DIAZABICYCLOALKANES WITH NITROGEN ATOMS IN THE NODAL POSITIONS. 3.* THE BENZO[b]-1,4-DIAZABICYCLO[2.2.2]-OCTENE SYSTEM

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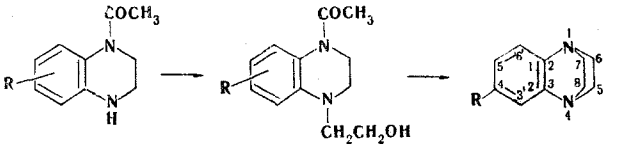
Benzo[b]-1,4-diazabicyclo[2.2.2]octene and 4'-methylbenzo[1',2'-b]-1,4-diazabicyclo[2.2.2]octene were synthesized by the reaction of N-acetyl-6-H- and 6-methyl-1,2,3,4-tetrahydroquinoxalines with ethylene oxide and subsequent cyclization of the N-(β-hydroxyethyl)-N'-acetyl derivatives in refluxing HBr. The errors of the published data on the benzo[b]-1,4-diazabicyclo[2.2.2]octene system are demonstrated.

The synthesis of the benzo[b]-1,4-diazabicyclo[2.2.2]octene system was reported in 1921 [2]. By the action of 1,2-dibromoethane on 6-methyl-1,2,3,4-tetrahydroquinoxaline the authors obtained a product that has strange properties (the high melting point of the base, brightly colored salts, etc.) to which they assigned the 4'-methylbenzo[1',2'-b]-1,4-diazobicyclo[2.2.2]octene (2,3-dihydro-1,4-ethano-6-methylquinoxaline or 1,4-endoethylene-6-methyl-1,2,3,4-tetrahydroquinoxaline) structure (I) in conformity with the method of synthesis and some analytical data. The cited communication has been reflected in a number of reviews [3-5] and has been entered in *Beilsteins Handbuch der Organischen Chemie* [6] and *The Ring Index* [7]. Meisenheimer and Wieger [8] made an attempt to synthesize benzo[b]-1,4-diazabicyclo[2.2.2]octene (II) by the action of 1,2-dibromoethane on 1,2,3,4-tetrahydroquinoxaline under conditions similar to those in [2] but obtained a resinous product from which they were unable to isolate individual compounds. The synthesis of benzo[b]-1,4-diazabicyclo[2.2.2]octene bis (methylbromide), the properties of which differ from the properties of the salts of I, which were described in [2], was recently reported [9].

Our attempts to reproduce the results in [2] were unsuccessful: we obtained a resinous multicomponent reaction mass. We synthesized I and II starting from the monoacetyl derivatives of 1,2,3,4-tetrahydroquinoxalines III and IV by the following scheme:



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

Compound IV was obtained by acetylation of 1,2,3,4-tetrahydroquinoxaline by the method in [10]. The use of similar conditions for the monoacetylation of 6-methyl-1,2,3,4-tetrahydroquinoxaline, probablyleads to the production of a mixture of isomeric III, which contain a methyl group in the 6 and 7 positions. According to the PMR spectral data, product III contains one acetyl group and behaves like an individual compound in various chromatographic systems. Its hydrochloride has an elementary composition that corresponds to the calculated composition; however, it melts over a broad temperature range. N-β-Hydroethyl derivatives V and VI were obtained by the reaction of ethylene oxide with III and IV in acetic acid. The data from the PMR spectra confirm that they are products of the addition of 1 mole of ethylene oxide to N-acetyltetrahydroquinoxalines III and IV. The dihydrobromides of I and

*See [1] for communication 2.

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II are obtained in 25-50% yields when V and VI are heated in concentrated hydrobromic acid.* The IR, PMR, and mass spectra of the bases and the salts of I and II are in agreement with the expected structures. In addition to signals of aromatic protons at 7.0-7.2 ppm and of the CH_3 group at 2.3 ppm for I, the PMR spectra of bases I and II contain a symmetrical multiplet of protons of CH_2 groups in exo and endo orientations relative to the phenyl ring at 2.4-3.2 ppm. A complex multiplet with similar character is observed in the PMR spectra of tetrafluorobenzo[b]bicyclo[2.2.2]octene [11] and benzo[b]bicyclo[2.2.2]octene [12] at 1.1-2.0 ppm. In addition to molecular-ion peaks, peaks of M − 28 and M − 56 fragments, which correspond to the successive splitting out of CH_2CH_2 fragments from structures I and II, are recorded in the mass spectra. The UV spectra of II in 0.1 N NH_3 and 0.1 N HCl differ very slightly; this is not characteristic for aromatic amines and indicates the absence of retention of the conjugation of the free electron pairs of the heteroatoms with the aromatic ring. Compounds I and II display relatively high basicities: $pK_a \sim 5.83$ and 2.4 for I, and pK_a 5.65 and 2.5 for II (4.47 and 2.0 for o-phenylenediamine [13]).

Treatment of base II with methyl iodide gives the corresponding bis(methiodide), the PMR spectrum of which contains a singlet of N-methyl protons at 3.9 ppm (6H), a symmetrical multiplet of protons of CH_2 groups at 3.9-4.8 ppm (8H), and a multiplet of the phenyl ring at 7.8 ppm (4H); this is in agreement with the literature data for the bis(methylbromide) of II [9].

The base and the dihydrochloride of I obtained in this research differ completely with respect to their physical and chemical properties from those described in the literature, and this makes it possible to conclude that the report of the synthesis of 4'-methylbenzo-[1',2'-b]-1,4-diazabicyclo[2.2.2]octene by Moore and Doubleday [2] is erroneous.

EXPERIMENTAL

The IR spectra of the compounds were recorded with a UR-20 spectrometer. The UV spectra were recorded with a Specord UV-vis spectrophotometer. The PMR spectra were recorded on the δ scale with a Varian A56/60A spectrometer with tetramethylsilane as the external standard. The mass spectra were obtained with an MS-902 spectrometer, and the molecular weights and empirical formulas were calculated on the basis of these data. The ionization constants were found by potentiometric titration of bases I and II in aqueous solution at 21°C with an RNM-22 potentiometer. Chromatography was carried out on Silufol UV-254 plates in a tert-butanol—methyl ethyl ketone—formic acid—water system (8:6:3:3).

N-(β-Hydroxyethyl)-N'-acetyl-1,2,3,4-tetrahydroquinoxaline (VI). An 11.8-ml (240 mmole) sample of ethylene oxide was added to a cooled (to 0°C) solution of 15.5 g (93 mmole) of N-acetyl-1,2,3,4-tetrahydroquinoxaline (IV) [10] in 50 ml of acetic acid, and the flask was sealed and maintained at 20°C for 50 h. The reaction mixture was then evaporated in vacuo, and the concentrate was neutralized with aqueous $NaHCO_3$ solution. The aqueous mixture was extracted with chloroform, and the extract was dried over $MgSO_4$ and evaporated to dryness to give 15.0 g (73%) of a viscous oil with R_f 0.74. IR spectrum (in $CHCl_3$): 1051 (C—OH); 1521, 1610 (aromatic C=C); 1648 cm^{-1} (C=O). PMR spectrum (in $CDCl_3$): 6.5-7.1 (4H, m, aromatic protons); 3.8 (4H, m, CH_2), 3.4 (4H, m, CH_2), 2.5 (1H, broad s, OH), and 2.2 ppm (3H, s, $COCH_3$).

Benzo[b]-1,4-diazabicyclo[2.2.2]octene Dihydrobromide (II·2HBr). A solution of 17.6 g (80 mmole) of VI in 200 ml of 48% HBr was refluxed for 5 h, after which it was evaporated in vacuo, and the residue was dissolved by heating in 100 ml of ethanol. The solution was cooled, and the precipitated crystals were separated to give 12.8 g (50%) of a colorless substance with mp 206-218°C (dec.) and R_f 0.34. IR spectrum (in KBr): 1341 (C—N); 1480, 1496 (aromatic C=C); 2000-2500 (N^+—H); 3000 cm^{-1} (C—H). PMR spectrum (in D_2O): 7.9 (4H, m, aromatic protons) and 3.5-4.4 ppm (8H, symmetrical m, CH_2). Found %: Br 49.5. $C_{10}H_{12}N_2 \cdot 2HBr$. Calculated %: Br 49.6.

Benzo[b]-1,4-diazabicyclo[2.2.2]octene (II). A methanol solution of 1.33 g (4 mmole) of the dihydrobromide of II was neutralized with 4 ml of a 2 N solution of sodium methoxide (8 mmole) in methanol and evaporated to dryness. The residue was sublimed at 100°C (5 mm) to give 0.6 g (90%) of a colorless crystalline substance with mp 127-129°C. Recrystallization from benzene—petroleum ether (70-100°C) (2:1) gave a product that sublimed at 120°C and

*The scheme via which this reaction occurs will be discussed in our next communication.

had mp 138-141°C (in a sealed capillary) and R_f 0.34. IR spectrum (in KBr): 817 (C–H); 1047 (C–N); 1473 (aromatic C=C); 2888, 2952, and 2974 cm^{-1} (C–H). UV spectrum in 0.1 NH_3, λ_{max} (ε): 204 (9000), 258 (370), and 265 nm (280); in 0.1 N HCl: 210 (16000), 256 (220), and 264 nm (160). PMR spectrum (in CCl_4): 7.2 (4H, m, aromatic protons) and 2.4-3.2 ppm (8H, symmetrical m, CH_2). Found %: N 17.6; M 160.0990. $C_{10}H_{12}N_2$. Calculated %: N 17.5; M 160.1000.

Benzo[b]-1,4-diazabicyclo[2.2.2]octene Dihydrochloride (II·2HCl). This compound, with mp 172-180°C (dec.) and R_f 0.34, was obtained by treatment of base II with hydrogen chloride in ethanol. IR spectrum (in KBr): 1345 (C–N); 1480, 1495 (aromatic C=C); 2100-2520 (N^+–H); 3005 cm^{-1} (C–H). Found %: N 12.1. $C_{10}H_{12}N_2 \cdot 2HCl$. Calculated %: N 12.1.

Benzo[b]-1,4-diazabicyclo[2.2.2]octene Bis(methiodide). This compound was similarly obtained by refluxing (for 14 h) a methanol solution of base II with excess methyl iodide and had mp 161-164°C (dec.) and R_f 0.21. IR spectrum (in KBr): 1050 (C–N); 1495 (aromatic C=C); 2950, 3005, and 3035 cm^{-1} (C–H). PMR spectrum (in CF_3COOH): 7.8 (4H, m, aromatic protons), 3.9-4.8 (8H, symmetrical m, CH_2), and 3.9 ppm (6H, s, CH_3). Found %: C 32.5; H 4.2; I 57.1; N 6.2. $C_{10}H_{12}N_2 \cdot 2CH_3I$. Calculated %: C 32.5; H 4.1; I 57.1; N 6.3.

N-Acetyl-6(and/or 7)-methyl-1,2,3,4-tetrahydroquinoxaline (III). The monoacylation of 5.48 g (37 mmole) of 6-methyl-1,2,3,4-tetrahydroquinoxaline with 3.4 ml (36 mmole) of acetic anhydride under the conditions in [10] led to the formation of 2.36 g (36%) of III in the form of an oil with R_f 0.80. IR spectrum (in $CHCl_3$): 1069 (C–N); 1524, 1590 (aromatic C=C); 1650 (C=O); 2880, 2950,3015 (C–H); 3450 cm^{-1} (N–H). PMR spectrum (in CF_3COOH): 7.3 (3H, m, aromatic protons), 4.0 (4H, m, CH_2), 2.3 (3H, s, CH_3), and 2.2 ppm (3H, s, $COCH_3$). The hydrochloride had mp 110-140°C (after reprecipitation from methanol saturated with HCl by the addition of absolute ether) and R_f 0.80. Found %: Cl 15.5; N 12.5. $C_{11}H_{14}N_2O \cdot HCl$. Calculated %: Cl 15.7 N 12.4.

N-(β-Hydroxyethyl)-N'-acetyl-6(and/or 7)-methyl-1,2,3,4-tetrahydroquinoxaline (V). A 1.18-ml (24 mmole) sample of ethylene oxide was added to a cooled (to 0°C) solution of 1.67 g (8.8 mmole) sample of III in 5.0 ml of acetic acid, and the mixture was worked up as described for VI to give 1.2 g (58%) of the reaction product in the form of a viscous oil with R_f 0.77. IR spectrum (in $CHCl_3$): 1045 (C–OH); 1521, 1583 (aromatic C=C); 1650 (C=O); 2940, 3020 cm^{-1} (C–H). PMR spectrum (in CF_3COOH): 7.3 (3H, m, aromatic protons): 3.5-4.2 (8H, m, CH_2), 2.3 (3H, s, CH_3), and 2.2 ppm (3H, s, $COCH_3$).

4-Methylbenzo[1',2'-b]-1,4-diazabicyclo[2.2.2]octene Dihydrobromide (I·2HBr). A solution of 1.85 g (7.9 mmole) of I in 20 ml of 48% HBr was refluxed for 5 h, after which the solvent was removed by evaporation, and the residue was recrystallized from ethanol to give 0.66 g (25%) of a colorless substance with mp 190-197°C (dec.) and R_f 0.40. IR spectrum (in KBr): 1340 (C–N); 1511 (aromatic C=C); 2000-2500 (N^+–H); 2650, 2730, and 2998 cm^{-1} (C–H). PMR spectrum (in CF_3COOH): 7.7 (3H, m, aromatic protons), 3.6-4.5 (8H, symmetrical m, CH_2), and 2.3 ppm (3H, s, CH_3). Found %: Br 47.6. $C_{11}H_{14}N_2 \cdot 2HBr$. Calculated %: Br 47.6.

4'-Methylbenzo[1',2'-b]-1,4-diazabicyclo[2.2.2]octene (I). This compound was obtained from 3.4 g of the dihydrobromide by the method described for II. The yield of base I, with mp 66-68°C and R_f 0.40, was 1.6 g (90%). IR spectrum (in KBr): 813 (C–H); 1047 (C–N); 1480 (aromatic C=C); 2872, 2940, 2958, and 2973 cm^{-1} (C–H). PMR spectrum (in CCl_4): 7.0 (3H, s, CH_3). Found %: N 16.2; M 174.1149. $C_{11}H_{14}N_2$. Calculated %: N 16.1; M 174.1156. According to the data in [2], this compound had mp 175°C (dec.) and M 168.177 (in acetic acid).

4'-Methylbenzo[1',2'-b]-1,4-diazabicyclo[2.2.2]octene Dihydrochloride (I·2HCl). This compound was obtained by treatment of an ethanol solution of base I with hydrogen chloride. The white crystalline substance had mp 194-200°C (dec.). IR spectrum (in KBr): 1335 (C–N); 1515 (aromatic C=C); 1900-2400 (N^+–H); 3020, 3040 cm^{-1} (C–H). Found %: N 11.2. $C_{11}H_{14}N_2$. Calculated %: N 11.3. According to the data in [2], this substance was a red-brown compound in the solid form and in aqueous solution.

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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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