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DIAZABICYCLOALKANES WITH NITROGEN ATOMS IN THE NODAL POSITIONS.

6.* SYNTHESIS AND SOME PROPERTIES OF BENZO[f]-1,5-DIAZABICYCLO[3.2.2]NONENE AND BENZO[g]-1,6-DIAZABICYCLO[4.2.2]DECENE

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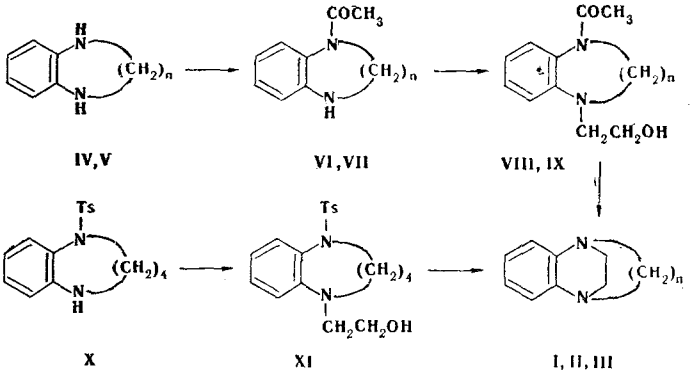
The reaction of N-acetyl derivatives of N,N'-trimethylene- and N,N'-tetramethylene-o-phenylenediamines with ethylene oxide gave the corresponding N-(β-hydroxyethyl)-N'-acetyl derivatives, the cyclization of which in refluxing hydrobromic acid leads to benzo[f]-1,5-diazabicyclo[3.2.2]nonene and benzo[g]-1,6-diazabicyclo[4.2.2.]decene.

We have previously obtained benzo[b]-1,4-diazabicyclo[2.2.2]octane (I) by cyclization of N-β-hydroxyethyl-1,2,3,4-tetrahydroquinoxaline [2]. In the present research we used a similar approach to synthesize benzo[f]-1,5-diazabicyclo[3.2.2]nonene (II) and benzo[g]-1,6-diazabicyclo[4.2.2]decene (III) in order to investigate the effect of the length of the polymethylene bridge on the properties of heterocyclic compounds of this type. N,N'-Trimethylene- and N,N'-tetramethylene-o-phenylenediamines (IV and V) were used as the starting compounds.



Compounds IV and V were acetylated under the conditions used for the monoacetylation of tetrahydroquinoxaline [3]. According to the results of analysis and the PMR spectra, the

*See [1] for Communication 5.

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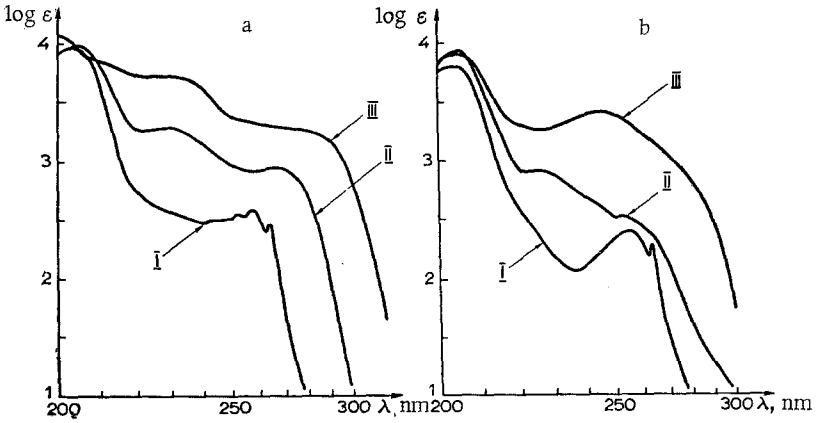

Fig. 1. UV spectra of I-III: a) in 0.1 N NH_4OH; b) in 0.1 N HCl.

resulting N-acetyl derivatives VI and VII contain one N-acetyl group. The action of ethylene oxide in acetic acid on VI and VII gave N-β-hydroxyethyl derivatives VIII and IX, which, according to the spectral and analytical data, are products of the addition of 1 mole of ethylene oxide to acetamides VI and VII. Compounds VIII and IX were cyclized by refluxing in concentrated hydrobromic acid. The dihydrobromides of II and III were obtained in ∿70% yields. A study of the cyclization and the behavior of the dihydrobromides of II and III under the reaction conditions by microcolumn liquid chromatography showed that, in contrast to the dihydrobromide of I, which exists under these conditions in equilibrium with N-β-bromoethyl-1,2,3,4-tetrahydroquinoxaline in a ratio of 7:3 [4], II and III are quite stable and do not give equilibrium mixtures, and the cyclization reaction proceeds completely to favor the formation of these compounds. The higher yields of the dihydrobromides of II and III in the cyclization reaction as compared with the yield of the dihydrobromide of I [2] are probably due to this. When N-β-hydroxyethyl-N'-(p-toluenesulfonamide) XI, obtained by hydroxyethylation of X [5], is refluxed in concentrated hydrobromic acid cyclization also occurs to give the dihydrobromide of III but in lower yield (30%). This decrease in the yield is probably associated with the higher hydrolytic stability of the toluene-sulfonamido group as compared with the acetamido group and with the occurrence of side redox reactions.

The spectral and analytical data for bases II and III and their salts are in agreement with the expected structures for these compounds. Three groups of signals are observed in the PMR spectra: protons of the central methylene groups of the trimethylene bridge (for II) in the form of two multiplets of two magnetically nonequivalent protons and the tetramethylene bridge (for III) in the form of a broad multiplet; protons of the methylene groups bonded to the nitrogen atom in the form of a broad multiplet; protons of an aromatic ring in the form of a singlet for the bases and in the form of a multiplet for the salts. In addition to molecular-ion peaks, fragments with M - 28 corresponding to splitting out of ethylene fragments are recorded in the mass spectra of II and III. The character of the fragmentation of II and III is similar to the fragmentation of I [2]. Compounds II and III, probably as a consequence of the +I effects of the additional methylene groups and the decrease in the conductivity of the inductive effect of thenitrogen atoms, are III (5.65 and 2.5 for I [2]). The decrease in the basicity of III as compared with II can be explained by an increase in the conjugation of the free electron pairs of the nitrogen atoms with the benzene ring as the number of methylene groups in the ring is increased. In fact, a comparison of the UV spectra of I, II, and III in 0.1 N NH_4OH (see Fig. 1a) shows the presence of a bathochromic shift of the absorption maximum as the number of methylene groups in the bridge is increased; this may be due to the development of conjugation of the nitrogen atoms with the benzene ring due to an increase in the angle between the free electron pairs of the nitrogen atoms and the plane of the benzene ring. The long-wave maxima vanish in the UV spectra of II and III in 0.1 N HCl (see Fig. 1b), whereas the UV spectrum of I remains virtually unchanged. It is apparent from Fig. 1 that the changes in the UV spectra of III on passing to an acidic medium are the most significant. This provides a basis for the assumption that the examined compounds are arranged in the following order with respect to the degree of conjugation of the free electron pair of the nitrogen atom of the heteroring with the benzene ring: III>II>I. A similar tendency in the change in the UV spectra as the length of the polymethylene chain was decreased was observed for [p]-1,3-benzimidazolophans [6].

It should be noted that the synthesis and properties of benzo[f]-1,5-diazabicyclo[3.2.2]-nonene (II) (1,4-endotrimethylene-6-methyltetrahydroquinoxaline) were described in 1921 by Moore and Doubleday [7] and have been included in the handbook literature [8, 9] and a number of reviews [10, 11]. A comparison of the properties of the base and its salts that we obtained with those presented in the literature shows that the previously published data on this heterocyclic system are erroneous.

EXPERIMENTAL

The IR spectra of KBr pellets 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 with a Varian A56/60A spectrometer (a Varian HA-100 spectrometer for II) with tetramethylsilane as the internal standard. The mass spectra were obtained with an MS-902 spectrometer, and the molecular masses and empirical formulas were calculated on the basis of these data. The ionization constants were found by potentiometric titration of the amines in aqueous solutions at 20°C with an EV-74 potentiometer with glass and calomel electrodes. The compositions of the reaction mixtures were analyzed by ion-exchange microcolumn chromatography on Aminex A7 cation-exchange resin in 2.0-4.0 N HCl under the conditions described in [4].

N,N'-Tri- and N,N'-tetramethylene-o-phenylenediamines (IV, V) and N-tosyl-N,N'-tetramethylene-o-phenylenediamine (X) were obtained by the method in [5].

N-Acetyl-N,N'-trimethylene-o-phenylenediamine (VI). A 1.4-ml (15 mmole) sample of acetic anhydride was added dropwise with stirring to a solution of 2.17 g (14.6 mmole) of IV in 22 ml of absolute ethanol while maintaining the temperature below 30°C. The mixture was then allowed to stand for 30 min, after which it was neutralized by the addition of 10% sodium hydroxide solution and extracted with benzene. The extract was dried with magnesium sulfate and filtered, and the benzene was removed by distillation *in vacuo*. The residue was recrystallized from benzene to give 2.12 g (76%) of a product with mp 134-135°C. IR spectrum: 780 (aromatic C–H); 1500, 1600 (aromatic C=C); 1640 (C=O); 2592 (C–H); 3320 cm^{-1} (N-H). PMR spectrum (in $CDCl_3$): 6.9 (4H, m, aromatic protons), 4.7 (1H, m, NH), 2.4-3.5 (4H, m, NCH_2), 1.8 (3H, s, CH_3), and 1.6-2.2 ppm (2H, m, CH_2). Found: C 69.4; H 7.5; N 14.9%. $C_{11}H_{14}N_2O$. Calculated: C 69.4; H 7.4; N 14.7%.

N-(β-Hydroxyethyl)-N'-acetyl-N,N'-trimethylene-o-phenylenediamine (VIII). A 2.7-ml (54 mmole) sample of ethylene oxide was added to a solution of 3.5 g (18 mmole) of VI in 35 ml of glacial acetic acid, and the mixture was maintained at room temperature for 24 h. It was then evaporated *in vacuo*, and the residue was neutralized with a saturated solution of sodium carbonate and extracted with chloroform. The extract was dried with magnesium sulfate and filtered, and the chloroform was removed by distillation. The residue was crystallized from benzene to give 2.2 g (51%) of a product with mp 93-95°C. The reaction product was chromatographically individual and was eluted with 2.7 N HCl. IR spectrum: 760 (aromatic C–H); 1510, 1600 (aromatic C=C); 1630 (C=O); 2860 (C–H); 3370 cm^{-1} (O–H). PMR spectrum (in $CDCl_3$): 7.0 (4H, m, aromatic protons), 4.6 (1H, m, OH), 2.4-3.8 (8H, m, NCH_2, OCH_2), 1.8 (3H, s, CH_3), and 1.4-2.1 ppm (2H, m, CH_2). Found: C 67.0; H 7.8; N 11.9%. $C_{13}H_{18}N_2O_2$. Calculated: C 66.6; H 7.7; N 12.0%.

Benzo[f]-1,5-diazabicyclo[3.2.2]nonene Dihydrobromide (II·2HBr). A solution of 2.08 g (8.9 mmole) of VIII in 40 ml of 48% hydrobromic acid was refluxed for 6 h, after which it was evaporated *in vacuo*, and 10 ml of absolute ethanol was added to the residue. The resulting precipitate was removed by filtration to give 2.21 g (74%) of a product with mp 210-215°C (dec., from methanol). IR spectrum: 780 (aromatic C–H); 1370 (C–N); 1490, 1508 (aromatic C=C); 2000-2500 cm^{-1} (N^+–H). Found: C 38.9; H 4.8; N 8.4%. $C_{11}H_{14}N_2 \cdot 2HBr$. Calculated: C 39.3; H 4.8; N 8.3%.

Benzo[f]-1,5-diazabicyclo[3.2.2]nonene (II). This compound was obtained by neutralization of an aqueous solution of the dihydrobromide with 10% sodium hydroxide solution. The base was extracted with ether, the ether was evaporated, and the residue was sublimed *in vacuo* at 100°C (2 mm) to give a product with mp 51-54°C in 90% yield. The product was chromatographically individual and was eluted with 3.7 N HCl. IR spectrum: 774 (aromatic C–H), 1482 (aromatic C=C), and 2920 cm^{-1} (C–H). PMR spectrum (in CCl_4): 6.9 (4H, s, aromatic protons), 2.7-3.3 (8H, m, NCH_2), 1.9-2.3 (1H, m, HCH), and 1.3-1.6 ppm (1H, m, HCH). Found: N 16.3%, M 174.1151. $C_{11}H_{14}N_2 \cdot 2HCl$. Calculated: N 16.1%; M 174.1156. The dihydrochloride was obtained by treatment of base II with hydrogen chloride in methanol and had mp 179-188°C (dec., from

absolute ethanol). IR spectrum: 780 (aromatic C–H); 1370 (C–N); 1490, 1508 (aromatic C=C); 2000-2500 cm^{-1} (N^+–H). Found: 11.3%. $C_{11}H_{14}N_2 \cdot 2HCl$. Calculated: N 11.3%. The methiodide was obtained by treatment of an ether solution of base II with methyl iodide and had mp 162-168°C (from absolute ethanol). IR spectrum: 795 (aromatic C–H), 1495 (aromatic C=C), and 2950 cm^{-1} (C–H). PMR spectrum (in CF_3COOH): 7.8 (4H, m, aromatic protons), 3.0-4.7 (10H, m, CH_2), and 3.8 ppm (3H, s, CH_3). Found: N 8.6%; $C_{12}H_{17}IN_2$. Calculated: N 8.9%.

N-Acetyl-N,N'-tetramethylene-o-phenylenediamine (VII). A 5.0-g (64%) sample of VII, with mp 125-127°C (from benzene), was obtained from 6.2 g of amine V by a procedure similar to that used to obtain VI. IR spectrum: 754 (aromatic C–H); 1509, 1610 (aromatic C=C); 1643 (C=O); 2940 (C–H); 3340 cm^{-1} (N–H). PMR spectrum (in $CDCl_3$): 6.8 (4H, m, aromatic protons), 4.7 (1H, m, NH), 2.7-4.0 (4H, m, NCH_3), 1.8 (3H, s, CH_3), and 1.5-1.9 ppm (4H, m, CH_2). Found: C 70.9; H 8.2; N 13.8%. $C_{12}H_{16}N_2O$. Calculated: C 70.6; H 7.9; N 13.7%.

N-(β-Hydroxyethyl)-N'-acetyl-N,N'-tetramethylene-o-phenylenediamine (IX). This compound, with mp 103-105°C (from benzene), was obtained in 45% yield by the method used to prepare VIII. The product was chromatographically individual and was eluted with 2.8 N HCl. IR spectrum: 790 (aromatic C–H); 1510, 1596 (aromatic C=C); 1640 (C=O); 2950 (C–H); 3440 cm^{-1} (O–H). PMR spectrum (in $CDCl_3$): 7.2-7.7 (4H, m, aromatic protons), 5.1 (1H, m, OH), 3.0-4.4 (8H, m, NCH_2, OCH_2), 1.8-2.3 (4H, m, CH_2), and 2.1 ppm (3H, s, CH_3). Found: N 116.%. $C_{14}H_{20}N_2O_2$. Calculated: N 11.3%.

N-(β-Hydroxyethyl)-N'-tosyl-N,N'-tetramethylene-o-phenylenediamine (XI). This compound was obtained by the method used to prepare VIII. A 5.7-g sample of amine X gave 5.7 g of hydroxyethyl derivative XI in the form of an oil, which was used for the cyclization without additional purification. PMR spectrum (in CCl_4): 6.3-7.9 (8H, m, aromatic protons), 3.1-3.8 (8H, m, NCH_2, OCH_2), 2.4 (3H, s, CH_3), and 1.4-1.8 ppm (4H, m, CH_2).

Benzo[g]-1,6-diazabicyclo[4.2.2]decene Dihydrobromide (III·2HBr). This compound was obtained by the procedure used to prepare the dihydrobromide of II. The reaction of 1 g of IX gave 0.92 g (65%) of III·2HBr. Another method was used to obtain 0.29 g (30%) of III·2HBr, with mp 215-222°C (dec., from methanol), from 1 g (3 mmole) of hydroxyethyl derivative XI and 0.26 g (2.8 mmole) of phenol by refluxing in 20 ml of 48% hydrobromic acid. IR spectrum: 778 (aromatic C–H), 1371 (C–N), 1482 (aromatic C=C), and 2000-2500 cm^{-1} (N^+–H). PMR spectrum (in CF_3COOH): 7.5-8.1 (4H, m, aromatic protons), 3.3-4.2 (8H, m, NCH_2), and 1.4-2.5 ppm (4H, m, CH_2). Found: C 41.2; H 5.1; N 8.1%. $C_{12}H_{16}N_2 \cdot 2HBr$. Calculated: C 41.2; H 5.2; N 8.0%.

Benzo[g]-1,6-diazabicyclo[4.2.2]decene (III). This compound was isolated in 80% yield by the method used to isolate base II and had mp 30-33°C. The product was chromatographically individual and was eluted with 3.6 N HCl. IR spectrum (in $CHCl_3$): 1369 (C–N), 1498 (aromatic C=C), and 2930 cm^{-1} (C-H). PMR spectrum (in CCl_4): 7.2 (4H, s, aromatic protons), 3.3-3.7 (8H, m, NCH_2), and 1.5-2.0 ppm (4H, m, CH_2). Found: M 188.1328. $C_{12}H_{16}N_2$. Calculated: M 188.1313. The dihydrochloride was obtained by treatment of base III with hydrogen chloride in methanol and had mp 127-136°C (dec., from absolute ethanol). IR spectrum: 782 (aromatic C-H), 1372 (C-N), 1482 (aromatic C=C), and 2000-2500 cm^{-} (N^+-H). Found: N 10.9%. $C_{12}H_{16}N_2 \cdot 2HCl$. The methiodide was obtained by refluxing base III with methyl iodide in methanol and had mp 160-163°C (from ethanol). IR spectrum: 763 (aromatic C–H); 1500, 1604 (aromatic C=C); 2920 cm^{-1} (C-H). PMR spectrum (in CF_3COOH): 7.5-8.1 (4H, m, aromatic protons), 3.5-4.6 (8H, m, NCH_2), 3.8 (3H, s, CH_3), and 1.3-2.4 ppm (4H, m, CH_2). Found: I 38.4; N 8.8%. $C_{13}H_{19}IN_2$. Calculated: I 38.4; N 8.5%.

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