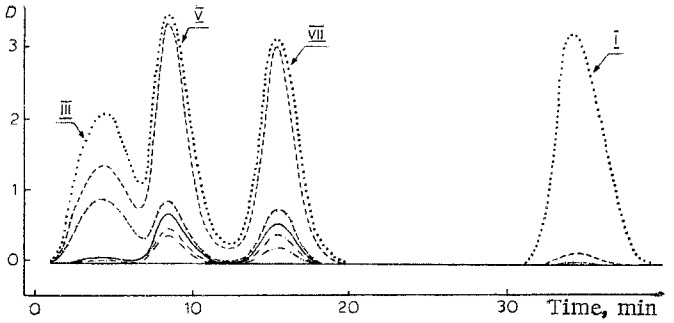
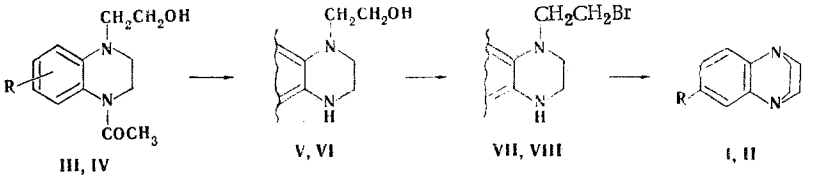


Fig. 1. Chromatogram of an artifical mixture of the investigated compounds with respect to the optical density (D) of the eluate at each time at discrete wavelengths: .....210, -|-|-|-| 230, — — — — 250, —·—·—·— 290, ——— 300, —··—··—·· 320, —|—|—|— 360 nm.

1,2,3,4-tetrahydroquinoxalines under similar conditions [3]. In this connection, one might have expected that the cyclization of hydroxyethyl derivatives III and IV proceeds through the intermediate formation of the corresponding bromoethyl derivatives via the scheme



I, III, V, VII R = H; II, IV, VI, IX R = CH_3

To confirm this pathway, by alkaline hydrolysis of the acetyl group of III we obtained V, treatment of which with phosphorus tribromide led to N-(β-bromoethyl)-1,2,3,4-tetrahydroquinoxaline (VII). Compounds V and VII were used as reference compounds in the quantitative analysis of the reaction mixtures by means of liquid chromatography (see Fig. 1 for an example of a chromatogram). A study of the behavior of III in refluxing hydrobromic acid showed that the amide group undergoes rapid hydrolysis under these conditions, after which the hydroxy groups under relatively slow exchange by bromine to give bromoethyl derivative VII (the half-conversion time was ~2 h), which is consumed in the formation of benzo[b]-1,4-diazabicyclo[2.2.2]octene (I) (the half-conversion time was ~30 min). The ratio of I and VII after 5 h was 7:3, respectively, whereas an increase in the reaction time did not change the relative percentages of these products in the mixture. When I was used as the starting compound, a gradual accumulation of VII to a constant I:VII ratio of 7:3 was observed under the same conditions; a reaction mixture of the same composition was formed when VII was heated in HBr (Fig. 2a). These facts indicate the existence under the reaction conditions of an equilibrium between benzo[b]-1,4-diazabicyclo[2.2.2]octene (I) and N-(β-bromoethyl)-1,2,3,4-tetrahydroquinoxaline (VII). A decrease in the temperature at which the reaction is carried out to 100°C leads to an increase in the time required to establish equilibrium to 12 h, while the ratio of the components in the mixture remains virtually unchanged.

A similar result was obtained when the specially synthesized hydrochloride of 7-methyl-N-(β-chloroethyl)-1,2,3,4-tetrahydroquinoxaline (VIII) was refluxed in hydrobromic acid; as a result of the established equilibrium, product IX, which is probably a mixture of 6- and 7-methyl-N-(β-bromoethyl)-1,2,3,4-tetrahydroquinoxalines, is formed along with II. This product is homogeneous in the chromatographic systems used and, with respect to its chromatographic mobility and the character of its UV spectrum, is very similar to starting VIII. Compound II and product IX exist in a ratio of ~ 3:2 in the equilibrium mixture, and the composition of the latter is independent of starting VIII or II (Fig. 2, curve b).*

The behavior of I and VII in acidic media can be represented by the scheme

*The quantitative composition of the mixture of II and IX was estimated on the basis of calibration with respect to analytical samples of II and VIII.

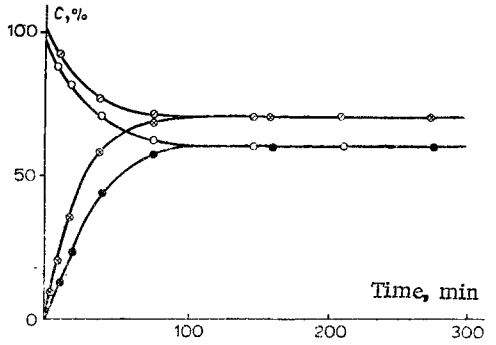
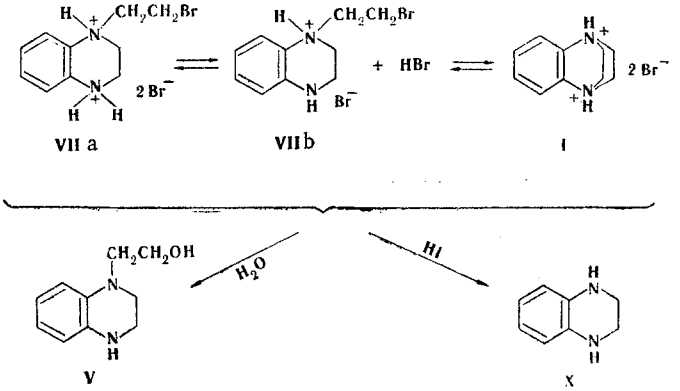


Fig. 2. Kinetics of the establishment of the I⇄VII and VIII→II⇄IX equilibria in refluxing 8.8 N HBr (126°C), where C, % is the relative percentage in the reaction mixture of I (a) in the presence of starting I (⌀) and VII (⊗) or of II (b) in the presence of starting II (○) and VIII (●).



Of the set of protonated forms of VII that exist in acid–base equilibrium in a strongly acidic medium, form VIIb, which bears a proton attached to the tertiary nitrogen atom, probably participates chiefly in the cyclization. Examples of the successful cyclization of monoquaternary salts with similar structures have been described [5, 6]. The dication of I probably participates primarily in the reverse reaction of opening of the 1,4-diazabicyclo-[2.2.2]octane ring. In this connection, one might have expected that both the acidity of the medium and the concentration of the bromide ion would affect the VIIa⇄VIIIb⇄I equilibrium. A decrease in the acidity of the medium should evidently lead to a shift of the equilibrium to the right due to an increase in the concentration of monoprotonated form VIIb. A decrease in the bromide ion concentration should shift the equilibrium in the same direction.

In fact, when I is heated in 3 N HBr, it undergoes ring opening to only a small extent (compare experiments 1 and 2 in Table 1), while the rate of cyclization of VII increases when the acidity of the medium is decreased (experiments 3 and 4). However, a decrease in the HBr concentration leads to competitive reaction of VII with water to give N-(β-hydroxyethyl)-1,2,3,4-tetrahydroquinoxaline (V), which becomes the predominant product at HBr concentrations at and below 0.1 N (experiments 1 and 4-6). A decrease in the acidity of the medium with retention of a high bromide ion concentration by means of LiBr shifts the equilibrium to favor the formation of I (experiments 1, 7, and 8), during which VII undergoes virtually no hydrolysis. In addition, as expected, an increase in the bromide ion concentration with retention of the high acidity of the medium promotes a decrease in the percentage of I in the equilibrium mixture (experiments 1 and 9), i.e., the equilibrium is shifted to the left.

TABLE 1. Behavior of I and VII in Acidic Media

Expt. No.	Starting compound	Composition of the reaction medium	Reaction time, h[a]	Relative percentages of the products in the mixture, mole %		
				I	VII	V
1	I or VII	8,8 N HBr	15	70	28	2
2	I	3,0 N HBr	15	93	1	6
3	VII	8,8 N HBr	1	20	80	0
4	VII	3,0 N HBr	1	47	41	12
5	VII	0,1 N HBr	1	27	3	70
6	VII	Water pH 3	1	24	0	76
7	I or VII	1,0 N LiBr 7,8 N HBr	15[b]	90	9	1
8	VII	10,0 N LiBr; pH 1 0,1 N HBr	30	95	2	3
9	I or VII	1,0 N LiBr; 8,8N. HBr	15[b]	51	49	0
10	I	7,8 N H_2SO_4	15	100	0	0
11	I	3,7 N $HClO_4$	15	100	0	0
12	I	3,7 N $HClO_4$	2	71	0	29
13	VII	10,0 N HCl	15	39	37	24
14	VII	7,8 N H_2SO_4	15	46	0	54
15	VII	3,7 N $HClO_4$	15	68	2	30
16	VII	Polyphosphoric acid	15	87	13	0
17	I or VII	7,4 N HI	6[c]	0	0	0
18	I or VII	8,8 N HBr	80[c]	0	0	0
19	I	7,4 N HI	0,17[c]	90	0	0

[a]The reaction temperature was 100°C; the reaction temperature in experiments 12 and 18 was 140°C. [b]A longer reaction time does not change the ratio of the components in the mixture. [c]The mixture contained 100% X in experiments 17 and 18, whereas it contained 10% X in experiment 19.

The character of the acid anion, which participates in ring opening, should evidently affect the state of the VIIa⇄VIIb⇄I equilibrium. Anions with greater nucleophilicity than Br should promote a shift of the equilibrium to the left, while those with lower nucleophilicity should shift it to the right. In fact, I is stable when it is treated with sulfuric acid of the same acidity as 8.8 N HBr, as well as with perchloric acid, under the standard reaction conditions (experiments 10 and 11). Partial hydrolysis of I is observed only when the reaction temperature is raised and leads to the formation of product V (experiment 12). The cyclization of VII in solutions of hydrochloric, sulfuric, and perchloric acids is accompanied by considerable hydrolysis (experiments 13-15). The hydrolysis of VII can be suppressed and can shift the reaction equilibrium to favor the formation of benzo[b]-1,4-diazabicyclo[2.2.2]octane (I) by carrying out the cyclization in anhydrous acid with an anion with a relatively low nucleophilicity such as polyphosphoric acid (experiment 15). An increase in the nucleophilicity of the acid anion leads to opening of the 1,4-diazabicyclo[2.2.2]octane ring in I. Thus, in an attempt to carry out the cyclization of VII in hydriodic acid, as in the case of treatment of I with it, we isolated 1,2,3,4-tetrahydroquinoxaline (X), which was detected as the only product in the reaction mixtures (experiment 17). A similar transformation is observed in hydrobromic acid, but under more severe conditions (experiment 18). The reaction probably takes place in two steps through an N-substituted 1,2,3,4-tetrahydroquinoxaline intermediate. In the case of hydriodic acid the second step of this transformation proceeds so rapidly that an intermediate cannot be detected even when this reaction is carried out to a small extent (experiment 19).

EXPERIMENTAL

The IR spectra of KBr pellets of the compounds were recorded with a UR-20 spectrometer. The PMR spectra of the compounds were recorded on the δ scale with a Varian A56/60A spectrometer and tetramethylsilane as the external standard. Chromatography was carried out on Silufol UV-254 plates in the tert-butanol–methyl ethyl ketone–formic acid–water system (8:6:3:3). Quantitative analysis of the compositions of the reaction mixtures was carried out by ion-exchange chromatography on Aminex A-7 cation-exchange resin in the H^+ form (the particle size was 9 ± 2 μm). The diameter of the microcolumn was 1.3 mm, and the height of the column was 30 mm. The products were applied to the column in a 0.4 N solution of HCl in aqueous ethanol (1:1). The eluent was 0.5 ml of linear-gradient 2.0-4.0 N HCl in aqueous

ethanol (1:1), and the rate of inflow of the gradient was 0.01 ml/min. The eluate was subjected to continuous spectrophotometry in UV light at 210, 230, 250, 290, 300, 320, and 360 nm. The recording apparatus was an Ob' ultramicrospectrophotomer (a prototype model from the Novosibirsk Institute of Organic Chemistry of the Siberian Branch of the Academy of Sciences of the USSR). A typical chromatogram is presented in Fig. 1. The chromatograms were calculated by comparison of the areas of the peaks at the analytical wavelengths (210 and 250 nm) with calibration data obtained from the chromatograms of artifical mixtures of the investigated compounds.

Investigation of the Transformations of Amines in Acidic Media. A solution of the amine (0.04 mole/liter) to be investigated in the medium of interest was sealed in a 0.1 ml ampul, and the ampul was allowed to stand in a thermostat for the necessary time. During the reaction, the ampuls were removed, and the composition of 0.001 ml of the reaction mixture was analyzed with the microcolumn. The results of the chromatographic analysis are presented in Table 1.

N-(β-Hydroxyethyl)-N'-acetyl-1,2,3,4-tetrahydroquinoxaline (III) was obtained by the method in [1].

N-(β-Hydroxyethyl)-1,2,3,4-tetrahydroquinoxaline (V). An emulsion of 10.2 g (46 mmole) of amide III in 25 ml of 50% ethanol was refluxed for 3 h in the presence of 15.2 g (260 mmole) of KOH, after which the product was extracted with ether. The ether extract was dried over CaO and evaporated to dryness, and the residue was dissolved in benzene. The solution was refluxed with activated charcoal, after which it was cooled and treated with a seed crystal, and the colorless crystalline product, which darkened rapidly in air, was removed to give 1.2 g (15%) of a substance with mp 60-65°C and R_f 0.50. IR spectrum: 1060 (C—OH); 1313 (C—O); 1361 (C—N)1 1521, 1608 (aromatic C=C); 2860, 2920 (C—H); 3250 cm^{-1} (O—H). PMR spectrum (in $CDCl_3$): 6.5 (4H, m, aromatic protons), 3.7 (1H, s, OH), 3.6 (1H, s, NH), and 3.3 ppm (8H, m, CH_2). Found %: C 67.1; H 7.9; N 15.9. $C_{10}H_{14}N_2O$. Calculated %: C 67.4; H 7.9; N 15.7.

N-(β-Bromoethyl)-1,2,3,4-tetrahydroquinoxaline Hydrobromide (VII·HBr). The ether extract obtained in the synthesis of V was treated with 6 ml of 48% HBr, and the mixture was evaporated to dryness. Sulfolane (12 ml) and 4.7 ml (50 mmole) of PBr_3 were added to the residue, and the mixture was heated at 140°C for 30 min. It was then cooled and poured into 150 ml of ethyl acetate, and the mixture was triturated until a crystalline gray precipitate formed. Recrystallization from n-propanol—ether (2:3) gave 7.0 g (47%) of a product with mp 135-139°C and R_f 0.67. IR spectrum: 1352 (C—N); 1524, 1623 (aromatic (C=C); 2430-2870 cm^{-1} (N^+—H). PMR spectrum (in CF_3COOH): 7.0 (4H, m, aromatic protons), 3.7 (6H, m, CH_2), and 3.3 ppm (2H, m, CH_2). Found %: C 37.3; H 4.4; N 8.4. $C_{10}H_{13}BrN_2 \cdot HBr$. Calculated %: C 37.3; H 4.4; N 8.7.

3-Bis(β-hydroxyethyl)amino-4-acetamidotoluene (XI). This compound, with mp 153-154°C and R_f 0.13, was obtained in 60% yield from 4-acetamido-m-toluidine by the method described for 2-bis(β-hydroxyethyl)aminoacetylaniline [7]. IR spectrum: 1065 (C—OH); 1530, 1600 (aromatic C=C); 1661 (C=O); 2830, 2959 (C—H); 3240-3370 cm^{-1} (O—H). PMR spectrum (in CF_3COOH) 7.0 (3H, m, aromatic protons), 3.6 (8H, m, CH_2), 2.2 (3H, s, CH_3), and 2.1 ppm (3H, s, $COCH_3$) Found %: N 11.1. $C_{13}H_{20}N_2O_3$. Calculated %: N 11.1.

3-Bis(β-chloroethyl)amino-4-acetamidotoluene (XII). This compound, with mp 81-86°C (from aqueous ethanol) and R_f 0.90, was obtained in 85% yield from XI by the method described for 2-bis(β-chloroethyl)aminoacetylaniline [7]. IR spectrum: 1310 (C—N); 1520, 1594 (aromatic C=C); 1672 (C=O); 3325 cm^{-1} (N—H), PMR spectrum (in CCl_4): 7.1 (3H, m, aromatic protons), 3.3 (8H, m, CH_2), 2.3 (4H, superimposition of the NH and CH_3 signals), 2.1 ppm (3H, s, $COCH_3$). Found %: C 54.1; H 6.1; Cl 24.1; N 9.5. $C_{13}H_{18}Cl_2N_2O$. Calculated %: C 54.0; H 6.3; Cl 24.5; N 9.7.

7-Methyl-N-(β-chloroethyl)-1,2,3,4-tetrahydroquinoxaline (VIII) Hydrochloride. This compound, with mp 147-150°C and R_f 0.76, was obtained in 35% yield from XII by removal of the acetyl group and intramolecular cyclization by the method described for the hydrochloride of N-(β-chloroethyl)-1,2,3,4-tetrahydroquinoxaline [7]. IR spectrum: 1340 (C—N); 1518, 1615 (aromatic C=C); 2400-3000 cm^{-1} (N^+—H). PMR spectrum (in CD_3OD): 6.8 (3H, m, aromatic protons), 4.8 (4H, m, CH_2), 3.6 (4H, m, CH_2), and 2.2 ppm (3H, s, CH_3). Found %: C 53.0; H 6.5; Cl 28.5; N 11.2. $C_{11}H_{15}ClN_2 \cdot HCl$. Calculated %: C 53.5; H 6.5; Cl 28.7; N 11.3.

Treatment of I and VII with Hydriodic and Hydrobromic Acids. Reaction mixtures from which 1,2,3,4-tetrahydroquinoxaline was isolated after evaporation and vacuum sublimation at 100°C (0.8 mm) were obtained by heating a solution of 0.32 g (2 mmole) of the dihydrobromide of I or the hydrobromide of VII in 6 ml of 56% HI in an ampul at 100°C for 6 h or in 10 ml of 48% HBr at 140°C for 60 h. In each case 0.12 g (48%) of a substance with mp 95°C was isolated. The characteristics of the compound obtained were in agreement with the data in [8].

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DERIVATIVES OF 1,2,5,6,9,12-HEXAAZACYCLOTETRADECATETRAENE AND 1,2,5,6,9,14-HEXAAZACYCLOHEXADECAHEXAENE BASED ON 2,3-DIHYDRAZINOQUINOXALINE

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A bis(hydrazone) was synthesized by the reaction of 2,3-dihydrazinoquinoxaline with 3-methyl-1-phenyl-1H-pyrazole-4,5-dione. Treatment of the bis(hydrazone) with $POCl_3$ and Et_3N gave a dichloro diazo compound, from which macrocyclic metal chelates, viz., derivatives of 1,2,5,6,9,12-hexaazacyclotetradecatetraene and 1,2,5,6,9,14-hexaazacyclohexadecahexaene, were obtained by reaction with diamines in dimethylformamide in the presence of Pd(II) and Ni(II)salts.

2,3-Dihydrazinoquinoxaline has been described [1, 2], but little study has been devoted to it. Moreover, it holds promise as the starting compound in the synthesis of bis(diazo) macrocyclic systems by nucleophilic substitution of the halogen of the bis(diazo) compound by arylamino groups. The synthesis was carried out via the scheme.

Compound III was obtained initially by the reaction of I and II. The IR absorption band of the stretching vibrations of the carbonyl groups lies at 1675 cm^{-1}, while the absorption band of the stretching vibrations of the NH groups at 3100-3300 cm^{-1} is broadened markedly, which is characteristic for hydrazones with a strong intramolecular hydrogen bond [3]. A broad singlet of an NH proton involved in an intramolecular hydrogen bond is observed in the PMR spectrum at 14.3 ppm (Table 1). The identical character of the chemical shifts of the 5-H and 8-H protons of the quinoxaline ring, as well as the 2-H and 6-H and 3-H and 5-H protons of the N-phenyl rings, constitutes evidence for symmetry of the molecule and equivalence of the N-phenyl rings. It follows from these data that III probably exists in the Z,Z-bis(hydrazone) form.

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