

Proton Magnetic Resonance Studies of Compounds with Bridgehead Nitrogen Atoms. IX (1)
 Configurational and Conformational Studies with
 Methyl-Substituted 8-Phenyl-1,8-diazabicyclo[4.3.0]nonanes

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The synthesis of a series of methyl-substituted 8-phenyl-1,8-diazabicyclo[4.3.0]nonanes is described. The preferred conformations of these compounds have been assigned on the basis of the 2850-2500 cm^{-1} region of their infrared spectra and of the geminal coupling constant of the C-9 methylene group.

In a previous paper (2) the configurations and preferred conformations of some 8-alkyl-1,8-diazabicyclo[4.3.0]nonanes (I, R = alkyl) and the corresponding 2-methyl substituted compounds were described. The preferred conformations of these compounds were deduced by reference to the 2850-2500 cm^{-1} region of the infrared spectra and from a study of the geminal coupling constant (J_{gem}) and of the chemical shift difference between the C-9 methylene protons. The interpretation of the infrared results was not as simple as in our studies (3,4) on 8-oxa- and 8-thia-1-azabicyclo[4.3.0]nonanes (II, X = O,S) since the 8-alkyl substituent itself gives rise to bands in the 2850-2500 cm^{-1} region. In order to eliminate this complicating factor a series of methylsubstituted 8-phenyl-1,8-diazabicyclo[4.3.0]nonanes (III) were prepared for conformational studies. Strong bands in the 2850-2500 cm^{-1} region of the spectra of any of these compounds will now only arise from the presence of *trans*-fused ring conformations (5).

The 8-phenyl compounds were synthesized by refluxing aniline with the methyl substituted 2-bromomethyl-piperidine hydrobromides. This produced the methyl-substituted 2-(*N*-phenylaminomethyl)piperidine which on reaction with formaldehyde gave the methyl-substituted 8-phenyl-1,8-diazabicyclo[4.3.0]nonane. The preparation and assignment of configuration to the 2-bromomethyl-piperidine hydrobromides was described in a previous paper (4).

The conformational arguments used in the discussion (2) of the 8-alkyl analogues apply to these compounds and so one would expect *cis*-2,6-*H*-2-methyl-, *trans*-3,6-*H*-3-methyl-, *cis*-4,6-*H*-4-methyl-, and *trans*-5,6-*H*-5-methyl-8-phenyl-1,8-diazabicyclo[4.3.0]nonane to exist predominantly in the *trans*-fused ring conformation (IV). On the other hand *cis*-3,6-*H*-3-methyl-, *trans*-4,6-*H*-4-methyl- and *cis*-5,6-*H*-5-methyl-8-phenyl-1,8-diazabicyclo[4.3.0]nonane might exist at room temperature as conformational mixtures containing an appreciable amount of the *cis*-fused ring conformation (V).

The infrared spectra clearly divide these compounds into two groups. The unsubstituted parent compound and those epimers which on the basis of chemical evidence will have an equatorial methyl group when the ring fusion is *trans* all show three strong bands at 2808-2798 (ϵ^a , 64-104), 2784-2772 (ϵ^a , 64-67), and 2742-2738 cm^{-1} (ϵ^a , 59-80). The compounds which will have an axial methyl group when the ring fusion is *trans* still have bands in the 2500-2850 cm^{-1} region of their infrared spectra though of much reduced intensity indicating a predominantly *cis*-fused ring conformation. Both of the 7-methyl epimers show strong bands in this region of the

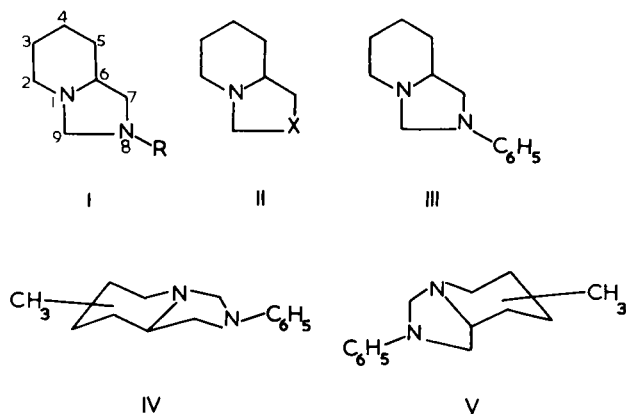


TABLE I

N.M.R. Spectra of *cis*-Fused-8-phenyl-1,8-diazabicyclo[4.3.0]nonanes

Compound	Coupling Constants (Hz) (a)		Chemical Shifts (τ) (b)	
	$J_{H_9H_9'}$	H_9	H_9'	$\Delta H_9H_9'$
<i>cis</i> -3,6- <i>H</i> -3-Methyl-8-phenyl-1,8-diazabicyclo[4.3.0]nonane	-6.0	5.78	6.12	0.34
<i>trans</i> -4,6- <i>H</i> -4-Methyl-8-phenyl-1,8-diazabicyclo[4.3.0]nonane	-6.0	5.84	6.21	0.37
<i>cis</i> -5,6- <i>H</i> -5-Methyl-8-phenyl-1,8-diazabicyclo[4.3.0]nonane	-6.0	5.78	6.15	0.37

(a) ± 0.3 Hz. (b) $\pm 0.05 \tau$.

TABLE II

N.M.R. Spectra of *trans*-Fused-8-phenyl-1,8-diazabicyclo[4.3.0]nonanes

Compound	Coupling Constants (Hz) (a)				Chemical Shifts (τ) (b)			
	$J_{H_9H_9'}$	$J_{H_7H_7'}$	$J_{H_7H_{6ax}}$	H_9	H_9'	H_7	H_7'	H_{2eq}
8-Phenyl-1,8-diazabicyclo[4.3.0]nonane	-3.8	-7.8	6.1	5.67	6.39	6.67	6.93	
<i>cis</i> -2,6- <i>H</i> -2-Methyl-8-phenyl-1,8-diazabicyclo[4.3.0]nonane	-3.7	-7.9	6.5	5.54	6.43	6.67	6.93	7.0
<i>trans</i> -3,6- <i>H</i> -3-Methyl-8-phenyl-1,8-diazabicyclo[4.3.0]nonane	-3.6	-7.9	6.7	5.66	6.43	6.62	6.94	7.0
<i>cis</i> -4,6- <i>H</i> -4-Methyl-8-phenyl-1,8-diazabicyclo[4.3.0]nonane	-3.7	-7.9	6.3	5.63	6.41	6.61	6.93	7.0
<i>trans</i> -5,6- <i>H</i> -5-Methyl-8-phenyl-1,8-diazabicyclo[4.3.0]nonane	-3.6	-7.9	6.0	5.64	6.41	6.56	6.88	7.0
<i>cis</i> -7,6- <i>H</i> -7-Methyl-8-phenyl-1,8-diazabicyclo[4.3.0]nonane	-3.7	-	6.4	5.60	6.62	6.32	-	6.87
<i>trans</i> -7,6- <i>H</i> -7-Methyl-8-phenyl-1,8-diazabicyclo[4.3.0]nonane	-4.3	-	-	5.77	6.32	-	6.63	7.10

(a) ± 0.3 Hz. (b) $\tau \pm 0.05$.

infrared spectrum indicating the presence of an appreciable amount of the *trans*-fused ring conformation in the equilibrium mixture at room temperature.

The n.m.r. spectra support this division of the compounds into two groups. Work on II (X = O,S) (3,4) has shown that compounds existing in predominantly *trans*-fused ring conformations show a large value (δ) for the geminal coupling constant in this type of system and a large chemical shift difference ($\Delta H_9 H_9'$) between the C-9 methylene protons. On the other hand *cis*-fused ring conformations are characterized by a more negative J_{gem} and a small chemical shift difference between these protons. This empirical rule can be seen to apply to the 8-phenyl-1,8-diazabicyclo[4.3.0]nonanes (Tables 1 and 2).

Compounds assigned predominantly *trans*-fused ring conformations on the basis of their infrared spectra have a J_{gem} for the C-9 methylene group of -3.6 to -3.7 Hz. The large $\Delta H_9 H_9'$ in these compounds together with the deshielding of H_9 in the 2-methyl epimer all support (3) the presence of a *trans*-fused ring conformation. The configurations of the 7-methyl epimers have been assigned using the same arguments employed (7) for the 8-oxa analogues. The J_{gem} of -3.7 Hz for the C-9 methylene group in the *cis*-7,6-*H*-7-methyl compound indicates that this compound exists predominantly in the *trans*-fused ring conformation. The more negative J_{gem} of -4.3 Hz in the *trans*-7,6-*H*-7-methyl compound suggests a conformational equilibrium containing ca. 30% of the *cis*-fused ring conformation, a fact not indicated by the infrared spectra. The remainder of the n.m.r. spectra in these compounds are similar to the 8-alkyl analogues and are summarized in Tables 1 and 2.

The three compounds assigned a *cis*-fused ring conformation on the basis of their infrared spectra, all exhibited a J_{gem} for the C-9 methylene protons of -6.0 Hz, somewhat more negative than that observed in the *trans*-fused ring conformers. This, together with the small $\Delta H_9 H_9'$ and the presence of signals corresponding to two equatorial protons next to nitrogen at ca. τ 7.45 supports the infrared assignment of a predominantly *cis*-fused ring conformation.

EXPERIMENTAL

All elemental analyses were carried out by Dr. F. Pascher and E. Pascher, Microanalytical Laboratory, Bonn, Germany. Melting points are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 457 grating instrument and measured as 0.075 *M* solutions in deuteriochloroform using 0.5 mm matched cells. The n.m.r. spectra were determined on a Perkin-Elmer R.10 Spectrometer as 10% solutions in deuteriochloroform with tetramethylsilane as internal reference.

Preparation of 2-(*N*-phenylaminomethyl)piperidines via 2-bromomethylpiperidine hydrobromides. General Procedure.

The 2-bromomethylpiperidine hydrobromide (15 g.) was re-

fluxed with aniline (15 g.) for three hours. The reaction mixture was cooled and triturated with ether to remove the excess amine. The resultant white solid was dissolved in the minimum amount of water and strongly basified with aqueous sodium hydroxide solution. The mixture was ether extracted, the ether solution was dried (sodium sulfate) and concentrated and the crude product was distilled or recrystallized.

2-(*N*-phenylaminomethyl)piperidine.

This compound (6.5 g., 59%) was obtained from 2-(bromomethyl)piperidine hydrobromide (15 g.) as a white crystalline solid, m.p. 63-64° from ether.

Anal. Calcd. for $C_{12}H_{18}N_2$: C, 75.74; H, 9.54; N, 14.72. Found: C, 75.29; H, 9.61; N, 14.76.

cis-6,2-*H*-6-methyl-2-(*N*-phenylaminomethyl)piperidine.

This compound (7.3 g., 66%) was obtained from 6-methyl-2-bromomethylpiperidine hydrobromide (15 g.) as a colourless viscous oil, b.p. 130-132°/0.4 mm, n_D^{20} 1.5565.

Anal. Calcd. for $C_{13}H_{20}N_2$: C, 76.42; H, 9.87; N, 13.71. Found: C, 75.78; H, 9.81; N, 13.69.

An epimeric mixture of the 5-methyl-2-(*N*-phenylaminomethyl)piperidines (14 g., 62%) was obtained from an epimeric mixture of 5-methyl-2-bromomethylpiperidine hydrobromide (30 g.), which had been prepared from 5-methyl-2-piperidylcarbinol obtained by catalytic hydrogenation, as a colourless viscous oil, b.p. 129-131°/0.6 mm. Trituration of the oil with ether gave a white solid which on recrystallization from ether gave epimerically pure *trans*-5,2-*H*-5-methyl-2-(*N*-phenylaminomethyl)piperidine (6.5 g.) as a white crystalline solid, m.p. 82-84°.

Anal. Calcd. for $C_{13}H_{20}N_2$: C, 76.42; H, 9.80; N, 13.71. Found: C, 76.42; H, 9.80; N, 13.92.

The remaining viscous oil was distilled to give an epimeric mixture (which was detected by NMR) of *cis*- and *trans*-5,2-*H*-5-methyl-2-(*N*-phenylaminomethyl)piperidine (6.5 g.) as a colourless viscous oil, b.p. 133-135°/0.55 mm.

Anal. Calcd. for $C_{13}H_{20}N_2$: C, 76.42; H, 9.87; N, 13.74. Found: C, 76.40; H, 9.76; N, 13.79.

An epimeric mixture of *cis* and *trans*-4,2-*H*-4-methyl-2-(*N*-phenylaminomethyl)piperidine (24.5 g., 83%) was obtained from an epimeric mixture of the 4-methyl-2-bromomethylpiperidine hydrobromides (40 g.) itself prepared from 4-methyl-2-piperidylcarbinol obtained by catalytic hydrogenation. The colourless viscous oil, b.p. 135-137°/0.85 mm, was triturated with petroleum ether to give a white crystalline solid. Recrystallization gave epimerically pure *cis*-4,2-*H*-4-methyl-2-(*N*-phenylaminomethyl)piperidine (9.7 g.) as white plates, m.p. 82-84° from ether.

Anal. Calcd. for $C_{13}H_{20}N_2$: C, 76.42; H, 9.87; N, 13.71. Found: C, 76.54; H, 9.73; N, 13.69.

The residual oil was distilled to give an epimeric mixture of the 4-methyl-2-(*N*-phenylaminomethyl)piperidines as a colourless viscous oil, b.p. 130-131°/0.3 mm.

Anal. Calcd. for $C_{13}H_{20}N_2$: C, 76.42; H, 9.87; N, 13.71. Found: C, 76.64; H, 9.79; N, 13.71.

cis-3,2-*H*-3-Methyl-2-(*N*-phenylaminomethyl)piperidine.

This compound (4.0 g., 71%) was obtained from 3-methyl-2-bromomethylpiperidine hydrobromide (7.5 g.), which had been prepared from 3-methyl-2-piperidylcarbinol obtained by sodium and ethanol reduction, as a white crystalline solid, m.p. 80-81° from ether.

Anal. Calcd. for $C_{13}H_{20}N_2$: C, 76.42; H, 9.87; N, 13.71. Found: C, 76.42; H, 9.81; N, 13.90.

An epimeric mixture of the 3-methyl-2-(*N*-phenylaminomethyl)-

piperidines (8.6 g., 77%) was obtained from 3-methyl 2-bromomethylpiperidine hydrobromide (15 g.) which had been prepared from 3-methyl-2-piperidylcarbinol obtained by catalytic reduction. This mixture (6.0 g.) was dissolved in ether and left overnight at 0°; in this way 1.4 g. of *cis*-3,2-*H*-3-methyl-2-(*N*-phenylaminomethyl)piperidine was removed leaving an enriched sample of epimerically impure *trans*-3,2-*H*-3-methyl-2-(*N*-phenylaminomethyl)piperidine.

An epimeric mixture of the *N*-phenyl-1-(2-piperidyl)ethylamines (13.6 g., 61%) was obtained from an epimeric mixture of the 2-bromomethylpiperidine hydrobromides (30 g.) as a colourless viscous oil, b.p. 134-135°/0.7 mm. The 2-bromomethylpiperidine hydrobromide was itself prepared from α -methyl-2-piperidylcarbinol by the action of hydrogen bromide gas and phosphorus tribromide and was obtained as a white crystalline solid from ethanol.

Anal. Calcd. for C₇H₁₄Br₂N: C, 30.88; H, 5.18; N, 5.15. Found: C, 30.95; H, 5.36; N, 3.86.

Preparation of 8-phenyl-1,8-diazabicyclo[4.3.0]nonanes from 2-(*N*-phenylaminomethyl)piperidines. General Procedure.

The 2-(*N*-phenylaminomethyl)piperidine was shaken with an excess of 36% formaldehyde for half an hour. The mixture was basified with aqueous sodium hydroxide and extracted with ether three times. The ether extract was dried (sodium sulfate) and evaporated and the residue was distilled or recrystallized to give the respective 8-phenyl-1,8-diazabicyclo[4.3.0]nonane.

8-Phenyl-1,8-diazabicyclo[4.3.0]nonane.

This compound (3.25 g., 88%) was obtained from 2-(*N*-phenylaminomethyl)piperidine (3.5 g.) as a white crystalline solid, from ether, m.p. 76-78°, ν max, 2802, 2774, 2741 cm⁻¹.

Anal. Calcd. for C₁₃H₁₈N₂: C, 77.18; H, 8.97; N, 13.85. Found: C, 77.53; H, 9.01; N, 14.07.

cis-2,6-*H*-2-Methyl-8-phenyl-1,8-diazabicyclo[4.3.0]nonane.

This compound (3.1 g., 98%) was obtained from *cis*-2,6-*H*-6-methyl-2-(*N*-phenylaminomethyl)piperidine (3.0 g.) as a colourless mobile oil, b.p. 122-124°/0.3 mm.; $n^{14.5}$ 1.5726; infrared ν max 2808, 2784, 2740, 2715, 2600 cm⁻¹.

Anal. Calcd. for C₁₄H₂₀N₂: C, 77.73; H, 9.32; N, 12.95. Found: C, 77.41; H, 9.56; N, 12.82.

trans-3,6-*H*-3-Methyl-8-phenyl-1,8-diazabicyclo[4.3.0]nonane.

This compound (1.8 g., 69%) was obtained from *trans*-5,6-*H*-5-methyl-2-(*N*-phenylaminomethyl)piperidine (2.5 g.) as a white crystalline solid, m.p. 88-90° from ether, infrared ν max 2803, 1777, 2742, 2708 cm⁻¹.

Anal. Calcd. for C₁₄H₂₀N₂: C, 77.73; H, 9.32; N, 12.9. Found: C, 77.55; H, 9.33; N, 12.52.

cis-3,6-*H*-3-Methyl-8-phenyl-1,8-diazabicyclo[4.3.0]nonane.

This compound (1.75 g.) was obtained from epimerically impure *cis*-5,6-*H*-5-methyl-2-(*N*-phenylaminomethyl)piperidine (2.5 g.) as a white crystalline solid, m.p. 61-63°, from ether; ν max 2803, 2740, 2710 cm⁻¹.

Anal. Calcd. for C₁₄H₂₀N₂: C, 77.73; H, 9.32; N, 12.95. Found: C, 77.97; H, 9.14; N, 12.76.

cis-4,6-*H*-4-Methyl-8-phenyl-1,8-diazabicyclo[4.3.0]nonane.

This compound (3.8 g., 72%) was obtained from *cis*-4,6-*H*-4-methyl-2-(*N*-phenylaminomethyl)piperidine (5.0 g.) as a white crystalline solid, m.p. 66-67° from 30-40° light petroleum;

ν max 2803, 2778, 2741 cm⁻¹.

Anal. Calcd. for C₁₄H₂₀N₂: C, 77.73; H, 9.32; N, 12.95. Found: C, 77.80; H, 9.30; N, 13.21.

trans-4,6-*H*-4-Methyl-8-phenyl-1,8-diazabicyclo[4.3.0]nonane.

This compound (2.9 g.) was obtained from an epimeric mixture of the 4-methyl-2-(*N*-phenylaminomethyl)piperidines (5.0 g.) as a white crystalline solid, m.p. 54-56° from light petroleum; ν max 2802, 2746 cm⁻¹.

Anal. Calcd. for C₁₄H₂₀N₂: C, 77.73; H, 9.32; N, 12.95. Found: C, 77.96; H, 9.30; N, 13.32.

trans-5,6-*H*-5-Methyl-8-phenyl-1,8-diazabicyclo[4.3.0]nonane.

This compound (2.9 g., 92%) was obtained from *trans*-3,6-*H*-3-methyl-2-(*N*-phenylaminomethyl)piperidine (3.0 g.) as white needles, m.p. 45-46° from light petroleum; ν max 2798, 2772, 2738 cm⁻¹.

Anal. Calcd. for C₁₄H₂₀N₂: C, 77.73; H, 9.32; N, 12.95. Found: C, 77.91; H, 9.30; N, 13.21.

cis-5,6-*H*-5-Methyl-8-phenyl-1,8-diazabicyclo[4.3.0]nonane.

This compound (2.4 g.) was prepared from an epimeric mixture of the 3-methyl-2-(*N*-phenylaminomethyl)piperidine (4.8 g.). The epimeric mixture of the methyl substituted 1,8-diazabicyclo[4.3.0]nonanes was passed down a 450 g. column of grade 1 Woelm natural, alumina using 40-60° petroleum ether. The *cis*-5,6-*H*-5-methyl epimer was the first fraction off the column and was obtained as a colourless viscous oil, b.p. 124-126°/0.4 mm; ν max, 2805, 2752 cm⁻¹.

Anal. Calcd. for C₁₄H₂₀N₂: C, 77.73; H, 9.32; N, 12.95. Found: C, 77.31; H, 9.04; N, 13.32.

cis- and *trans*-7,6-*H*-7-Methyl-8-phenyl-1,8-diazabicyclo[4.3.0]nonane.

These Compounds (28.8 g., 91%) were obtained from an epimeric mixture of *N*-phenyl- α -(2-piperidyl)ethylamines (30 g.) as a colourless viscous oil, b.p. 134-135°/0.7 mm. Separation was achieved by passing 5.0 g. of the mixture down a 300 g. neutral grade 1 Woelm alumina column in 30-40° light petroleum.

Anal. Calcd. for C₁₄H₂₀N₂: C, 77.73; H, 9.32; N, 12.95. Found: C, 77.57; H, 9.34; N, 13.05.

trans-7,6-*H*-7-Methyl-8-phenyl-1,8-diazabicyclo[4.3.0]nonane.

This compound (0.7 g.) was the first isomer off the column and was obtained as a colourless viscous oil, b.p. 137-139°/0.8 mm., n^{19} 1.5723, ν max 2798, 2743, 2692, 2677 cm⁻¹.

cis-7,6-*H*-7-Methyl-8-phenyl-1,8-diazabicyclo[4.3.0]nonane.

This compound (1.5 g.) was a colourless viscous oil, b.p. 135-137°/0.5 mm., n^{19} 1.5710; ν max 2799, 2741, 2695, 2679 cm⁻¹.

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