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DIAZABICYCLOALKANES WITH NITROGEN ATOMS IN THE JUNCTION POSITIONS.

11.* SYNTHESIS OF DIBENZO[b,e]-1,4-DIAZABICYCLO[2.2.2]OCTADIENE

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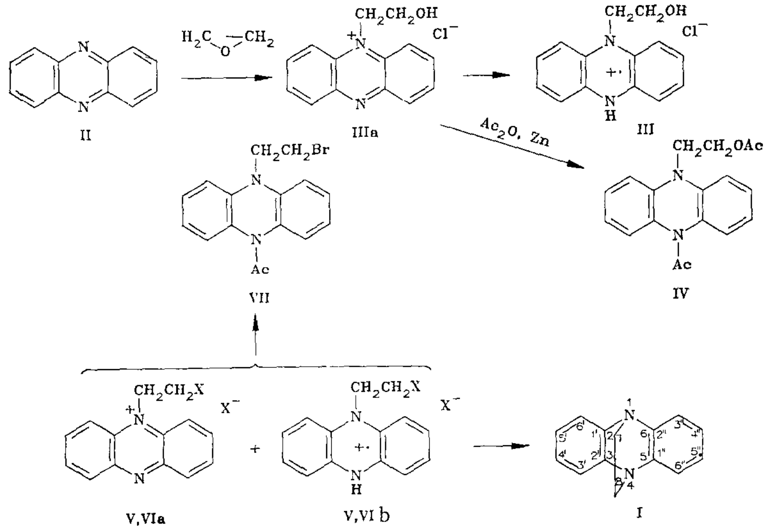
The reaction of ethylene oxide with phenazine followed by treatment with HCl gives N-(2-hydroxyethyl)phenazinium chloride, which yields N-2-haloethyl derivatives of phenazine in a mixture with products of their one-electron reduction when the hydroxyl group is exchanged for a halogen. Heating of these mixtures in the presence of sodium borohydride results in intramolecular cyclization with the formation of a new heterocyclic system, viz., dibenzo[b,e]-1,4-diazabicyclo[2.2.2]octadiene.

Continuing the investigation of the influence of the annelation of benzene rings on the properties of diazabicycloalkenes with nitrogen atoms in the junction positions [1], we carried out the synthesis of a new heterocyclic system, viz., dibenzo[b,e]-1,4-diazabicyclo [2.2.2]-octadiene (5,10-ethano-5,10-hydrophenazine) (I). The synthesis was carried out with phenazine (II) as the starting compound according to the following scheme:



Va, b X=Br; VIa,b X=Cl

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*For report 10 see [1].

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It was possible to obtain the desired N-(2-hydroxyethyl)phenazinium chloride (IIIa) with a satisfactory yield only by treating II with a large excess of ethylene oxide in acetic acid due to the low nucleophilicity of the nitrogen atoms in phenazine. Purification of hydroxyethyl derivative IIIa by reprecipitation made it possible to obtain a sample whose spectroscopic and analytical characteristics correspond completely to the expected values. The electronic absorption spectrum of this sample coincides with the spectrum of N-(3-sulfonatopropyl)phenazinium [2]. The attempts to recrystallize IIIa from alcohols, especially in the presence of hydrohalic acids, or changes in its isolation conditions result in changes in the color of the product. It acquires a green color, absorption appears at 2600-2800 cm^{-1} (NH^+) in the IR spectrum, a number of bands in the 1300-1500-cm^{-1} range vanish, and the PMR spectrum of such samples is not detected in the usual region, although its chromatographic behavior remains unchanged. This points out the ease of the one-electron reduction of compound IIIa with the formation of the 5-(2-hydroxyethyl)-5,10-dihydrophenazine radical cation (IIIb). The repeated crystallization of compound IIIa from ethanol containing HCl gives compound IIIb with an electronic spectrum corresponding to the spectrum of the 5,10-dimethyl-5-dihydrophenazine radical cation in [3], and an evaluation with the aid of the ESR spectrum demonstrates the presence of a ∿90% concentration of radical particles in the crystalline sample. The correctness of the structures established for compounds IIIa and IIIb was confirmed by their reductive acetylation to 5-acetyl-10-(2-acetoxyethyl)-5,10-dihydrophenazine (IV), whose structure was determined according to spectroscopic and analytical data. When diacetyl derivative IV is heated in a 0.01 N water—methanol solution of HCl, it undergoes hydrolysis, giving back radical cation IIIb, which is identical to the original. Such behavior of the intermediate 5-(2-hydroxyethyl)-5,10-dihydrophenazine is probably attributable to the low oxidation potential of substituted dihydrophenazines [4].

The exchange of the hydroxyl groups for bromine in compound IIIa was carried out under the action of phosphorus tribromide, a product of dark green color, whose elemental analysis conforms to the empirical formula of N-(2-bromoethyl)phenazinium bromide, being obtained. However, the presence of a signal in the ESR spectra and the electronic absorption spectrum attest to the radical cation nature of this product. An evaluation of the concentration of the radical particles on the basis of the ESR spectra for the crystalline sample gives a value of ∿30%, while the data from the electronic spectrum of a solution in ethanol indicate that the value is ∿60%. The product obtained is probably a mixture of variable composition of the radical cation and its oxidized form (Va and b). The reductive acetylation of a mixture of Va and b gives 5-acetyl-10-(2-bromoethyl)-5,10-dihydrophenazine (VII), whose spectroscopic and analytical characteristics correspond to the expected values. Hydroxyethyl derivative IIIa behaves similarly under the action of phosphorus oxychloride. The green crystalline product (VIa and b) contains ∿30% radical particles, according to the data from the ESR spectra, and ∿60% radical particles, according to an evaluation based on the electronic spectrum of a solution in ethanol. It should be noted that TLC of haloalkyl derivatives Va, Vb, VIa, and VIb on Silufol plates reveals the presence of one green component, and only the addition of oxidizing agents to the mobile phase results in the appearance of a yellow component with a lower R_f (clearly quaternary salts of phenazine), which gradually takes on a green color.

Taking into account the ease of the occurrence of redox reactions in the series of N-alkylated phenazines, we carried out the reduction of the mixtures of Va and b and of VIa and b to the corresponding 5-(2-haloethyl)-5,10-dihydrophenazines and their subsequent intramuscular cyclization in a single step without isolating the intermediate products by heating them in diglyme with an excess of sodium borohydride. The cyclization is accompanied by the formation of fairly complex mixtures, from which compound I can be isolated by preparative TLC with a ∿40% yield. The main secondary process is the dealkylation of the N-substituted phenazines, as in evinced by the recovery of phenazine from the reaction mixtures with a yield up to 20%. In the mass spectrum of I, along with the peak of the molecular ion there is a fragment ion with a mass equal to M - 28, which corresponds to the elimination of an ethylene bridge, as is characteristic of compounds containing a diazabicyclooctane fragment [5]. The PMR spectrum shows three groups of signals: a singlet at 3.31 ppm, which corresponds to the protons of the ethylene bridgge and points out the symmetric arrangement of the annelated benzene rings in compound I, and two multiplets in the region of aromatic protons at 7.24 and 7.42 ppm, which correspond to the protons of ortho-disubstituted benzene. An analysis of these signals in the approximation of an AA'XX' system gives $J_{3'4'} = J_{5'6'} = J_{3''4''} = J_{5''6''} = 7.98$, $J_{4'5'} = J_{4''5''} = 6.09$, and $J_{3'5'} = J_{4'6'} = J_{3''5''} = J_{4''6''} = 1.22$ Hz.

The electronic spectrum of compound I practically coincides with the spectrum of the dibenzoquinuclidine heterocyclic system, which has a similar geometry [6]. With consideration of the elemental analysis, this set of data allows us to assign the structure of dibenzo[b, e]-1,4-diazabicyclo[2.2.2]octadiene to compound I. Compound I is stable in neutral and alkaline solutions and can be stored well in air, but it gradually decomposes in solutions of acids. In contrast to benzo[b]-1,4-diazabicyclo[2.2.2]octene, which forms an equilibrium mixture with 1-(2-bromothyl)-1,2,3,4-tetrahydroquinoxaline upon heating in conc. HBr[7], compound I irreversibly opens the bicyclic fragment to form the 5-(2-bromoethyl)-5,10-dihydrophenazine radical cation in a mixture with its oxidized form (Va, b). This product was recovered in an ~70% yield from the reactive mixture.

Thus, it has been established that under the action of sodium borohydride, N-(2-haloethyl)phenazinium halides and the products of their one-electron reduction can be subjected to reduction and intramolecular cyclization with the formation of dibenzo[b,e]-1,4-diazabicyclo[2.2.2]octadiene in a single step.

EXPERIMENTAL

The IR spectra were recorded on a UR-20 instrument in KBr tablets, the electronic absorption spectra were recorded on a Specord UV-VIS spectrometer in ethanol, the ESR spectra were recorded on an RÉ 1306 spectrometer, and the PMR spectra were recorded on Varian A56/60A and Bruker WP-200SY spectrometers with HMDS as an internal reference. The molecular weights were determined on an MS-902 mass spectrometer. Thin-layer chromatography (TLC) was carried out on Silufol UV-254 plates in the following systems: 8:6:3:3 tert-butanol—methyl ethyl ketone—formic acid—water (A), 8:6:3:3:1 tert-butanol—methyl ethyl ketone—formic acid—water—30% H_2O_2 (B), and 10:1 chloroform—ether (C). The identical nature of the structure of the compounds obtained by different methods was proved with the aid of TLC and the PMR and IR spectra.

N-(2-Hydroxyethyl)phenazinium Chloride (IIIa). A solution of 10 g (56 mmole) of phenazine in 100 ml of glacial acetic acid is given an addition of 50 ml of ethylene oxide at 10°C. The reaction mixture is held for 6 days at 20°C in a closed flask. Then 10 ml of conc. HCl are introduced, and the mixture is evaporated in a vacuum. The dark brown viscous mass is treated twice with 50 ml of a 1:1 mixture of toluene with heptane, which is distilled off in a vacuum. The residue is given an addition of ~150 ml of ether until a stable suspension forms and is left to stand overnight. The precipitate is filtered out and washed with acetone and ether. Reprecipitation from methanol by ether gives 10.5 g (72%) of the brown crystalline compound IIIa, mp 340-350°C (with decomposition), R_f 0.58 and 0.26 (system A), R_f 0.27 (system B). IR spectrum: 770 (=C—H); 1075, 1370 (C—O—H), 1560 (C=N), 1610 (C=C), 2840, 2950 (—CH_2—), 3030 (=C—H), 3230-3400 cm^{-1} (—O—H). Electronic spectrum, λ_{max} (log ε): 262 (4.89), 387 (4.39), 440 nm (3.47). PMR spectrum (CD_3OD) : 7.93-9.03 (8H, m, arom. H), 5.45-5.95 (2H, m, $—CH_2N^+$), 4.20-4.44 ppm (2H, m, CH_2O). Found: C, 64.5; H, 5.1; N, 10.5%. Calculated for $C_{14}H_{13}ClN_2O$: C, 64.5; H, 5.0; N, 10.7%.

Chloride of the 5-(2-Hydroxyethyl)-5,10-dihydrophenazine Radical Cation (IIIb). A sample of compound IIIa is crystallized four times from ethanol with an addition of a drop of conc. HCl. Dark green acicular crystals of IIIb are obtained with mp 350°C (with decomposition), R_f 0.58 (system A), and R_f 0.27 (system B). IR spectrum: 760 (=C—H); 1060, 1360 (C—O—H); 1525 (C=N); 1600 (C=C); 2500-2700 (NH^+), 2845-2920 (—CH_2—); 3050 (=C—H); 3250-3400 cm^{-1} (—O—H). Electronic spectrum, λ_{max}(log ε): 210 (4.30), 263 (4.62), 390 (4.33), 452 (3.59), 600 (3.05), 650 (3.20), 720 nm (3.13). Found: C, 64.2; H, 5.7; N, 10.6%. Calculated for $C_{14}H_{14}ClN_2O$: C, 64.2; H, 5.4; N, 10.7%.

5-Acetyl-10-(2-acetoxyethyl)-5,10-dihydrophenazine (IV). A solution of 3 g (11.5 mmole) of IIIa in a mixture of 20 ml of glacial acetic acid and 30 ml of acetic anhydride is cautiously given an addition of 3 g of zinc filings. The reaction mixture is held for 10 h at 20°C, the given an additional 1-g portion of zinc filings, and boiled with a reflux condenser for 0.5 h. The precipitate is filtered out, and the filtrate is evaporated in a vacuum. The residue is treated with a saturated solution of Na_2CO_3 and extracted with chloroform. The extract is dried with $MgSO_4$ and filtered, the chloroform is distilled off, and the residue is introduced into a column (2 × 40 cm) with silica gel. Elution by a 5:1 chloroform—ethyl acetate system gives 2.16 g (60%) of compound IV, mp 108-109°C (from an acetone—water mixture), R_f 0.37 (system C). IR spectrum: 1050, 1230 (C—O—C); 1680 (amide C=O); 1740 (esteric C=O); 2850, 2915, 2950 (—CH_2— and CH_3); 3080 cm^{-1} (=C—H). PMR spectrum (CCl_4): 6.80-7.32 (8H, m, aromatic H), 4.12-4.35 (2H, m, CH_2O), 3.78-4.07 (2H, m, CH_2N), 2.01 (3H, s, CH_3COO), 1.87 ppm (3H, s, CH_3CON). Found: C, 69.8; H, 5.7; N, 9.0%. Calculated for $C_{18}H_{18}N_2O_3$: C, 69.8; H, 5.8; N, 9.0%.

Mixture of the Bromide of the 5-(2-Bromoethyl)-5,10-dihydrophenazine Radical Cation and N-(2-Bromoethyl)phenazinium Bromide (Va, b). A solution of 2 g (7.7 mmole) of IIIa in 20 ml of sulfolane and 4 ml of PBr_3 is held for 10 h at 20-25°C and the heated to 140°C over the course of 20 min. After cooling, the reaction mixture is poured into 60 ml of dioxane, and an addition of ether results in the precipitation of a dark green substance, which is filtered out and washed with chloroform and ether. The yield of the mixture of Va and b is 2.3 g (82%), m; 250-260°C (with decomposition), R_f 0.78 (system A), R_f 0.42 (system B). IR spectrum: 760 (=C—H); 1530 (C=N); 1600 (C=C); 2850, 2950 (—CH_2—); 3060 cm^{-1} (=C—H). Electronic spectrum, λ_{max} (log ε): 210 (4.35), 262 (4.70), 390 (4.09), 451 (3.64), 604 (2.82), 657 (2.98), 723 nm (2.91). Found: C, 46.0; H, 3.7; Br, 41.6; N, 7.3%. Calculated for $C_{14}H_{13}Br_2N_2$: C, 45.6; H, 3.6; Br, 43.3; N, 7.6%.

5-Acetyl-10-(2-bromoethyl)-5,10-dihydrophenazine (VII). A suspension of 1 g (2.7 mmole) of the mixture of Va and b in 15 ml of acetic anhydride and 5 ml of acetic acid is hydrogenated at atmospheric pressure and 20°C over 10% Pd/C. Then the reaction mixture is heated for 5 h at 60°C, the catalyst is filtered out, and the filtrate is evaporated in a vacuum. The residue is given an addition of 30 ml of water, and the emulsion obtained is extracted by chloroform (four 10-ml portions). The extract is washed with 5% $NaHCO_3$, dried over $MgSO_4$, filtered, and evaporated. The residue consists of 0.8 g of a colorless oil, from which 0.5 g of VII (56%) with mp 114-116°C (from acetone) and R_f 0.63 (system C) is isolated by chromatography on silica gel (2 × 40 cm column with chloroform as the eluent). IR spectrum: 770 (=C—H); 1590 (C=C); 1680 (amide C=O); 2860, 2970 (—CH_2); 3070 cm^{-1} (=C—H). PMR spectrum (CCl_4): 6.70-7.36 (8H, m, arom. H), 4.03 (2H, t, CH_2N), 3.39 (2H, t, CH_2Br), 1.90 ppm (3H, s, CH_3CO). Found: C, 58.1; H, 4.4; N, 8.4%. Calculated for $C_{16}H_{15}BrN_2O$: C, 58.0; H, 4.6; N, 8.5%.

Mixture of N-(2-Chloroethyl)phenazinium Chloride and the Chloride of the 5-(2-Chloroethyl)-5,10-dihydrophenazine Radical Cation (VIa, b). A suspension of 2 g (5.4 mmole) of IIIa in 10 ml of $POCl_3$ is boiled with a reflux condenser for 3 h. The reaction mixture is evaporated in a vacuum, the residue is dissolved in 10 ml of absolute ethanol, the solution is boiled for 20 ml, and the alcohol is distilled off in a vacuum. The residue is redissolved in 10 ml of ethanol, and an addition of ether results in the precipitation of dark green crystals of VIa and b, which are filtered out, washed with ether, and purified by reprecipitation from methanol by ether. The yield of the mixture of VIa and b is 1.8 g (84%), mp 350°C (with decomposition), R_f 0.84 (system A), R_f 0.47 (system B). IR spectrum: 760 (=C—H); 1530 (C=N); 1600 (C=C); 2840, 2960 (—CH_2—); 3060 cm^{-1} (=C—H). Electronic spectrum, λ_{max} (log ε): 210 (4.29), 262 (4.74), 390 (4.13), 451 (3.66), 604 (2.84), 657 (3.00), 723 nm (2.93). Found: Cl, 25.1; N, 9.6%. Calculated for $C_{14}H_{13}Cl_2N_2$: Cl, 25.3; N, 10.0%.

Dibenzo[b,e]-1,4-diazabicyclo[2.2.2]octadiene (I). A. A suspension of 0.4 g (10 mmole) of sodium borohydride in 25 ml of diethylene glycol dimethyl ether is gradually given an addition of 1 g (3.6 mmole) of the mixture of VIa and b with continual stirring. The mixture is held at 20°C until the evolution of the gas ceases and is heated in an argon atmosphere for 30 min at 70°C. The temperature is then increased to 160°C and held for 4 h. The precipitate is filtered out and washed with ether, and the combined filtrates are evaporated in a vacuum. The residue is given an addition for 10 ml of methanol, and the solution obtained is passed through a column (2 × 30 cm) with the KRS-2P resin in the H^+ form. The column is washed with methanol, and the reaction mixture is eluted by 2 N NH_3 in methanol. The eluate is evaporated, and the residue is dissolved in 5 ml of chloroform and applied to a 35 × 25 cm plate with a layer of silica gel KSK. The separation is carried out in a 10:1 chloroform—ether system. The bands are detected in UV light. The fraction with R_f 0.5 is collected, and compound I is desorbed by a 1:1 mixture of chloroform with methanol. The solvent is distilled off, and the residue is sublimed at 110°C (2 mm Hg). The yield of I is 0.28 g (37%), mp 147-149°C (from hexane), R_f 0.28 (system C). IR spectrum: 770 (=C—H); 2890, 2980 (—CH_2—); 3050 cm^{-1} (=C—H). UV spectrum (in ether), λ_{max} (log ε): 267 (3.18), 274 nm (3.18). PMR spectrum (in CCl_4): 7.42 (4H, m, aromatic H), 7.24 (4H, m, aromatic H), 3.31 ppm (4H, s, —CH_2CH_2—). Found: C, 80.7; H, 5.8; N, 13.4%; M 208.0944. Calculated for $C_{14}H_{12}N_2$: C, 80.7; H, 5.8; N, 13.4%; M 208.1.

B. A 0.085-g yield (37%) of compound I with mp 146-148°C (from hexane) is obtained from 0.4 g (1.1 mmole) of the mixture of Va and b under the action of 0.15 g (4 mmole) of sodium borohydride in 10 ml of diethylene glycol dimethyl ether by the method described above.

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