DIAZABICYCLOALKANES WITH NITROGEN ATOMS IN THE NODAL POSITIONS.

7.* SYNTHESIS AND CONFIGURATION OF 2,3-DIPHENYL-1,4-DIAZABICYCLO[2.2.2]-OCTANE

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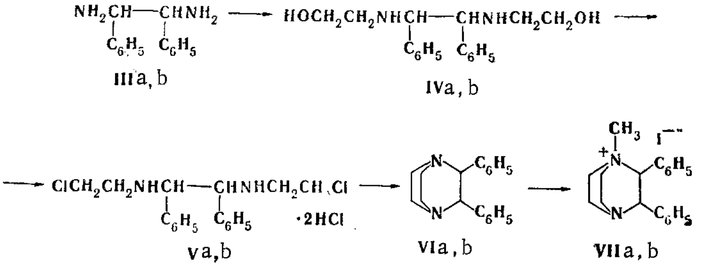
The reaction of ethylene oxide with the meso and d,*l* diasteromers of 1,2-diphenylethylenediamine gave N,N'-bis(β-hydroxyethyl)-1,2-diphenylethylenediamines, which upon refluxing with $SOCl_2$ form N,N'-bis(β-chloroethyl)-1,2-ethylenediamines. The latter upon heating in dimethylformamide (DMF) at 150°C undergo cyclization to give, respectivley, cis- and trans-2,3-diphenyl-1,4-diazabicyclo[2.2.2]octane. Evidence for the spatial orientation of the phenyl substituents in the diazabicyclooctanes obtained was obtained by means of an analysis of the multiplicity of the methylene protons in the PMR spectra. The vicinal spin–spin coupling constants for the benzyl protons of the isomeric 2,3-diphenyl-1,4-diazabicyclo[2.2.2]octanes in the ^{13}C–H satellites were measured. The values obtained were compared with the literature data and with the dihedral angles calculated from mechanical models of the molecules.

The preparation of 1,4-diazabicyclo[2.2.2]octane (I) by double intramolecular cyclization of N,N'-bis(β-chloroethyl)-N,N'-bis(β-cyanoethyl)ethylenediamine (II) has been reported [2]. It seemed of interest to investigate the possibility of the use of a similar approach for the synthesis of disubstituted derivatives of this heterocyclic system and to evaluate the effect of the spatial orientation of the substituents on this reaction. The meso and d,*l* forms of 1,2-diphenylethylenediamine (IIIa,b) were used as the starting compounds [3, 4].



N,N'-Bis(β-hydroxyethyl) derivatives IVa,b were obtained in 77-84% yields by the action of ethylene oxide on IIIa,b. The reaction proceeds quite smoothly and is virtually unaccompanied by the formation of tri- and tetrahydroxyethyl derivatives; this constitutes evidence for the relatively low nucleophilicity of the β-hydroxyethylamino groups in IVa, b. This made it possible to assume that the optimum nucleophilicity of the nitrogen atoms that is necessary for the occurrence of double intramolecular alkylation has already been reached and that it is not necessary to introduce additional N-β-cyanoethyl groups, as in [2]. The structures of the products obtained were established by means of the PMR spectra and elementary analysis.

Replacement of the hydroxy groups of IVa,b by chlorine atoms was accomplished by the action of thionyl chloride. As a result, we obtained dihydrochlorides Va,b in 52-78% yields. It should be noted that products IVa and Va, which were obtained from meso form IIIa, have

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*See [1] for Communication 6.

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higher melting points than the corresponding products IVb and Vb, whereas the IR spectra of amines IVa, b and Va, b are similar.

The double intramolecular cyclization of Va,b was carried out in dimethylformamide (DMF) at 150°C. Since it was assumed that a different spatial orientation of the bulky phenyl substituents in diastereomers Va,b can affect the rate of cyclization, the course of the reaction was followed from the accumulation of chloride ions in the reaction mixture by potentiometry and from the change in the concentration of bis(chloroethyl)amines Va,b qualitatively by means of thin-layer chromatography (TLC). We found that under the selected conditions the rates of double intramolecular alkylation for Va,b to give 2,3-diphenyl-1,4-diazabicyclo[2.2.2]octanes (VIa,b) are virtually the same, i.e., the spatial orientation of the phenyl substituents has little effect on the cyclization reaction. A comparison of these results with previous observations of the double intramolecular cyclization of bis(chloroethyl)amine II [2] shows that the overall rate of the process is considerably higher in the latter case than the rates that we found for Va,b. This is probably associated with the difference in the rate of the second step in the cyclization, which takes place in the intermediately formed piperazine derivatives that contain a β-chloroethyl group, since the rate of elimination of the first equivalent of chloride ion from Va,b is comparable to the rate of double cyclization for II (several minutes). The large difference in the rate of the second step of the cyclization may be due to the fact that the β-chloroethyl group, after the first step of the cyclization, is attached to a quaternary nitrogen atom in the case of II, whereas it is attached to a tertiary nitrogen atom in the case of Va,b. However, it is known [5] that piperazine derivatives that contain β-chloroethyl groups attached to a quaternary nitrogen atom readily undergo cyclization to give quaternary salts of 1,4-diazabicyclo[2.2.2]octane.

Bicyclic isomeric VIa,b, which have identical elementary compositions and similar IR spectra but differ with respect to their melting points (Table 1) and PMR spectra, were isolated in 51-65% yields from the reaction mixtures obtained by heating diastereomers Va,b in DMF. One might have expected that 2,3-diphenyl-1,4-diazabicyclo[2.2.2]octane with a cis orientation of the phenyl substituents should have been formed from meso form Va as a result of double cyclization and that the trans isomer should have been formed from d,*l* form Vb.

The PMR spectra of VIa,b (see the experimental section) contain three groups of signals with an integral intensity ratio of 5:1:4, the chemical shifts of which correspond to aromatic, benzyl, and methylene protons, respectively. As a consequence of the equivalence of the benzyl protons in the 2 and 3 positions, in the spectra of both the cis and trans isomers the signals of these protons show up in the form of singlets; however, a study of the ^{13}C—H satellites for these protons made it possible to measure the $J_{H_2H_3}$ SSCC. According to these data, the constant for VIa is 10 Hz, and the constant for VIb is 8.6 Hz. The close values of the constants obtained make it impossible to use them for the assignment of the isomers. We therefore used an analysis of the multiplicity of the CH_2 groups in the PMR spectra to prove the spatial orientation of the phenyl substituents in VIa,b.

In the spectrum of the cis isomer of 2,3-diphenyl-1,4-diazabicyclo[2.2.2]octane (VIa) the signals of the CH_2 groups of the ethylene bridges, which are under the anisotropic influence of the phenyl rings, should, in the general case in view of the symmetry of the compound, show up in the form of symmetrical multiplets of AA'BB' systems. However, since both phenyl groups are directed to the same side, one may expect that they have an anisotropic effect on the chemical shifts of the protons of primarily one of the ethylene bridges (the one closer to the phenyl substituents), the signals of the protons of which should appear in the spectrum in the form of a symmetrical multiplet of an AA'BB' system. The effect of the protons of the CH_2 groups of the second bridge (the remote one) on the chemical shifts may be insignificant. In this case the chemical shifts of the protons of the CH_2 groups of this bridge will be equal and, disregarding the long-range couplings, will show up in the form of a solitary signal, the chemical shift of which is close to that of the signal of unsubstituted 1,4-diazabicyclo[2.2.2]octane (2.72 ppm in $CDCl_3$ [6]). In fact, the PMR spectrum of VIa contains a singlet at 2.91 ppm corresponding to four protons, and this provides a basis for assigning it to the 5,6-CH_2 groups, while the symmetrical multiplet of the AA'BB' type can be assigned to the 7.8-CH_2 groups (see Fig. 1a).

A theoretical calculation of the spectrum by means of the ITRCAL iteration program made it possible to determine the chemical shifts and SSCC: $\delta_A = 2.50$, $\delta_B = 2.83$ ppm; $J_{cis} = J_{AA'} = J_{BB'} = 9.7$; $J_{gem} = J_{AB} = J_{A'B'} = -13.9$; $J_{trans} = J_{AB'} = J_{A'B} = 6.1$ Hz, with a mean square deviation of 0.1 Hz. For comparison, the theoretical spectrum with the parameters indicated above and line width $\Delta_{\nu 1/2} = 1.8$ Hz is also presented in Fig. 1b.

TABLE 1. Compounds IV-VII

Compound	mp, °C	R_f (system)	M	Found, %				Empirical formula	Calc., %				Yield, %
				C	H	N	Cl(I)		C	H	N	Cl(I)	
IVa	143,5—145^{a}	0,47 (B)	300	71,6	8,0	9,7	—	$C_{18}H_{24}N_2O_2$	72,0	8,1	9,3	—	84
IVb	79—82^{a}	0,59 (B)	300	71,4	8,1	9,3	—	$C_{18}H_{24}N_2O_2$	72,0	8,1	9,3	—	77
Va	209—210^{b}	0,77 (A)^{c}	—	53,1	5,9	6,9	34,6	$C_{18}H_{24}Cl_4N_2$	52,7	5,9	6,8	34,6	78
Vb	179—182^{b}	0,61 (A)^{c}	—	—	—	6,8	—	$C_{18}H_{24}Cl_4N_2$	52,7	5,9	6,8	—	52
VIa	154—157^{d}	0,52 (B)	264	82,0	7,7	10,4	—	$C_{18}H_{20}N_2$	81,8	7,6	10,1	—	51
VIb	58—62^{e}	0,50 (B)	264	81,6	7,8	10,6	—	$C_{18}H_{20}N_2$	81,8	7,6	10,1	—	65
VIIa	262—264^{b}	0,71 (B)	—	56,3	5,9	7,1	(30,6)	$C_{19}H_{23}IN_2$	56,2	5,7	6,9	(31,2)	93
VIIb	283,5—285^{b}	0,72 (B)	—	55,9	5,9	6,6	(31,1)	$C_{19}H_{23}IN_2$	56,2	5,7	6,9	(31,2)	72

^{a}From water. ^{b}From methanol. ^{c}With prior neutralization with ammonium hydroxide at the starting line. ^{d}From petroleum ether (70-100°C). ^{e}Sublimed twice at 120°C (1 mm).

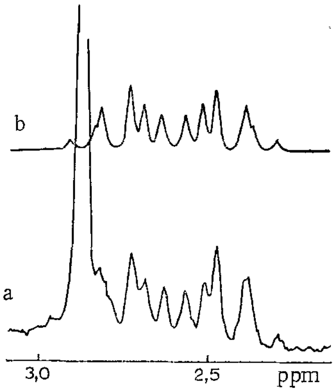

Fig. 1

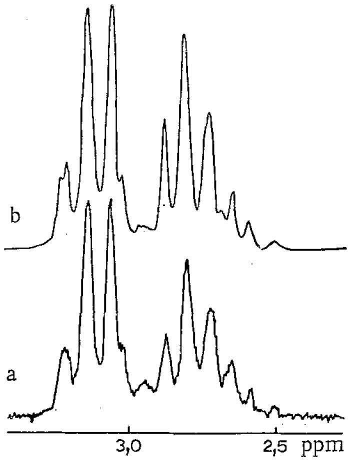

Fig. 2

Fig. 1. Experimental (a) and theoretical (b) spectra of the methylene part of cis-2, 3-diphenyl-1,4-diazabicyclo[2.2.2]octane (VIa).

Fig. 2. Experimental (a) and theoretical (b) spectra of the methylene part of trans-2,3-diphenyl-1,4-diazabicyclo[2.2.2]octane (VIb).

In the spectrum of trans isomer VIb the signals of the protons of the two ethylene bridges should, in the general case, be identical unsymmetrical multiplets of a spin system of the ABCD type, since the phenyl rings are oriented symmetrically relative to both ethylene bridges and have the same effect on the chemical shifts of the protons of the CH_2 groups. In fact, in the experimental spectrum of VIb the signals of the protons of the ethylene bridges appear as an unsymmetrical multiplet of the ABCD type (see Fig. 2a).

A calculation of the theoretical spectrum of VIb by means of the SSCC found for the cis isomer and the chemical shifts $\delta_A = 2.40$, $\delta_B = 2.54$, $\delta_C = 2.78$, and $\delta_D = 2.79$ ppm satisfactorily reproduces the experimental spectrum at the wavelength of the theoretical spectrum $\Delta_{\nu_{1/2}} = 2$ Hz (see Fig. 2b). Thus one may regard it as an established fact that VIa is the cis isomer and VIb is the trans isomer of 2,3-diphenyl-1,4-diazabicyclo[2.2.2]octane.

The $J_{H_2H_3}$ value for VIa obtained by means of an analysis of the ^{13}C–H satellites corresponds to the usually observed value of the vicinal constants for cis isomers [7]; however, the value of the trans constant for VIb exceeds the expected value, which is usually 2-6 Hz [7]. The corresponding monomethiodides VIIa,b, respectively, were obtained in order to obtain additional information regarding the vicinal SSCC in 2,3-diphenyldiazabicyclooctanes by the action of methyl iodide on diamines VIa,b. The vicinal $J_{H_2H_3}$ constant observed in the PMR spectra is 10.7 Hz for cis isomer VIIa and 9.65 Hz for trans isomer VIIb. These values are quite close to the $J_{H_2H_3}$ constants of VIa,b; a similar overstatement of the trans constant is observed. In the case of the quinuclidine system, the geometry of which is similar to that of 1,4-diazabicyclo[2.2.2]octanes, it is assumed that the increase in J_{trans} is associated with a change in the H—C_2—C_3—H dihedral angle due to van der Waals interaction between the substituents [8]. It is known [9] that the I molecule permits this change in the conformation due to rotation of the tetrahedra of the bonds of the nitrogen atoms relative to one another (about an axis passing through these atoms). Calculation of mechanical models of the molecules of VIIa,b by means of the program in [10] gives the following values of the H—C_2—C_3—H dihedral angles: 4° for the cis isomer and 135° for the trans isomer. The use of the calculated angles for the calculation of the Karplus SSCC values from the equation in [11] gives $J_{H_2H_3}$ = 9.5 Hz for the cis isomer and 8.5 Hz for the trans isomer. These values are quite close to the experimentally observed constants for VIIa,b and very close to the $J_{H_2H_3}$ values observed in the ^{13}C—H satellites for VIa,b, and this confirms the existence of changes in the geometry of the molecules that are evidently associated with pushing apart of the phenyl substituents. It should be noted that for 2,3-disubstituted quinuclidines, according to the estimates in [8] made on the basis of a study of the SSCC values, the deviation of the H—C_2—C_3—H dihedral angles from 120°C for the trans isomers is +15°, which corresponds to the value of the dihedral angle that we found for trans isomer VIIb (135°).

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 with Varian HA-100 and Bruker WP-80 spectrometers with hexamethyldisiloxane as the internal standard. The SSCC in the ^{13}C—H satellites were determined in the PMR spectra recorded with a Varian XL-200 spectrometer for 3% (cis) and 10% (trans) concentrations of VI (150 accumulations). The molecular masses were determined with an MS-902 high-resolution mass spectrometer. The mathematical calculations of mechanical models of the molecules were made with a Minsk-32 computer, while the calculations with the ITRCAL program were made with a BNC-28 computer. The chloride ion concentration was determined by titration of aliquots with a solution of $AgNO_3$ with an LPU-01 potentiometer. Thin-layer chromatography (TLC) was carried out on Silufol UV-254 plates in chloroform—alcohol (10:1 by volume) (A) and tert-butanol—methyl ethyl ketone—formic acid—water (40:30:15:15) (B) systems with development by iodine.

N,N'-Bis(β-hydroxyethyl)-1,2-diphenyl-1,2-ethylenediamine (IVa,b). IVa. From meso-1,2-diphenyl-1,2-ethylenediamine (IIIa). A 19-ml (0.58 mole) sample of ethylene oxide was added to a cooled solution of 30 g (0.14 mole) of diamine IIIa in 400 ml of methanol, and the mixture was maintained at 20°C for 3 days. The methanol was removed *in vacuo*, and the residue was triturated with ether. The resulting precipitate was washed with ether and recrystallized from water to give 35.7 g of IVb. From d,*l*-1,2-diphenyl-1,2-ethylenediamine (IIIb). This compound was similarly obtained as described above from 1 g (4.72 mmole) of diamine IIIb and 0.6 ml (12 mmole) of ethylene oxide in 11.5 ml of methanol. The yield was 1.09 g.

N,N'-Bis(β-chloroethyl)-1,2-diphenyl-1,2-ethylenediamine Dihydrochloride (Va,b). Va. From meso form IVa. A 7.87-g (0.026 mole) sample of IVa was added in small portions to 57 ml (0.8 mole) of freshly distilled $SOCl_2$, during which spontaneous heating and foaming of the reaction mixture was observed. The solution was refluxed for 1 h, after which the excess $SOCl_2$ was removed by vacuum distillation, and the residue was treated with dry acetone. The precipitate was removed by filtration and washed with dry acetone to give 8.45 g of Vb. From the d,*l* form of IVb. The substitution reaction was carried out similarly starting from 0.5 g (1.67 mmole) of IVb and 3.6 ml (50 mmole) of $SOCl_2$. After removal of the excess $SOCl_2$, the residue was treated with 2 ml of absolute acetone and 4 ml of absolute ether, and the mixture was stored in a refrigerator for 1 h. The precipitate was removed by filtration and washed with absolute acetone. The yield was 0.351 g.

2,3-Diphenyl-1,4-diazabicyclo[2.2.2]octane (VIa,b). VIa. From meso form Va. A solution of 3 g (7.3 mmole) of dihydrochloride Va in 300 ml of dry DMF was heated at 150°C for 4.5 h. The course of the reaction was followed by chromatography in system A, and 1 ml aliquots were selected for titration with a solution of $AgNO_3$. The DMF was evaporated, and the residue was treated with 50 ml of a saturated solution of Na_2CO_3 and extracted with ether (five 50-ml portions). The ether solution was washed with water, dried with Na_2CO_3, and evaporated. The residue was triturated with 10 ml of ether, and the precipitate was removed by filtration to give 0.71 g of a colorless product. The ether mother liquor was evaporated, and the residue was extracted with hot petroleum ether (70-100°C) (two 10-ml portions). The solution was evaporated twice and allowed to stand in a refrigerator. The resulting precipitate was separated and washed with two portions of petroleum ether (70-100°C) to give another 0.27 g of product. The overall yield of VIa was 0.98 g. IR spectrum: 755, 773 (CH_2, pendulum vibrations); 1460, 2887, 2950 cm^{-1} (CH_2, deformation vibrations).* PMR spectrum (in $CDCl_3$): 2.33-3.00 (8H, m, methylene protons), 4.53 (2H, s, benzyl protons), and 6.84-7.11 ppm (10H, m, aromatic protons). VIb. From d,*l* form Vb. The cyclization was carried out similarly with 0.5 g (1.22 mmole) of Vb in 50 ml of DMF. After evaporation of the DMF, the reaction mixture was treated with 20 ml of a saturated solution of Na_2CO_3 and extracted with chloroform (five 20-ml portions). The chloroform solution was dried with K_2CO_3 and evaporated, and the residual oil was extracted with boiling petroleum ether (70-100°C) (six 10-ml portions). The organic solution was evaporated, and the residue was sublimed at 120°C (1 mm) to give 0.209 g of a substance that crystallized rapidly. IR spectrum: 1450, 2880, 2895, 2930, and 2950 cm^{-1} (CH_2, deformation vibrations).* PMR spectrum (in $CDCl_3$): 2.49-3.31 (8H, m, methylene protons), 4.08 (2H, s, benzyl protons), and 7.10-7.55 ppm (10H, m, aromatic protons).

1-Methyl-2,3-diphenyl-1,4-azoniaazabicyclo[2.2.2]octane Iodide (VIIa,b). VIIa. From cis isomer VIa. A solution of 0.15 g (0.57 mmole) of diamine VIa and 0.2 ml (4 mmole) of freshly distilled CH_3I in 10 ml of dry ether was allowed to stand for 24 h, after which the precipitate was removed by filtration and recrystallized from a small amount of methanol to give 0.215 g of product. PMR spectrum (in d_6-DMSO): 2.59 (3H, s, CH_3 group); 5.03, 5.49 (2H, d, benzyl protons), and 6.45-7.64 ppm (10H, m, aromatic protons). VIIb. From trans form VIb. This compound was similarly obtained from 0.088 g (0.33 mmole) of diamine VIb and 0.1 ml (2 mmole) of freshly distilled CH_3I in 5 ml of dry ether. The yield was 0.098 g. PMR spectrum (in d_6-DMSO): 2.56 (3H, s, CH_3 group); 4.76, 5.08 (2H, d, benzyl protons), 7.42-7.55 (3H, m, β and γ protons of the 2-C_6H_5 group), 7.71-8.00 (2H, m, α protons of the 2-C_6H_5 group), and 7.25 ppm (5H, s, 3-C_6H_5 group).

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*The assignment of the bands was made on the basis of the information in [12].