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DIAZABICYCLOALKANES WITH NITROGEN ATOMS IN THE NODAL POSITIONS. 9.* INTRAMOLECULAR CYCLIZATION OF N-(γ-BROMOPROPYL)-TETRAHYDROQUINOXALINES AND BEHAVIOR OF BENZO[f]-1,5-DIAZABICYCLO[3.2.2]NONENE IN HYDROBROMIC ACID

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UDC 547.863.13'859.5.7'896'897.07:543.422'51

The introduction of an N,N'-trimethylene bridge in the tetrahydroquinoxaline molecule is complicated by cyclization of γ-bromopropyl derivatives of tetrahydroquinoxaline at the carbon atom of the aromatic ring. The reaction of N-R-tetrahydroquinoxalines (R = H, $COCH_3$) with 1,3-dibromopropane leads to products of cyclization at the aromatic ring (1,2,3,5,6,8,9,10-octahydropyrazino[1,2,3,4-*l*,m,n][1,10]phenanthroline and N-acetyl-1,2,6,7-tetrahydro-3H,5H-pyrido[1,2,3-d,e]quinoxaline) and to an N-alkylation product [N-acetyl-N'-(γ-bromopropyl)-1,2,3,4-tetrahydroquinoxaline]. Benzo[f]-1,5-diazabicyclo[3.2.2]nonene is formed in only trace amounts in the cyclization of N-(γ-bromopropyl)tetrahydroquinoxaline and upon heating in HBr can be isomerized with migration of the trimethylene bridge to the aromatic ring.

Continuing our search for methods for the preparation of diazabicycloalkanes with nitrogen atoms in the nodal positions we investigated the possibility of the synthesis of the previously described benzo[f]-1,5-diazabicyclo[3.2.2]nonene (I) system [2] by the introduction of a trimethylene bridge in the 1,2,3,4-tetrahydroquinoxaline (II) molecule. The introduction of a trimethylene bridge in an aromatic diamine molecule has been described in the literature. Thus naphtho[1,8-f,g]-1,5-diazabicyclo[3.3.3]undecene was obtained by the reaction of 1,8-diaminonaphthalene with 1,3-dibromopropane [3], while benzo[j]-1,5-diazabicyclo[3.3.2]-decene was obtained from o-phenylenediamine under similar conditions [4]. However, the yields of these compounds were only 5 and 3.7%, respectively. The data on the synthesis of 4'-methylbenzo[1',2'-f]-1,5-diazabicyclo[3.2.2]nonene by the action of dibromopropane on 6-methyl-1,2,3,4-tetrahydroquinoxaline [5] were not confirmed when they were checked [2]. The formation of I also was not observed in the action of excess 1,3-dibromopropane on II in the presence of calcium oxide. According to the results of elementary analysis and the mass spectrum, the principal reaction product contained two trimethylene fragments per molecule of tetrahydroquinoxaline. The PMR spectrum of this compound contains a singlet of two aromat-

*See [1] for Communication 8.

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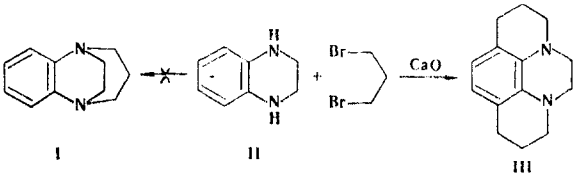
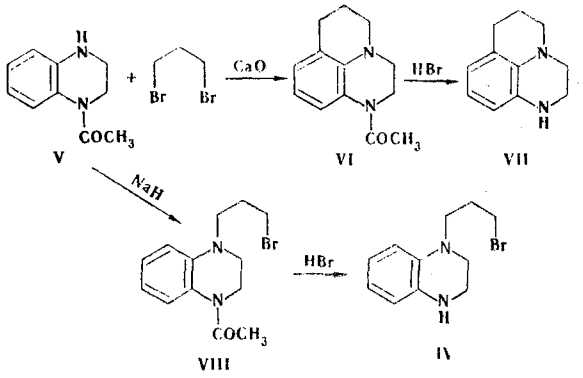
ic protons at 6.5 ppm, a multiplet of signals of benzyl protons and an ethylene bridge at 3.4 ppm (8H), a triplet of N-methylene groups of propylene bridges at 2.9 ppm (4H), and a multiplet of central methylene groups of propylene bridges at 2.2 ppm (4H). The alkylation of tetrahydroquinoxaline with dibromopropane under these conditions evidently leads to a product of substitution in the aromatic ring, and the spectral and analytical data for the compound obtained correspond to the 1,2,3,5,6,8,9,10-octahydropyrazino[1,2,3,4-*l*,m,n][1,10]-phenanthroline [1,8:4,5-bis(trimethylene)-1,2,3,4-tetrahydroquinoxaline] structure (III).



I II III

To ascertain the possibility of realization of intramolecular cyclization of N-γ-bromopropyl derivatives at the adjacent nitrogen atom it was necessary to synthesize N-(γ-bromopropyl)-1,2,3,4-tetrahydroquinoxaline (IV). In an attempt to synthesize IV by the reaction of 1,3-dibromopropane with N-acetyl-1,2,3,4-tetrahydroquinoxaline (V) in the presence of calcium oxide we observed that the reaction is again complicated by intramolecular C-alkylation of the aromatic ring. As a result, we isolated a substance, the spectral and analytical data for which correspond to the N-acetyl-1,2,6,7-tetrahydro-3H,5H-pyrido[1,2,3,d,e]quinoxaline (VI) structure. Hydrolysis of this amide leads to 1,2,6,7-tetrahydro-3H,5H-pyrido[1,2,3-d,e]quinoxaline (1,8-trimethylene-1,2,3,4-tetrahydroquinoxaline) (VII). A multiplet of three aromatic protons at 6.3 ppm, a multiplet of protons of an ethylene bridge at 3.5 ppm, a multiplet of protons of a benzyl group and an NH group at 3.3 ppm, a triplet at 2.7 ppm, and a multiplet at 1.9 ppm from other protons of the propylene bridge are observed in the PMR spectrum of VII.



V VI VII VIII IV

The reaction can be stopped at the step involving the formation of N-acetyl-N'-(γ-bromopropyl)-1,2,3,4-tetrahydroquinoxaline (VIII) only under milder conditions and in the presence of sodium hydride as the base; brief refluxing of VIII in hydrobromic acid leads to the desired IV, which was isolated and characterized in the form of the hydrobromide.

We have previously shown [2] that N-(β-X-ethyl)-N,N'-alkylene-o-phenylenediamines (X = OH or Hal) in refluxing hydrobromic acid readily undergo intramolecular N-alkylation to give diazabicycloalkanes condensed with an aromatic ring in high yields. The cyclization of γ-bromopropyl derivative IV under these conditions occurs only upon prolonged refluxing in hydrobromic acid; cyclization takes place primarily via a C-alkylation pathway, and VII was isolated from the reaction mixture in 40% yield. Intramolecular C-alkylation product VII is similarly primarily formed (in 37% yield) in the cyclization of IV in dimethylformamide (DMF); only a small amount of I is formed.

We have previously established that benzo[b]-1,4-diazabicyclo[2.2.2]octene (IX) upon heating in hydrobromic acid is capable of undergoing reversible conversion to N-(β-bromoethyl)-1,2,3,4-tetrahydroquinoxaline (X), whereas upon prolonged heating it undergoes irreversible conversion to 1,2,3,4-tetrahydroquinoxaline (II) [6].

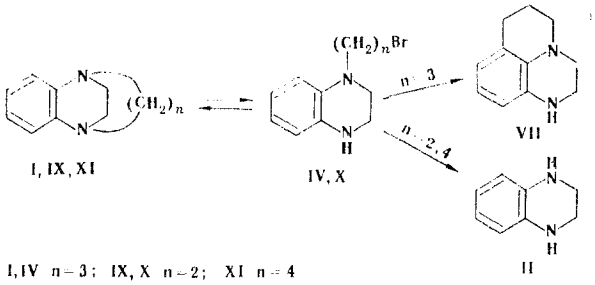
In checking the stability of I in hydrobromic acid we observed that at 140°C it undergoes irreversible isomerization to VII. This reaction most likely proceeds through initial

TABLE 1. Spectral Properties of 1,2,3,4-Tetrahydroquinoxaline Derivatives (III, IV·HBr, VI-VIII)

Compound	IR spectrum,[a] cm^{-1}				Chemical shifts in the PMR spectra, δ, ppm					
	C–H	C–O	C=C	C–N	solvent	aromatic protons	NCH_2CH_2N	$ArCH_2$, NH	CH_2N, CH_2Br	CH_2, CH_3
III	2921, 2842	—	1580	1360	$CDCl_3$	6,5 (2H, s)	3,5 (4H, s)	3,3 (4H, m)	2,9 (4H, t)	2,2 (4H, m)
IV·HBr	3000	—	1623	1350	CD_3OD	7,0 (4H, m)	3,6 (4H, m)	—	3,4 (4H, m)	2,2 (2H, m)
VI	3015, 2948	1640	1520	1322	$CDCl_3$	6,5 (3H, m)	3,0 (4H, m)	3,3 (2H, m)	2,7 (2H, t)	2,2 (2H, m, 3H, s)
VII	2933, 2840	—	1598	1357	$CDCl_3$	6,3 (3H, m)	3,0 (4H, m)	3,3 (3H, m)	2,7 (2H, t)	1,9 (2H, m)
VIII	3017	1650	1611	1340	CCl_4	7,0 (4H, m)	4,1 (4H, m)	—	3,7 (4H, m)	2,4 (2H, m, 3H, s)

[a]The IR spectra were obtained from KBr pellets (or from a solution in $CHCl_3$ in the case of VIII).

opening of the trimethylene bridge under the influence of the bromide ion to give intermediate IV, which undergoes intramolecular C-alkylation. Rearrangement products were not observed for the next homolog of this series, viz., benzo[g]-1,6-diazabicyclo[4.2.2]decene (XI), in the case of prolonged heating in hydrobromic acid. As in the case of diazabicyclooctene IX, dealkylation to give II is observed. The results make it possible to assume that the following reactions occur in hydrobromic acid in the case of diazabicycloalkanes condensed with an aromatic ring:



The driving factor in the isomerization of I is possibly cleavage of the strained seven-membered ring and the formation of thermodynamically stable (under these conditions) isomerization product VII with a less strained six-membered ring. The similar isomerization of IX and XI requires the formation of strained five- and seven-membered rings, respectively, and dealkylation is therefore preferable in these cases.

It might be assumed that one of the principal processes in the synthesis of diazabicyclic compounds by the reaction of aromatic diamines with dibromopropane (see, for example, [3, 4]) is intramolecular C-alkylation leading to compounds similar to those that we obtained, which explains the low yields of diazabicycloalkanes with nitrogen atoms in the nodal positions.

EXPERIMENTAL

The IR spectra of the compounds were recorded with a UR-20 spectrometer. The PMR spectra were obtained with a Varian A 56/60 A spectrometer on the δ scale with tetramethylsilane as the external standard. The molecular masses were measured mass spectrometrically with an MS-902 spectrometer.

All of the products were isolated from the reaction mixtures by preparative chromatography in a thin layer of silica gel with a luminescent additive (30 by 40 cm plates, elution with chloroform). The substances were detected in UV light, and the fractions with the corresponding R_f values were eluted with chloroform–ethanol (10:1); where possible, the products were sublimed in vacuo.

1,2,3,5,7,8,9,10-Octahydropyrazino[1,2,3,4-*l*,m,n][1,10]phenanthroline (III). A 0.5-g (8.9 mmole) sample of ground calcium oxide was added to a solution of 0.27 g (2.0 mmole) of

1,2,3,4-tetrahydroquinoxaline (II) in 2 ml of 1,3-dibromopropane, and the mixture was heated with stirring in an atmosphere of dry argon at 130-140°C for 20 h. It was then filtered, and the precipitate was washed with ether. The combined filtrates were evaporated to dryness, and the residue was treated with water and extracted with ether. The extract was evaporated, and the product was isolated by thin-layer chromatography (TLC) (R_f 0.8) and sublimed in vacuo at 110°C (0.14 mm) to give 56 mg (13%) of III with mp 125-129°C (from methanol). Found: C 78.7; H 8.4; N 13.1%; M 214. $C_{14}H_{18}N_2$. Calculated: C 78.5; H 8.5; N 13.1%; M 214.

N-Acetyl-1,2,6,7-tetrahydro-3H,5H-pyrido[1,2,3-d,e]quinoxaline (VI). A 0.3-g (5.4 mmole) sample of ground calcium oxide was added to a solution of 0.35 g (2.0 mmole) of N-acetyl-1,2,3,4-tetrahydroquinoxaline (V) in 2 ml of 1,3-dibromopropane, and the mixture was heated with stirring in an atmosphere of dry argon at 125-130°C for 9 h. The product was isolated as in the preparation of III, chromatographed (R_f 0.4), and sublimed in vacuo at 110°C (0.14 mm) to give 0.10 g (23%) of an oil. Found: C 72.4; H 7.6; N 12.7%. $C_{13}H_{16}N_2O$. Calculated: C 72.2; H 7.5; N 13.0%.

N-(γ-Bromopropyl)-N'-acetyl-1,2,3,4-tetrahydroquinoxaline (VIII). A 0.1-g (4.3 mmole) sample of ground sodium hydride was added to a solution of 0.35 g (2.0 mmole) of V in 2 ml of 1,3-dibromopropane, and the mixture was heated with stirring in an atmosphere of dry argon at 110-120°C for 15 h. The product was isolated as in the preparation of III, chromatographed (R_f 0.4), and evaporated and dried in vacuo to give 0.24 g (40%) of an oil. Found: M 296; 298. $C_{13}H_{17}BrN_2O$. Calculated: M 296; 298.

N-(γ-Bromopropyl)-1,2,3,4-tetrahydroquinoxaline Hydrobromide (IV·HBr). A solution of 0.30 g (1.0 mmole) of VIII in 5 ml of 8.8 N HBr was refluxed in an argon atmosphere for 20 min, after which it was evaporated in vacuo, and the residue was treated with 10% NaOH and extracted with ether. The product was isolated by TLC (R_f 0.3), acidified with HBr, and reprecipitated from ethanol by means of absolute ether. The yield of IV·HBr, with mp 180°C (dec.), was 0.23 g (90%). Found: C 38.9; H 4.8; Br 48.0; N 8.0%. $C_{11}H_{15}BrN_2 \cdot HBr$. Calculated: C 39.3; H 4.8; Br 47.6; N 8.3%.

1,2,6,7-Tetrahydro-3H,5H-pyrido[1,2,3-d,e]quinoxaline (VII). A solution of 0.22 g (1.0 mmole) of VI in 5 ml of 8.8 N HBr was refluxed in an argon atmosphere for 30 min, after which it was evaporated in vacuo, and the residue was treated with 10% NaOH and extracted with ether. The product was isolated by TLC (R_f 0.5) and sublimed in vacuo at 90°C (0.14 mm) to give 0.10 g (60%) of a substance with mp 65-68°C (from methanol–water). Found: C 76.1; H 8.0; N 16.2%; M 174. $C_{11}H_{14}N_2$. Calculated: C 75.8; H 8.1; N 16.1%; M 174.

Isomerization of benzo[f]-1,5-diazabicyclo[3.2.2]nonene (I) to VII. A solution of 0.17 g (1.0 mmole) of I in 5 ml of 8.8 N HBr was heated in a sealed ampul in an argon atmosphere at 140°C for 24 h, after which the product was isolated as described above. The yield of VII, with mp 66-68°C, was 47 mg (27%).

Cyclization of IV in Hydrobromic Acid. A solution of 0.26 g (1.0 mmole) of IV·HBr or 0.3 g (1.0 mmole) of VIII in 5 ml of 8.8 N HBr was refluxed in an argon atmosphere for 48 h, after which it was evaporated in vacuo, and the residue was treated with 10% NaOH and extracted with ether. The reaction products were isolated by TLC. The yield of VII (R_f 0.5), with mp 66-68°C, was 70-78 mg (40-45%). The yield of I* (R_f 0.1), with mp 50-54°C [the product was sublimed in vacuo at 60°C (0.14 mm)], was 2 mg (∿1%).

Cyclization of IV in DMF. A solution of 0.26 g (1.0 mmole) of IV·HBr in 5 ml of DMF was heated in an argon atmosphere at 140°C for 1 h, after which it was worked up as described above. The yield of VII, with mp 66-68°C, was 64 mg (37%). The yield of I,* with mp 50-54°C, was 1 mg (∿1%).

Behavior of Benzo[g]-1,6-diazabicyclo[4.2.2]decene (XI) in Hydrobromic Acid. A solution of 0.19 g (1.0 mmole) of XI (obtained by the method in [2]) in 5 ml of 8.8 N HBr was heated in a sealed ampul in an argon atmosphere at 140°C for 24 h, after which it was evaporated in vacuo, and the residue was treated with 10% NaOH and extracted with ether. The principal reaction product was extracted by means of TLC (R_f 0.3) and was sublimed in vacuo at 80°C. The yield of II, with mp 95°C, was 20 mg (15%).

*The characteristics of the substances obtained were in agreement with the data for genuine samples of I and II.

The spectra characteristics of all of the compounds obtained are presented in Table 1.

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DIAZABICYCLOALKANES WITH NITROGEN ATOMS IN THE NODAL POSITIONS. 10.* INTRAMOLECULAR CYCLIZATION OF β-BROMOETHYL- AND γ-BROMOPROPYL-N,N'-ALKYLENE-o-PHENYLENEDIAMINES

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The overall scheme of the intramolecular cyclization of bromoalkyl derivatives of N,N'-alkylene-o-phenylenediamines in HBr was established, and the rates of the individual steps of this complex process were estimated. It is shown that N-(β-bromoethyl)-N,N'-trimethylene-o-phenylenediamine undergoes virtually irreversible cyclization at a high rate to give benzo[f]-1,5-diazabicyclo[3.2.2]-nonene in significant yield, while the cyclization of N-(γ-bromopropyl)-1,2,3,4-tetrahydroquinoxaline proceeds at commensurable rates via two pathways, viz., C- and N-alkylation. This makes it impossible to use the latter reaction to obtain benzo[f]-1,5-diazabicyclo[3.2.2]nonene in high yield.

We have previously shown that N-acyl-N'-(β-hydroxyethyl)-N,N'-trimethylene-o-phenylenediamines undergo cyclization in hydrobromic acid to give benzo[f]-1,5-diazabicyclo[3.2.2]-nonene (I) [2], whereas the cyclization of N-(γ-bromopropyl)-1,2,3,4-tetrahydroquinoxaline (II) leads primarily to 1,2,6,7-tetrahydro-3H,5H-pyrido[1,2,3-d,e]quinoxaline (III) [1] and only trace amounts of I.

In order to find the optimum conditions for the synthesis of diazabicycloalkanes annelated with an aromatic ring and containing nitrogen atoms in the nodal positions and to determine more precisely the sequence of the reactions leading to heterocyclic system III we quantitatively evaluated, by means of our previously used chromatographic method [3], the rates of the reactions that occur in the intramolecular cyclization of bromoalkyl derivatives of N,N'-alkylene-o-phenylenediamines.

It is known that N-(β-bromoethyl)-1,2,3,4-tetrahydroquinoxaline (IV) upon heating in hydrobromic acid forms an equilibrium mixture with benzo[b]-1,4-diazabicyclo[2.2.2]octene (V) in a ratio of 3:7 [3], whereas N-acetyl-N'-(β-hydroxyethyl)-N,N'-trimethylene-o-phenylenediamine under these conditions undergoes cyclization to give only I [2]. To evaluate the possibility of the equilibrium N-(β-bromoethyl)-N,N'-trimethylene-o-phenylenediamine (VI) ⇌ benzo[f]-1,5-diazabicyclo[3.2.2]nonene (I) it was necessary to have VI at our disposal. With this in mind, we realized the synthesis of N-(β-X-ethyl)-N,N'-trimethylene-o-phenylenediamines — potential sources of VI — via the scheme

*See [1] for Communication 9.

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